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AN OBSERVATIONAL STUDY ON TYPE 2 DIABETES MELLITUS PATIENTS: TO ASSESS TREATMENT REGIMEN, GLYCEMIC CONTROL, AND MEDICATION ADHERENCE, IN PATIENTS ADMITTED IN A CORONARY CARE UNIT WITH ACUTE EVENTS

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ABSTRACT

Background: Diabetes is an important risk factor for cardiovascular disease. Despite polypharmacy patients have uncontrolled blood glucose. Some oral hypoglycemic agents can themselves increase the risk of hypoglycemia and cardiovascular dysfunction. The additional risk factor contributing to cardiovascular dysfunction in the diabetic population is improper medication adherence. **Objective:** The purpose of this study was to observe the association between diabetic treatment regimen, glycemic control, and medication adherence in type 2 diabetics admitted in the coronary care unit with acute events. **Methods:** This prospective observational study was conducted on patients hospitalized in a tertiary care hospital from February 2019 to July 2019. Data on 155 patients with acute cardiac events along with diabetes were collected. Data on previous OHA'S, hypoglycemic events, medication adherence, and the necessary clinical and laboratory values were collected from the respective case sheets. Chi-square test and p-value were calculated. **Results:** Among all the patients in study, it was observed that only 14.19% patients had adequate glycemic control (HbA1C <7) and 36.12% patients developed hypoglycemia. Although majority (70.96%) of the patients had appropriate medication adherence, 54.54% had uncontrolled blood glucose. Echocardiogram revealed only 35.48% patients had adequate left ventricular function and 7.09% patients under severe LV dysfunction. **Conclusion:** Within study, poor medication adherence was noted in patients who were on multiple OHA: majority of patients admitted with cardiac event, with severe left ventricular dysfunction had poor glycemic control. The patients who were on insulin monotherapy and those on combination therapy with glimepiride developed severe LV dysfunction.

KEYWORDS: acute coronary events, cardiovascular risk, diabetes mellitus, insulin preparations, medication adherence, oral hypoglycemic agents.

INTRODUCTION

A set of metabolic syndrome contributing to abnormalities in insulin secretion or its action within the body, or both resulting in elevated blood glucose levels is defined as diabetes mellitus. Persistently elevated uncontrolled blood sugar levels associated with diabetes contribute to permanent damage or dysfunction and failure of multiple organs including the eyes, kidneys, nerves, and cardiovascular system culminating in complications of diabetes.[1]

These long term effects of diabetes can vary from microvascular to macrovascular complications.[2] The former includes diabetic retinopathy with a potential loss of vision, diabetic nephropathy contributing to renal failure, peripheral neuropathy with increased risk of foot ulcerations, unhealed wounds, and amputations.[3,4,5,6] while the later complications affect the cerebrovasculature, peripheral arteries, and atherosclerotic transformation of blood vessels.[7] Dysregulation of the lipoprotein metabolism and hypertension are other frequently occurring co-morbidities along with diabetes mellitus.[8,9] In patients with diabetes mellitus, cardiovascular disease (CVD) tends to be the principal cause of morbidity, mortality, and disability.[10]

Understanding the multifactorial and complex mechanism and pathophysiology that correlates diabetes

to CVD can help clinicians to provide adept treatment for cardiovascular disease in diabetic patients. Moreover understanding these profound mechanisms can also assist them to prevent devastating complications. Shreds of evidence are suggesting that the primary cause of ischemic events contributing to the damage of the myocardium in diabetic patients is hyperglycemia. However, it is not the sole factor responsible for the complication since the other factors such as metabolic syndrome and pre-diabetes in normoglycemic patients also increase the risk of acute coronary events.[11] The justification of tight glycemic control in the long-term to reduce the cardiovascular deaths associated with diabetes cannot be concluded although, this can slow the progression of microvascular diabetic complications.[18]

Acute coronary syndrome and diabetes are interrelated and are prevalent in coexisting together in patients where the likelihood of developing one condition into the other is high. Diabetes mellitus was identified as an independent risk factor for acute coronary syndrome with hazard ratios (HR) of 1.85 and 1.74 as per NHANES and the Cardiovascular Health Study respectively.[12] In contrast to this scenario, various categories of drugs used to treat diabetes are contraindicated in the case of ACS.[11,14]

As newer classes of drugs are being effectively introduced with the claim of controlling hyperglycemia in case diabetes, the efficacy of these anti-diabetic medications may not assure cardiovascular safety. Hence, there have been numerous trials aimed to evaluate the safety of anti-diabetic drugs in cardiac patients in recent years.[13] It is also necessary to investigate the potential of these medications paving the way to the development of acute coronary syndrome despite the intertwined correlation between prolonged hyperglycemia and hyperinsulinemia,[15] towards cardiovascular complications.

