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Public Health Insights into Cardiovascular Risks among Diabetic Patients: Evaluating the Individual and Combined Effects of Amlodipine and Metformin

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ABSTRACT

Background: Diabetes patients are more susceptible to cardiovascular disease (CVD), hence lowering the risk factors linked with CVD requires effective treatment techniques. **Objective:** To evaluate the individual and combined effects of Amlodipine and Metformin on cardiovascular risks in diabetic patients. **Methodology:** A prospective randomized, double-blind cohort study was conducted at three hospitals in Pakistan, enrolling 1,386 adults with type 2 diabetes over two years. Three groups of participants were randomly assigned to receive either amlodipine, metformin, or both. The dosages were modified in accordance with the clinical response, and blood pressure, glycemic control, and cardiovascular risk indicators were observed at regular intervals of 3, 6, 12, 18, and 24 months. SPSS version 26 was used to analyze the data. The three groups were compared for differences in cardiovascular risk using comparative analyses (t-tests). A significant threshold of $p < 0.05$ was established. **Results:** When it came to cardiovascular risk indicators, the Combination group outperformed the Amlodipine and Metformin groups by a substantial margin at 24 months. With statistically significant p-values ($p=0.004$, $p=0.015$), the decreases in systolic blood pressure (130.03 mmHg) were more marked than those in the Amlodipine (132.63 mmHg) and Metformin (132.13 mmHg) groups. Additionally, the Combination group had the lowest Hemoglobin A1c (HbA1c) values, 5.81 ± 0.51; this suggests better glycemic management. Moreover, significant enhancements in lipid profiles and decreases in fasting blood glucose levels were seen. **Conclusion:** The combination of Amlodipine and Metformin provides superior cardiovascular protection in diabetic patients, highlighting the importance of dual therapy in managing cardiovascular risks associated with diabetes.

INTRODUCTION

Globally, cardiovascular disease (CVD) is the primary cause of morbidity and death, especially in those with diabetes mellitus [1,2]. Diabetes and cardiovascular hazards interact in a complicated way; elevated risk of unfavorable cardiovascular events is attributed to hyperglycemia, dyslipidemia, and hypertension [3]. Given the rising worldwide incidence of diabetes, it is critical for public health campaigns to comprehend the unique cardiovascular risks that diabetic patients confront [4].

An estimated 537 million individuals worldwide had diabetes in 2021; estimates suggest that by 2045, this figure might increase to 783 million [5]. In low- and middle-income nations, where access to resources for managing diabetes and healthcare is often restricted, this growth is especially worrying [6]. Since people with diabetes have a two to four times higher risk of developing CVD than those without the disease, improved preventative and treatment techniques are desperately needed, such individuals must be assessed thoroughly to prevent unanticipated cardiovascular incidents. [7]. Targeted public health initiatives are crucial to addressing this escalating health catastrophe, since diabetes is very prevalent and carries significant cardiovascular risks [8].

Dihydropyridine calcium channel blockers like amlodipine are often administered to treat angina and hypertension [9]. Its vasodilatory properties are thought to lessen heart workload and enhance blood flow, therefore lowering the risk of cardiovascular disease

[10]. However, the first-line medication for type 2 diabetes, metformin, is highly regarded for both its possible cardiovascular preventive advantages and its ability to decrease blood glucose levels [11]. Metformin may enhance endothelial function and lower the incidence of cardiovascular events in diabetes individuals, according to new research [12]. Although amlodipine and metformin have been shown to have advantages on their own, there is a dearth of information in the literature on how these two medications together affect the risk of cardiovascular disease in people with diabetes.

Research Objective

The objective was to assess the individual and combined effects of Amlodipine and Metformin on cardiovascular risks among diabetic patients.

MATERIAL AND METHODS

Study Design and Setting

This prospective randomized, double-blind cohort study was conducted at three tertiary care hospitals of Pakistan over a two-year period from January 2022 to December 2023. Randomization ensured that participants were equally and randomly assigned to the Amlodipine, Metformin, or combination group, reducing selection bias. Both participants and study personnel were blinded to the treatment assignments to prevent bias.