Metformin had withstood the odds and is regarded as the initial drug of choice treatment for diabetes. Sulphonylureas are the oldest anti-diabetic medications considered as the second-line agent for the management of diabetes. However, the increasing numbers of cardiovascular adverse events are being linked to its use and are often outstripped by other classes of oral hypoglycemic agents.[13] The efficacy of combination therapy in beneficial blood glucose control is well known yet, the beneficiary effects of metformin and sulfonylurea combination in preventing macro- and microvascular events are not proven.[16] An increasing rate of mortality of diabetics with coronary artery disease has been reported with an average of 7.7 years of sulfonylurea and metformin combinational therapy.[17] In the case of NYHA class III and IV heart failure, the use of glitazones is contraindicated.[19,20] Incretin-based therapies have reassuring impacts on cardiovascular risk factors.[13,21] The cardiovascular safety, effectiveness, and outcomes of meglitinides are mostly unknown.[22,23,24] while that of alpha-glucosidase inhibitors is controversial.[25] In contrast, the CV safety of sodium-glucose cotransporter-2 inhibitors is convincing.[26,27] Increased cardiovascular morbidity and mortality are also associated with insulin use in patients with type 2 diabetes.[28,29] Patients diagnosed with diabetes with or without other cardiovascular risk factors should be ensured cardio-protection while designing the optimal approach to manage their disease state and the efficacy of anti-diabetic medications should be evaluated before use.

The paramount objective of the treatment of a person diagnosed with diabetes is the maintenance of HbA1c or the glycated hemoglobin values under the normal limit for the prevention of complications associated with type 2 diabetes mellitus.[30,31] The measurement of the HbA1c is considered to be the gold standard for surveillance of progression of T2DM towards complications and monitoring the effectiveness of treatment.[30,32] Moreover, for a 1% reduction in the HbA1c value, there will be a significant reduction of about 14% of acute coronary events like myocardial infarction.[33]

Medication adherence is another prime factor associated with diabetes and related metabolic disorders culminating in long-term macro-vascular and micro-vascular complications and associated mortality.[34] Since T2DM is a chronic medical condition, medication adherence is the soul to prevent the progress of the disease into its complications. To assess patients' level of adherence to medications, various scales have been employed throughout the literature based on questionnaires that utilize plenty of questions as modalities to assess the patients' adherence without confounding bias. The 4-item Morisky Medication Adherence Scale (MMAS-4) is the simplest and quickest tool to score patients based upon their level of adherence using closed question format. This scale is widely utilized for research purposes where the "yes-saying" answers are an indicator of nonadherence.[35,36,37,38]

MATERIALS AND METHODS

Hypothesis: This study was designed to evaluate the risk of acute coronary events in diabetic patients receiving various anti-diabetic therapies for more than a year and to determine the extent of glycemic control and medication adherence in such patients and turn its potential to the incidence of macro-vascular complications.

The required sample size for the study was calculated using an automated software program(Qualtrics^{XM}: https://www.qualtrics.com/blog/calculating-sample-size/). The study was conducted for six months from February 2019 to July 2019 in a tertiary care hospital in Coimbatore, India and the study population comprised of 155 patients selected consecutively, with a history of type 2 diabetes mellitus admitted to the cardiac unit with an acute coronary syndrome such as CAD, unstable

angina, STEMI, and NSTEMI of either gender, aged 18 to 80 years who were previously receiving treatment for T2DM for over a year. Patients with Type 1 diabetes, gestational diabetes, structural or congenital heart defects, heart failure, and the vulnerable subjects were explicitly excluded from the study. Patients who have given informed consent to participate in the study were only included in the study.

The data collection was done using specifically designed data collection forms and the data for each eligible patient were collected obtained from either the hospital's individual database management software or by reviewing the medical records prospectively throughout the study duration. Information regarding the hypoglycemic events and medication adherence were assimilated by face-to-face interviews from the patients.

The subjects were classified into 9 categories based on the treatment they have received for T2DM. For each patient, the demographic details, glycated hemoglobin value, left ventricular function; medication adherence, and occurrence of hypoglycemic events were collected. The biochemical marker used to correlate the blood glucose levels over a certain period of around 3 months is the HbA1C.(39,40)The HbA1C value helped to determine the glycemic control of the patients besides fasting and postprandial blood sugar levels and was further categorized into those with controlled, uncontrolled, and moderately controlled glycemic levels. HbA1C value of 7 or under was considered to be controlled while the value between 7-8 as moderately controlled and above 8 as uncontrolled blood glucose levels. The LV function was noted from the echocardiogram tests to evaluate the severity of the cardiac dysfunction. Moreover, the incidence of recent hypoglycemic events as experienced by the patients was accounted. The extent of medication adherence to the previously prescribed oral hypoglycemic agents and insulin preparations were also assessed for each patient with a scale known as Morisky Medication Adherence Scale 4(MMAS-4). The scale comprised of 4 questions with a dichotomous response: either 'yes' or 'no' and the scores ranged from 0 to 4. The positive answers or 'yes' were scored zero points each and the negative answers or 'no' were given one point each. The subjects who scored a value of 'zero' from the questionnaire were regarded as the ones with proper medication adherence while, those who scored '1', '2', '3', or '4' without proper adherence.

Each subject's glycemic control (HbA1C value) was correlated to their LV function with adequate LV function, borderline-moderate dysfunction, and severe dysfunction respectively. Besides, the level of adherence to medication and the HbA1C levels were correlated to the hypoglycaemic events.

Statistical Analysis: The data collected regarding all the selected cases were recorded in a master chart. Percentages were calculated. Chi-square test was performed using the SPSS software version 20 and a P-value of <0.05 was considered to be significant. The Chi-square test was used to compare the HbA1C, LV function, Medication Adherence, and occurrence of hypoglycemia for each medication regimen. It was also used to determine the correlation between LV function and HbA1c control, medication adherence and hypoglycemic events, and medication adherence and HbA1C.

RESULTS AND DISCUSSION

Demographic and co-morbidities related data

The study comprised of 155 subjects, out of which the majority (72.25%, n= 112) were males and the rest (27.74%, n=43) were females and the mean± SD age of the patients were 60.80± 7.43% years. Upon assessing the co-morbidities with potential for cardiovascular complications other than diabetes in the patients, it was observed that a large proportion of the patients were hypertensive (43.22%, n=67). Dyslipidemia was observed in 8 (5.1%) patients whereas, 25(16.12%) patients were both hypertensive and dyslipidemic. No other co-morbidities other than type 2 diabetes were observed in 55(35.48%) patients.

Treatment regimen

21.29% (n=33) of the patients were only on monotherapy with OAD agents, out of which 25 were on metformin monotherapy and 11 were on glimepiride monotherapy while, as low as 2.58% (n=4) were on insulin monotherapy.

Biguanides(Metformin) was the most commonly used oral hypoglycemic agent which was either used as monotherapy(n=25) or used in combination with other antidiabetic agents. Metformin was mostly a part of a dual drug regimen, used along with sulphonylureas (29.03%, n=45), or with insulin (7.74%, n=12). It was also used in a triple-drug regimen which included insulin and sulphonylureas (8.39%, n=13). The sulphonylureas other than glimepiride were all used in combination with other OAD agents (13.55%, n=21). T2DM in 24 (15.48%) patients were treated with other OAD combinations which included either thiazolidinediones or alpha-glucosidase inhibitors or DPP-4 inhibitors, with or without metformin, sulphonylureas, and insulin.

Glycemic exposure

Table 1: Drug Regimen and HbA1c Levels.

HbA1c Levels	Treatment regimen				Total patients	Percentage
	Metformin Monotherapy n=25	Glimepiride Monotherapy n=11	Insulin Monotherapy n=4	SU+ Metformin n=45		
Controlled	7(28%)	3(27.27%)	1(25%)	5(11.1%)	22	14.19%
Moderately Controlled	2(8%)	4(36.36%)	0(0%)	20(44%)	40	25.8%
Uncontrolled	16(64%)	4(36.36%)	3(75%)	20(44%)	93	60%
	Metformin + Insulin n=12	Glimepiride + Combination n= 21	Insulin + Metformin+ SU n=13	Other Combinations n=24		
Controlled	0(0%)	2(9.50%)	0(%)	4(16.66%)		
Moderately Controlled	2(16.66%)	6(28.57%)	2(15.38%)	4(16.66%)		
Uncontrolled	10(83.3%)	13(61.9%)	11(84.61%)	16(66.66%)		
SU: Sulfonyl Ureas				n: Number of patients in each regimen.		

The majority of the patients admitted to the coronary care unit had uncontrolled blood glucose levels with their glycaemic index greater than 8.1(60%, n=93) monitored using the HbA1c test. The mean (±SD) HbA1c levels measured in the study subjects was 8.99±1.978%. This indicates that patients without good glycaemic control are at risk of developing MACE(major advance cardiovascular events).[41] Table 1 represents the glycated hemoglobin levels in the patients admitted with acute coronary events, for each regimen of antidiabetic agents administered in the study subjects. It was observed that the patients on metformin monotherapy(28%) had greater glycemic control in contrast to those on a triple-drug regimen with a combination of insulin, metformin, and sulphonylureas (84.61%) with uncontrolled glycemic levels. Considering the drug regimen, the patients treated with metformin, glimepiride, and insulin monotherapy had adequate control of blood glucose (28%, 27.27%, and 25% respectively) while the combination of more than one antidiabetic medication had inappropriate control. Therefore, it was observed that the patients on monotherapy had greater glycemic control than those on combination therapy. This observation was in contrast to the study conducted by Mariko Oishi et.al., in 2013.[42]

Medication adherence

Table 2: Drug Regimen and Medication Adherence.