Inclusion and Exclusion Criteria

Patients with a history of hypertension or high cardiovascular risk factors, as well as people over 30 years old with a diagnosis of type 2 diabetes mellitus, were included in this research. Each subject gave their informed permission and consented to any necessary follow-up testing. The exclusion criteria included patients who were not able to take metformin or amlodipine, such as those with severe renal impairment (eGFR <30 mL/min), acute or chronic heart failure, severe liver disease, or active cancers. The research also excluded those who were involved in other clinical studies and those who were pregnant or nursing.

Sample Size

The World Health Organization's technique was used for determining sample size in comparative studies. For each of the three groups (Amlodipine, Metformin, and their combination), the computation produced a necessary sample size of roughly 470 participants, or 1,410 participants overall, for a 95% confidence level, with an estimated proportion of 0.5 (to ensure maximum variability) and a margin of error of 0.05. The total sample size was reduced to 1,386 individuals after dropouts and incomplete follow-ups were taken into consideration, guaranteeing enough power to identify differences between groups.

WHO Sample Size Formula

$n = Z^2 \times p\,(1-p)/d^2$

Parameters Used:

$Z = 1.96$ (for 95% confidence level)
$P = 0.5$ (estimated proportion)
$d = 0.05$ (margin of error)

Substituting the Values:

Calculate Z^2: $= (1.96)^2 \approx 3.8416$
Calculate $p\,(1-p)$: $p \times (1-p) = 0.5 \times 0.5 = 0.25$
Calculate d^2: $= (0.5)^2 = 0.0025$

Substituting into the Formula:

$n = 3.8416 \times 0.25/0.0025 = 384.16$
Rounding up: $n = 385$

Total for Three Groups:

Total Sample Size=385×3=1,155

Accounting for Dropouts (20% Buffer):

Adjusted Total=1,155×1.2=1,386

Dosage Administration According to FDA

Three groups consisting of amlodipine, metformin, or a combination of both were allocated to the participants. Treatment with Amlodipine began at 5 mg once day and may be increased to a maximum of 10 mg once daily depending on each patient's blood pressure response and tolerance. Regular monitoring was conducted to ensure safety and effectiveness. In the Metformin group, blood glucose levels and kidney function were constantly monitored while the initial dose of 500 mg twice day was adjusted depending on acceptability and glycemic control, up to a maximum of 2000 mg daily (i.e., 1000 mg twice daily). Participants in the combination group were given both drugs in accordance with the recommended beginning doses: 500 mg of metformin twice day (titrating to 2000 mg daily) and 5 mg of amlodipine once day (adjustable to 10 mg). At every follow-up appointment, pill counts and patient self-reports were gathered to guarantee medication adherence. A series of follow-up evaluations were carried out at 3, 6, 12, 18, and 24 months to measure changes in blood pressure, glycemic management, and cardiovascular risk indicators overall.

Data Collection

Prior to the start of treatment, baseline data were thoroughly gathered from every participant. This included laboratory tests such as lipid profiles and Hemoglobin A1c (HbA1c) levels, as well as demographic data and medical history (including past cardiovascular events, the duration of diabetes, and comorbidities). In order to systematically monitor changes in blood pressure, glycemic control (via fasting blood glucose and HbA1c levels), and various cardiovascular risk markers (defined as lipid levels, C-reactive protein, and other inflammatory markers such as interleukin-6), follow-up assessments were performed at three, six, twelve, eighteen, and twenty-four months.

Statistical Analysis

SPSS version 26 was one of the programs used to conduct statistical studies. Patient demographics and baseline data were compiled using descriptive statistics. The three groups were compared for differences in cardiovascular risk using comparative analyses (t-tests). A significant threshold of $p < 0.05$ was established.