Medication Adherence	Treatment regimen				Total Patients	Percentage
	Metformin Monotherapy n=25	Glimepiride Monotherapy n=11	Insulin Monotherapy n=4	SU+ Metformin n=45		
With Adherence	19(76%)	8(72.72%)	4(100%)	35(77.77%)	110	70.69%
Without Adherence	6(24%)	3(27.28%)	0(0%)	10(22.23%)	45	29.03%
	Metformin + Insulin n=12	Glimepiride + Combination n= 21	Insulin + Metformin+ SU n=13	Other Combinations n=24		
With Adherence	9(75%)	9(42.85%)	7(53.84%)	19(75%)		
Without Adherence	3(25%)	12(57.15%)	6(46.16%)	5(25%)		
SU: Sulfonyl Ureas				n: Number of patients in each regimen		

Medication adherence of the subjects was analyzed with the help of the Morisky scale and further scored based on their answers. The majority of the patients had appropriate medication adherence (70.69%, n=110). The mean (±SD) medication adherence score according to the MMAS-4 scale was 3.24±1.33%. Table 2 depicts the number of patients with or without medication adherence in each drug regimen observed in the study subjects. As

stated earlier, 70.96% of the patients had proper adherence to their antidiabetic medications, while the rest 29.31% failed to adhere properly to their diabetic drugs.

The patients on the triple-drug regimen with insulin, metformin, and sulphonylurea (46.16%) and those on combination therapy with glimepiride (57.15%) were the ones with poor medication adherence when compared to other classes of medications observed in the study. Among the 110 patients with good adherence, the ones on insulin monotherapy had the highest level of adherence. Therefore, it is evident that an increase in drug combination or treatment complexity decreases medication adherence.[47]

Out of 110 patients with high medication adherence, 60(54.54%) patients had elevated HbA1C levels (Table 5). Patient's medication adherence and glycaemic control (HbA1C values) represent an inverse relationship as most of the patients with high adherence to medication had HbA1C>8.1(uncontrolled glycaemic index). However, various other studies have reported the direct relationship between medication adherence and glycemic control.[43-46]

Left ventricular function

Table 3: Drug Regimen and LV function.

LV function	Treatment regimen					Percentage
	Metformin Monotherapy n=25	Glimepiride Monotherapy n=11	Insulin Monotherapy n=4	SU+ Metformin n=45		
Adequate	7(28%)	4(36.36%)	1(25%)	19(42.20%)	55	33.54%
Borderline – Moderate	17(68%)	7(63.63%)	2(50%)	21(46.60%)	89	59.35%
Severe	1(4%)	0(0%)	1(25%)	5(11.10%)	11	7.09%
	Metformin + Insulin n=12	Glimepiride + Combination n=21	Insulin + Metformin+ SU n=13	Other Combinations n=24		
Adequate	5(41.66%)	7(33.33%)	4(30.76%)	8(33.33%)		
Borderline – Moderate	7(58.33%)	10(47.61%)	9(69.23%)	16(66.66%)		
Severe	0(0%)	4(19.04%)	0(0%)	0(0%)		
SU: Sulfonyl Ureas n: Number of patients in each regimen. LV: left ventricular function						

Monitoring the LV function is a prime diagnostic parameter for assessing the cardiac function from the electrocardiography test. This study utilizes the ECHO to detect left ventricular dysfunction which in turn indicates the level of cardiac abnormality in patients with ACE's. Adequate LV function interprets normal cardiac function whereas the borderline-moderate and severe LV dysfunction stipulate the abnormality. Table 3 represents the left ventricular function in the study subjects treated with the corresponding anti-diabetic drug regimen. A dominant proportion of the subjects had LV dysfunction (64.51%, n=100), out of which most of them showed borderline- moderate dysfunction (59.35%,n=89) and the rest had severe LVD(7.09%, n=11). Although each patient had an incidence of an acute coronary event, 33.54 %(n=55) of them managed to have adequate LV function. Hence, impaired glycaemic control in diabetic patients eventually leads them to a MACE with left ventricular dysfunction.[48] The patients on the dual drug regimen of OHA's like metformin-sulphonyl urea (42.40%), and metformin-insulin(41.66%) were the ones mostly with adequate LV function. This is suggestive of the cardiovascular prognosis achieved with metformin in combination when compared to other anti-diabetic medications.[49] On the other hand, the patients on insulin monotherapy (25%), and those on combination therapy with glimepiride(19.04%) developed severe LV dysfunction than the other regimens. Even though the risk for cardiovascular complications are high with exogenous insulin therapy, the UKPDS and several other studies could not find supporting evidence for this statement.[50]

Hypoglycemic events

Table 4: Drug Regimen And Hypoglycemic Events (N=155).

Hypoglycemic Events:	Treatment regimen				Total Patients	Percentage
	Metformin Monotherapy n=25	Glimepiride Monotherapy n=11	Insulin Monotherapy n=4	SU+ Metformin n=45		

Yes	5(20%)	7(63%)	1(25%)	14(31.1%)	56	36.12%
No	20(80%)	4(36%)	3(75%)	31(68.8%)	99	63.87%
	Metformin + Insulin n=12	Glimepiride + Combination n=21	Insulin + Metformin+ SU n=13	Other Combinations n=24		
Yes	5(41.66%)	9(42.85%)	5(38.46%)	10(41.66%)		
No	7(58.33%)	12(57.14%)	8(61.53%)	14(58.33%)		
SU: Sulfonyl Ureas			n: Number of patients in each regimen.			

The occurrence of hypoglycemia in diabetics often impedes the efficacy of the treatment of diabetes, the metabolic disorder. Incidence rates of hypoglycemia vary according to the type of drugs and regimen, and the hypoglycaemic potential of the medications used to treat the condition in each patient. Table 4 represents the data of the occurrence of hypoglycaemic events in the patients on various drug regimens included in the study. Hypoglycemia was reported among 56 patients (36.12%) and the others did not have any episode of clinically evident hypoglycemia. The patients on glimepiride monotherapy (63%) had the highest incidence of hypoglycemia. Other regimens with increased frequency of hypoglycemia were dual drug regimen with metformin and insulin(41.66%), triple-drug regimen of metformin, insulin and sulphonylurea(38.46%), glimepiride in combination with other drugs(42.85%), and other combination regimens (41.66%) while monotherapy with metformin and insulin had only a few incidences of hypoglycemia. Therefore, as tighter glycaemic controls were aimed with two or more anti-diabetic drug combinations, the incidence of hypoglycemia was high.[52] Sulphonyl urea, especially glimepiride was the most common cause of hypoglycemia as per the study.[53]

Correlation between Medication Adherence, Glycaemic Control And Hypoglycaemic Events Of Each Regimen

Table 5: Correlating medication adherence and glycaemic control of the drug regimens.

Drug regimen	HbA1C Levels	With Adherence N_1=110	Without adherence N_2=45
Metformin Monotherapy (n=25)	Controlled	5	2
	Medium controlled	2	-
	Uncontrolled	12	4
	Total	**19**	**6**
Glimepiride Monotherapy (n=11)	Controlled	3	-
	Moderately controlled	3	1
	Uncontrolled	2	2
	Total	**8**	**3**
Insulin Monotherapy (n=4)	Controlled	1	-
	Moderately controlled	0	-
	Uncontrolled	3	-
	Total	**4**	**-**
SU+ Metformin (n=45)	Controlled	4	1
	Moderately controlled	17	3
	Uncontrolled	14	6
	Total	**35**	**10**
Metformin + Insulin (n=12)	Controlled	-	3
	Moderately controlled	2	-
	Uncontrolled	7	-
	Total	**9**	**3**
Glimepiride + Combination (n=21)	Controlled	1	1
	Moderately controlled	4	2
	Uncontrolled	4	9
	Total	**9**	**12**
Insulin + Metformin+ SU (n=13)	Controlled	-	-
	Moderately controlled	1	1
	Uncontrolled	6	5
	Total	**7**	**6**
Other Combinations (n=24)	Controlled	3	1
	Moderately controlled	4	-
	Uncontrolled	12	4
	Total	**19**	**5**

SU: Sulfonyl Ureas, n: Number of patients in each regimen,
N_1: Number of patients with adherence
N_2: Number of patients without adherence

Out of 110 patients with high medication adherence, 60(54.54%) patients had elevated HbA1C levels (Table 5). Patient's medication adherence and glycaemic control (HbA1C values) represent an inverse relationship as most of the patients with high adherence to medication had HbA1C>8.1(uncontrolled glycaemic index). However, various other studies have reported the direct relationship between medication adherence and glycemic control.[43-46] However in this study, most of the patients had appropriate medication adherence, they did not have adequate glycemic control.

Table 6: Correlating medication adherence and the incidence of hypoglycaemic events of the drug regimens.

Drug Regimen	Hypoglycaemic events reported	With adherence (N_1=110)	Without adherence (N_2=45)
Metformin Monotherapy (n=25)	Yes	4	1
	No	15	5
Total		**19**	**6**
Glimepiride Monotherapy (n=11)	Yes	4	3
	No	4	-
Total		**8**	**3**
Insulin Monotherapy (n=4)	Yes	1	-
	No	3	-
Total		**4**	**-**
SU+ Metformin (n=45)	Yes	11	3
	No	24	7
Total		**35**	**10**
Metformin + Insulin (n=12)	Yes	3	2
	No	6	1
Total		**9**	**3**
Glimepiride + Combination (n=21)	Yes	4	5
	No	5	7
Total		**9**	**12**
Insulin + Metformin+ SU (n=13)	Yes	5	-
	No	2	6
Total		**7**	**6**
Other Combinations (n=24)	Yes	8	2
	No	11	3
Total		**19**	**5**
SU: Sulfonyl Ureas n: Number of patients in each regimen N_1: Number of patients with adherence N_2: Number of patients without adherence			

Table 6 contains the data regarding medication adherence and the incidence of hypoglycemia in each regimen included in the study. Upon observing the patients with proper medication adherence to the drug regimens, the majority of subjects had no hypoglycemic events reported except, those on the triple-drug regimen compared to those without proper adherence who had frequent hypoglycemic episodes. This implies that the hypoglycemic incidence within each drug regimen increased with a decrease in the adherence towards the medication.[47]

Correlation between LV Function and HbA1C Levels

Table 7: Association of glycaemic exposure and control (HbA1C levels) to left ventricular function.