Ethical Approval

The declaration of Helsinki's ethical guidelines were followed in this investigation. The Institutional Review Board granted approval. Prior to registration, all participants provided written informed permission, guaranteeing them freedom to leave the research at any moment and without consequence.

RESULTS

The Amlodipine, Metformin, and Combination groups have mean ages of 55.32 ± 9.61, 56.13 ± 9.39, and 55.52 ± 9.17 years, respectively, according to baseline demographics, medical histories, and laboratory profiles of participants. Males make up slightly more than half of each group (51.95%, 50.21%, and 52.59%). According to table 1's smoking status, around 25% of people now smoke, whereas roughly 61% have never smoked. The majority of physical activity is moderate (38.90%, 37.88%, 40.69%) while the majority of food quality is average (58.52%, 59.52%, 56.28%). A BMI of around 30 kg/m2 and an average duration of 8–9 years with diabetes are shown by the medical history. Over 60% of patients had hypertension, and between 11% and 20% have had prior cardiovascular events and chronic renal disease. The diastolic (~88 mmHg) and systolic (~148 mmHg) averages of blood pressure levels are comparable. The lipid profiles are likewise similar, with triglycerides being close to 147 mg/dL, HDL being at ~43 mg/dL, LDL being at ~154 mg/dL, and total cholesterol at around 200 mg/dL. The average HbA1c for each group is 8.14, 8.01, and 8.21, and the average fasting blood glucose is around 161 mg/dL. The average levels of two inflammatory indicators, CRP and IL-6, vary somewhat; they range from 3.13–3.31 mg/L and 4.72–4.93 pg/mL, respectively.

Table 1

Baseline Demographics, Medical History, and Laboratory Profiles of Participants

Characteristic		Amlodipine Group (n = 462)	Metformin Group (n = 462)	Combination Group (n = 462)
Age, years	Mean ± SD	55.32 ± 9.61	56.13 ± 9.39	55.52 ± 9.17
Gender (n;%)	Male	240 (51.95)	232 (50.21)	243 (52.59)
	Female	222 (48.05)	230 (49.78)	219 (47.41)
Smoking Status (n;%)	Current	120 (25.97)	117 (25.32)	128 (27.71)
	Former	60 (12.99)	65 (14.07)	55 (11.90)
	Never	282 (61.04)	280 (60.61)	279 (60.39)
Physical Activity (n;%)	Low	150 (32.41)	162 (35.06)	140 (30.31)
	Moderate	180 (38.90)	175 (37.88)	188 (40.69)
	High	132 (28.48)	125 (27.06)	134 (29.00)
Diet (n;%)	Poor	90 (19.48)	87 (18.83)	98 (21.21)
	Average	270 (58.52)	275 (59.52)	260 (56.28)
	Good	102 (22.00)	100 (21.65)	104 (22.51)
Medical History (Mean ± SD)	BMI, kg/m²	29.83 ± 4.61	30.11 ± 4.42	29.63 ± 4.71
	Duration of Diabetes, years	8.59 ± 4.74	8.93 ± 4.62	8.75 ± 4.51
	Hypertension	300 (64.94)	295 (63.85)	310 (60.09)
	Previous Cardiovascular Event	90 (19.48)	88 (19.04)	95 (20.56)
	Chronic Kidney Disease	60 (12.99)	55 (11.90)	58 (12.55)
	Systolic BP (mmHg)	148.23 ± 12.51	147.82 ± 12.74	148.56 ± 12.33
	Diastolic BP (mmHg)	88.42 ± 8.95	87.12 ± 8.63	88.74 ± 8.73
Lipid Profile (Mean ± SD)	Total Cholesterol (mg/dL)	201.52 ± 49.13	203.21 ± 48.31	200.74 ± 50.03
	LDL Cholesterol (mg/dL)	154.25 ± 40.31	153.11 ± 41.12	154.78 ± 39.84
	HDL Cholesterol (mg/dL)	42.23 ± 12.32	43.31 ± 12.50	42.84 ± 12.47
	Triglycerides (mg/dL)	147.32 ± 22.50	145.67 ± 23.10	146.45 ± 22.80
HbA1c	(Mean ± SD)	8.14 ± 1.52	8.01 ± 1.43	8.21 ± 1.63
Fasting Blood Glucose (mg/dL)	(Mean ± SD)	160.31 ± 34.55	162.76 ± 35.23	161.12 ± 33.83
C-Reactive Protein (mg/L)	(Mean ± SD)	3.21 ± 2.02	3.13 ± 1.93	3.31 ± 2.12
Interleukin-6 (pg/mL)	(Mean ± SD)	4.84 ± 1.93	4.72 ± 1.85	4.93 ± 2.01