HbA1C level N=155	Adequate LV function (n=55)	Borderline to Severe LV dysfunction (n=100)
Controlled	9	13
Moderately controlled	17	23
Uncontrolled	29	64
P value :(0.202)		Chi-square:(5.965)
N= Total number of subjects included in the study.		

n= Number of patients in each category of LV function.
LV: Left Ventricular

Table 7 provides the data required for identifying the correlation between the glycaemic control in the study subjects and the left ventricular function in them. In the 100 patients with LV dysfunction, 64 patients (64%) had HbA1C>8, 23 patients (23%) with HbA1C from 7-8, and 13 patients (13%) with adequate glycaemic control (≤7). Similarly among the 55 patients with adequate LV function, 29 patients (52.72%) had HbA1C>8, 17 patients (30.90%) with HbA1C from 7-8, and 9 patients (16.36%) with appropriate glycaemic control. The P-value derived for this correlation was not significant (P=0.202) and hence the study could not identify that the adequate glycaemic control in patients with T2DM prevented them from the occurrence of adverse cardiac events, similar to ACCORD study, ADVANCE study, and VADT.[51]

CONCLUSION

In conclusion, these data suggest that the susceptibility of T2DM patients to acute coronary events is favored by several factors including uncontrolled hyperglycemia, lack of adherence to antidiabetic drugs and the scenario is further worsened by recurrent hypoglycemia resultant from the target to achieve adequate control over the blood glucose levels. A great proportion of these diabetic patients who eventually develop an ACE have left ventricular dysfunction.

Apart from the micro-vascular complications exhibited by long-term diabetes, the patients' health-related quality of life (HRQOL) grossly declines due to the incidence of a coronary event. An optimal multifactorial management plan should be devised for each patient diagnosed with T2DM based on his or her current health status and the physician's expertise in the selection of the appropriate cardio safe drug regimen to prevent macrovascular complications and to meet patient satisfaction.

Based on the observations from the study, monotherapy of antidiabetic medications had better glycemic control in patients than those on a multi-drug regimen probably due to lack of adherence in the patients even in an era where fixed-dose combinations of medications are available.

The complexity of the treatment regimen is a contributor to improper medication adherence in patients with T2DM. Hence, adopting adequate measures to improve the burdensome and complex drug regimens should be established in case of treating patients with DM for ensuring medication adherence. Although the beneficial role of strict glycaemic control in preventing ACE has been controversial over the years, this study did not identify significant supporting information regarding the same.

To minimize the long-term complications, to reduce the hypoglycaemic risks, and to ensure adequate glycemic control, the patients should be educated and updated about the major hindrances like improper medication adherence apart from the selection of appropriate regimens by the physicians.

ABBREVIATIONS

ACCORD: Action to Control Cardiovascular Risk in Diabetes study; ACE: Acute Coronary Events; ACS: Acute Coronary Syndrome; ADVANCE: Action in Diabetes and Vascular Disease study; CAD: Coronary artery disease; CV: Cardiovascular disease;CVD: Cardiovascular Disease; DPP-4: Dipeptidyl peptidase-4 Inhibitors; ECHO: Echocardiogram; HR: Hazard ratio; HbA1c: Glycated Hemoglobin; LVD: Left ventricular dysfuntion; MACE: Major adverse cardiac event; MMAS-4: Morisky medication adherence scale-4; NHANES: National Health and Nutrition Examination Survey; NSTEMI: Non-ST elevated myocardial infarction ; NYHA: New York heart association; OAD: oral anti-diabetic drugs; OHA: Oral hypoglycemic agents; SD: Standard deviation; STEMI: ST elevated myocardial infarction; SU: sulphonyl urea; T2DM: Type 2 diabetes mellitus; UKPDS: the United Kingdom Prospective Diabetes Study; VADT: Veterans Affairs Diabetes Trial

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REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care, 2010 Jan 1; 33(Supplement 1): S62-9.
2. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Physical therapy, 2008 Nov 1; 88(11): 1322-35.
3. Lopez Rowe V. Diabetic Foot Ulcers: Practice Essentials, Pathophysiology, Etiology [Internet]. Emedicine.medscape.com, 2020. Available from: https://emedicine.medscape.com/article/460282-overview
4. International Diabetes Federation – Diabetes Complications [Internet]. Idf.org. 2020. Available from:

https://www.idf.org/aboutdiabetes/complications.html.
5. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL, Klein R. Retinopathy in diabetes. Diabetes Care, 2004 Jan 1; 27(suppl 1): s84-7.
6. Schena FP, Gesualdo L. Pathogenetic mechanisms of diabetic nephropathy. Journal of the American Society of Nephrology, 2005 Mar 1; 16(3 suppl 1): S30-3.
7. MJ F. Microvasculares e macrovascular do diabetes. Clin Diab, 2008; 26: 77-82.
8. Tseng LN, Tseng YH, Jiang YD, Chang CH, Chung CH, Lin BJ, Chuang LM, Tai TY, Sheu WH. Prevalence of hypertension and dyslipidemia and their associations with micro-and macrovascular diseases in patients with diabetes in Taiwan: an analysis of nationwide data for 2000–2009. Journal of the Formosan Medical Association, 2012 Nov 1; 111(11): 625-36.
9. Ji L, Hu D, Pan C, Weng J, Huo Y, Ma C, Mu Y, Hao C, Ji Q, Ran X, Su B. Primacy of the 3B approach to control risk factors for cardiovascular disease in type 2 diabetes patients. The American journal of medicine, 2013 Oct 1; 126(10): 925-e11.
10. Wang CC, Hess CN, Hiatt WR, Goldfine AB. Atherosclerotic cardiovascular disease and heart failure in type 2 diabetes–mechanisms, management, and clinical considerations. Circulation, 2016 Jun 14; 133(24): 2459.
11. Dokken BB. The pathophysiology of cardiovascular disease and diabetes: beyond blood pressure and lipids. Diabetes Spectrum, 2008 Jul 1; 21(3): 160-5.
12. MacDonald MR, Petrie MC, Hawkins NM, Petrie JR, Fisher M, McKelvie R, Aguilar D, Krum H, McMurray JJ. Diabetes left ventricular systolic dysfunction and chronic heart failure. European heart journal, 2008 May 1; 29(10): 1224-40.
13. Xu J, Rajaratnam R. Cardiovascular safety of non-insulin pharmacotherapy for type 2 diabetes. Cardiovascular diabetology, 2017 Dec 1; 16(1): 18.
14. Azoulay L, Suissa S. Sulfonylureas and the risks of cardiovascular events and death: a methodological meta-regression analysis of the observational studies. Diabetes Care, 2017 May 1; 40(5): 706-14.
15. Soylu A, Ülgen MS, Düzenli MA. Antidiabetic Treatment In Diabetic Patients With Coronary Artery Disease.
16. Olsson J, Lindberg G, Gottsäter M, Lindwall K, Sjöstrand Å, Tisell A, Melander A. Increased mortality in Type II diabetic patients using sulphonylurea and metformin in combination: a population-based observational study. Diabetologia, 2000 May 1; 43(5): 558-60.
17. Fisman EZ, Tenenbaum A, Adler Y, Motro M, Boyko V, Benderly M, Friedensohn A, Kohanovski M, Rotzak R, Schneider H, Behar S. Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7.7-year follow-up. Clinical cardiology, 2001 Feb; 24(2): 151-8.
18. Harding I, Yellon DM, Bell RM. Pharmacological cardioprotection in diabetes. Diabetes Management, 2015 Mar 1; 5(2): 89.
19. de Jong M, van der Worp HB, van der Graaf Y, Visseren FL, Westerink J. Pioglitazone, and the secondary prevention of cardiovascular disease. A meta-analysis of randomized controlled trials. Cardiovascular diabetology, 2017 Dec; 16(1): 1-1.
20. Highlights of prescribing information. 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s044lbl.pdf. Accessed, 13 Sep 2020.
21. Petrie JR. The cardiovascular safety of incretin-based therapies: a review of the evidence. Cardiovascular diabetology, 2013 Dec 1; 12(1): 130.
22. Azimova K, San Juan Z, Mukherjee D. Cardiovascular safety profile of currently available diabetic drugs. Ochsner Journal, 2014 Dec 21; 14(4): 616-32.
23. Fisman EZ, Motro M, Tenenbaum A. Non-insulin antidiabetic therapy in cardiac patients: current problems and future prospects. In Cardiovascular Diabetology: Clinical, Metabolic and Inflammatory Facets, 2008; 45: 154-170. Karger Publishers.
24. Fisman EZ, Tenenbaum A. A cardiologic approach to non-insulin antidiabetic pharmacotherapy in patients with heart disease. Cardiovascular diabetology, 2009 Dec 1; 8(1): 38.
25. Coleman RL, Scott CA, Lang Z, Bethel MA, Tuomilehto J, Holman RR. A meta-analysis of the impact of alpha-glucosidase inhibitors on incident diabetes and cardiovascular outcomes. Cardiovascular diabetology, 2019 Dec 1; 18(1): 135.
26. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nature Reviews Cardiology, 2020 Jul 14; 1-2.
27. Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC: Basic to Translational Science, 2020 Jun 1; 5(6): 632-44.
28. Saitz R, Palfai TP, Cheng DM, Alford DP, Bernstein JA, Lloyd-Travaglini CA, Meli SM, Chaisson CE, Samet JH. Screening and brief intervention for drug use in primary care: the ASPIRE randomized clinical trial. Jama, 2014 Aug 6; 312(5): 502-13.
29. Mannucci E, Ferrannini E. Cardiovascular safety of insulin: Between real-world data and reality. Diabetes, Obesity, and Metabolism, 2017 Sep; 19(9): 1201-4.
30. Nazir SU, Hassali MA, Saleem F, Bashir S, Aljadhey H. Disease-related knowledge, medication adherence, and glycaemic control among patients with type 2 diabetes mellitus in Pakistan. Primary care diabetes, 2016 Apr 1; 10(2): 136-41.