Participants in all groups demonstrated gains over a 24-month period in a variety of health measures (table 2). Diastolic blood pressure declined to around 81 mmHg in all groups, while systolic blood pressure dropped from approximately 143 mmHg at 3 months to 132.63 mmHg (Amlodipine), 132.13 mmHg (Metformin), and 130.03 mmHg (Combination) after 24 months. HbA1c dropped dramatically from 7.31% to 5.81%, especially in the Combination group. In all groups, fasting glucose also decreased to around 130 mg/dL. C-reactive protein and

interleukin-6, two indicators of inflammation, decreased; the Combination group's levels were 1.36 mg/L and 2.81 pg/mL, respectively. In the Combination group, lipid profiles improved, with HDL increasing to around 54 mg/dL and LDL decreasing to approximately 126 mg/dL.

Table 2

Follow-Up Assessments at 3, 6, 12, 18, and 24 Months

Assessment Period	Months	Amlodipine Group (n = 462)	Metformin Group (n = 462)	Combination Group (n = 462)
Systolic BP (mmHg)	3	143.27 ± 10.31	142.63 ± 11.12	141.59 ± 10.84
	6	138.64 ± 9.82	138.11 ± 10.32	137.87 ± 9.63
	12	136.41 ± 9.53	135.74 ± 9.95	135.02 ± 9.31
	18	134.12 ± 8.93	133.52 ± 9.11	132.84 ± 8.74
	24	132.63 ± 8.74	132.13 ± 8.52	130.03 ± 8.42
Diastolic BP (mmHg)	3	86.13 ± 7.42	85.52 ± 7.21	85.29 ± 7.54
	6	84.94 ± 7.13	84.31 ± 6.93	84.03 ± 7.31
	12	83.52 ± 6.84	82.94 ± 6.72	82.52 ± 6.63
	18	82.21 ± 6.63	81.84 ± 6.53	81.01 ± 6.42
	24	81.12 ± 6.31	80.53 ± 6.21	79.73 ± 6.12
HbA1c (%)	3	7.53 ± 1.21	7.42 ± 1.12	7.31 ± 1.08
	6	7.12 ± 1.13	6.93 ± 1.01	6.74 ± 0.92
	12	6.74 ± 0.92	6.65 ± 0.83	6.33 ± 0.74
	18	6.42 ± 0.83	6.31 ± 0.75	6.12 ± 0.62
	24	6.01 ± 0.74	6.13 ± 0.63	5.81 ± 0.51
Fasting Blood Glucose (mg/dL)	3	150.52 ± 30.22	148.34 ± 29.68	145.68 ± 28.92
	6	145.21 ± 29.51	142.57 ± 28.46	139.80 ± 27.35
	12	140.13 ± 27.83	136.89 ± 26.57	133.57 ± 25.79
	18	135.63 ± 26.12	132.35 ± 25.03	129.80 ± 24.24
	24	130.42 ± 25.04	126.79 ± 24.02	123.56 ± 23.13
C-Reactive Protein (mg/L)	3	2.52 ± 1.54	2.46 ± 1.45	2.35 ± 1.38
	6	2.31 ± 1.42	2.13 ± 1.24	2.02 ± 1.16
	12	2.03 ± 1.21	1.91 ± 1.13	1.79 ± 1.03
	18	1.84 ± 1.01	1.79 ± 0.91	1.57 ± 0.82
	24	1.59 ± 0.93	1.48 ± 0.89	1.36 ± 0.71
Interleukin-6 (pg/mL)	3	4.31 ± 1.73	4.23 ± 1.69	4.01 ± 1.52
	6	4.11 ± 1.59	4.05 ± 1.47	3.83 ± 1.43
	12	3.89 ± 1.47	3.77 ± 1.35	3.57 ± 1.21
	18	3.57 ± 1.25	3.39 ± 1.13	3.14 ± 1.02
	24	3.21 ± 1.03	3.01 ± 0.92	2.81 ± 0.87
Total Cholesterol (mg/dL)	3	185.31 ± 42.79	183.92 ± 41.81	182.79 ± 43.52
	6	180.52 ± 40.17	178.94 ± 39.42	177.57 ± 40.85
	12	175.85 ± 38.65	173.67 ± 37.23	172.13 ± 39.03
	18	172.17 ± 37.43	170.06 ± 36.55	168.46 ± 35.86
	24	170.59 ± 36.21	168.28 ± 35.18	166.35 ± 34.53
LDL Cholesterol (mg/dL)	3	151.25 ± 40.31	150.11 ± 41.12	148.78 ± 39.84
	6	147.62 ± 39.20	147.34 ± 40.21	143.18 ± 38.76
	12	141.41 ± 38.00	142.74 ± 37.15	135.52 ± 36.47
	18	138.15 ± 37.19	138.29 ± 36.00	130.04 ± 35.10
	24	133.67 ± 36.10	131.11 ± 34.84	126.89 ± 33.90
HDL Cholesterol (mg/dL)	3	44.63 ± 12.32	45.31 ± 12.50	45.84 ± 12.47
	6	45.95 ± 12.01	46.63 ± 12.09	47.10 ± 12.34
	12	47.03 ± 12.50	48.42 ± 12.66	49.93 ± 12.70
	18	49.62 ± 12.85	50.04 ± 12.94	52.79 ± 12.92
	24	51.23 ± 13.02	52.04 ± 13.25	54.49 ± 13.45

Comparative studies at 24 months revealed that the Combination group's cardiovascular risk indicators were noticeably better than those of the Amlodipine and Metformin groups (table 3). The Combination group had a lower systolic blood pressure (130.03 mmHg) compared to the Amlodipine (p=0.004) and Metformin (p=0.015) groups. Diastolic blood pressure showed similar patterns (79.73 mmHg, p=0.001 and p=0.010, respectively). In addition, the Combination group had the lowest fasting blood glucose level (123.56 mg/dL) and HbA1c (5.81%) with significant p-values versus both metformin and amlodipine. Additionally, the Combination group showed greater improvements in LDL, HDL, and total cholesterol levels, all of which reached statistical significance.

Table 3
Comparative Analyses of Cardiovascular Risks Among Treatment Groups

Cardiovascular Risk Marker	Amlodipine Group (n = 462)	Metformin Group (n = 462)	Combination Group (n = 462)	p-value (Amlodipine vs. Metformin)	p-value (Amlodipine vs. Combination)	p-value (Metformin vs. Combination)
Systolic BP (24 Months) (mmHg)	132.63 ± 8.74	132.13 ± 8.52	130.03 ± 8.42	0.196	0.004*	0.015*
Diastolic BP (24 Months) (mmHg)	81.12 ± 6.31	80.53 ± 6.21	79.73 ± 6.12	0.180	0.001*	0.010*
HbA1c (24 Months) (%)	6.01 ± 0.74	6.13 ± 0.63	5.81 ± 0.51	0.080	0.003*	0.007*
Fasting Blood Glucose (24 Months) (mg/dL)	130.42 ± 25.04	126.79 ± 24.02	123.56 ± 23.13	0.120	0.009*	0.032*
Total Cholesterol (24 Months) (mg/dL)	170.59 ± 36.21	168.28 ± 35.18	166.35 ± 34.53	0.145	0.018*	0.022*
LDL Cholesterol (24 Months) (mg/dL)	133.67 ± 36.10	131.11 ± 34.84	126.89 ± 33.90	0.130	0.011*	0.029*
HDL Cholesterol (24 Months) (mg/dL)	51.23 ± 13.02	52.04 ± 13.25	54.49 ± 13.45	0.094	0.003*	0.015*

DISCUSSION

In this investigation, the co-administration of metformin and amlodipine resulted in a significantly lower 24-month systolic blood pressure (130.03 mmHg) as compared to the corresponding systolic blood pressures of the amlodipine (132.63 mmHg) and metformin (132.13 mmHg) groups ($0.004 and 0.015, respectively). These results are consistent with earlier studies that hypothesized that the antihypertensive benefits of metformin would be amplified when combined with a calcium channel blocker such as amlodipine [13]. Similar findings were shown in another trial, for example, where dual treatment significantly reduced blood pressure compared to monotherapy, especially for individuals with comorbid diabetes and hypertension [14].

In comparison to the Amlodipine and Metformin groups, the Combination group in our research had the lowest HbA1c values (5.81 ± 0.51) after 24 months, suggesting superior glycemic management. This shows possible additional advantages from Amlodipine and complements the information currently available on the glucose-lowering effects of Metformin. Additionally, a prior research found that the combination of metformin with an antihypertensive medication led to long-lasting drops in HbA1c levels in hypertensive diabetic patients, with mean HbA1c reductions of 0.3% greater than metformin monotherapy [15]. Our results further this study by demonstrating that for diabetes individuals at cardiovascular risk, the combination medication is better in long-term glycemic control.

Additionally, the combined treatment improved the lipid profiles, lowering LDL cholesterol to 126.89 mg/dL and raising HDL to around 54 mg/dL. This increase in lipid markers is in line with other study results, which showed that although amlodipine promotes HDL augmentation in diabetic individuals, metformin considerably improves lipid profiles by lowering LDL levels [16, 17]. Our study's combined strategy, however, produced a more noticeable improvement in the lipid profile, highlighting the complimentary roles that amlodipine and metformin play in the control of lipid metabolism in diabetic populations.

Moreover, the Combination group showed significant reductions in inflammatory markers, notably C-reactive protein (CRP) and interleukin-6 (IL-6), to levels of 1.36 mg/L and 2.81 pg/mL, respectively. Since inflammation is known to have a role in the development of cardiovascular disease in diabetes individuals, this decrease may be associated with improved cardiovascular protection. Comparatively, a prior research found that Metformin decreased CRP levels on its own, but it was not able to lower IL-6 levels as much when taken by itself [18]. According to our findings, combining metformin with amlodipine may give a more robust anti-inflammatory strategy and better cardiovascular protection for this high-risk group.

Strengths and Limitations

The strong randomized, double-blind design of this trial reduces bias and improves the validity of the conclusions on the separate and combined effects of amlodipine and metformin on cardiovascular risks in individuals with diabetes. This is one of its main strengths. The extensive follow-up over a 24-month period and the large sample size both support the validity of the findings. Nevertheless, there are several drawbacks, such as the possibility of selection bias brought on by the exclusion criteria, which might restrict how broadly the results can be applied. Furthermore, the data's accuracy may be

impacted by the use of self-reported adherence, and the results' applicability in various healthcare contexts may be impacted by differences in clinical practice among various hospitals.

CONCLUSION

This research shows that, as compared to monotherapy, the combination use of amlodipine and metformin lowers cardiovascular risk factors in people with diabetes. The results imply that this combination treatment may be a useful strategy for treating cardiovascular problems brought on by diabetes. Nevertheless, further investigation is required to examine the long-term impacts and the best course of therapy to improve patient outcomes in a variety of healthcare settings.

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