31. Hoerger TJ, Segel JE, Gregg EW, Saaddine JB. Is glycemic control improving in US adults?. Diabetes Care, 2008 Jan 1; 31(1): 81-6.
32. Kilpatrick ES, Winocour PH. ABCD position statement on hemoglobin A1c for the diagnosis of diabetes. Practical Diabetes International, 2010 Sep; 27(7): 306-10.
33. The United Kingdom Prospective Diabetes Study Group. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): a prospective observational study. BMJ., 2000; 321(7251): 405-12.
34. Khunti K, Seidu S, Kunutsor S, Davies M. Association between adherence to pharmacotherapy and outcomes in type 2 diabetes: a meta-analysis. Diabetes Care, 2017 Nov 1; 40(11): 1588-96.
35. Lam WY, Fresco P. Medication adherence measures: an overview. BioMed research international, 2015 Oct 11; 2015.
36. Lavsa SM, Holzworth A, Ansani NT. Selection of a validated scale for measuring medication adherence. Journal of the American Pharmacists Association, 2011 Jan 1; 51(1): 90-4.
37. Tan X, Patel I, Chang J. Review of the four-item Morisky medication adherence scale (MMAS-4) and eight-item Morisky medication adherence scale (MMAS-8). Innovations in Pharmacy, 5(3): Article 165.
38. Culig J, Leppée M. From Morisky to Hill-bone; self-reports scales for measuring adherence to medication. Collegium anthropological, 2014 Mar 31; 38(1): 55-62.
39. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clinical chemistry, 2002 Mar 1; 48(3): 436-72.
40. Gonen B, Rochman H, Rubenstein A, Tanega S, Horwitz D. Haemoglobin A1: an indicator of the metabolic control of diabetic patients. The Lancet, 1977 Oct 8; 310(8041): 734-7.
41. Kassaian SE, Goodarzynejad H, Boroumand MA, Salarifar M, Masoudkabir F, Mohajeri-Tehrani MR, Pourhoseini H, Sadeghian S, Ramezanpour N, Alidoosti M, Hakki E. Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. Cardiovascular diabetology, 2012 Dec 1; 11(1): 82.
42. Oishi M, Yamazaki K, Okuguchi F, Sugimoto H, Kanatsuka A, Kashiwagi A, Japan Diabetes Clinical Data Management Study Group. Changes in oral antidiabetic prescriptions and improved glycemic control during the years 2002–2011 in Japan (JDDM 32). Journal of diabetes investigation, 2014 Sep; 5(5): 581-7.
43. Kunasegaran S, Beig J, Khanolkar M, Cundy T. Adherence to medication, glycaemic control, and hospital attendance in young adults with type 2 diabetes. Internal medicine journal, 2018 Jun; 48(6): 728-31.
44. Pladevall M, Williams LK, Potts LA, Divine G, Xi H, Lafata JE. Clinical outcomes and adherence to medications measured by claims data in patients with diabetes. Diabetes Care, 2004 Dec 1; 27(12): 2800-5.
45. Lawerence DB, Ragucci KR, Long LB, Parris BS, Helfer LA. Relationship of oral antihyperglycemic (sulfonylurea or metformin) medication adherence and hemoglobin A1c goal attainment for HMO patients enrolled in a diabetes disease management program. Journal of Managed Care Pharmacy, 2006 Jul; 12(6): 466-71.
46. Schectman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. Diabetes Care, 2002 Jun 1; 25(6): 1015-21.
47. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient preference and adherence, 2016; 10: 1299.
48. Leung M, Wong VW, Hudson M, Leung DY. Impact of improved glycemic control on cardiac function in type 2 diabetes mellitus. Circulation: Cardiovascular Imaging, 2016 Mar; 9(3): e003643.
49. Varjabedian L, Bourji M, Pourafkari L, Nader ND. Cardioprotection by metformin: beneficial effects beyond glucose reduction. American Journal of Cardiovascular Drugs, 2018 Jun 1; 18(3): 181-93.
50. Ruige JB, Assendelft WJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and risk of cardiovascular disease: a meta-analysis. Circulation, 1998 Mar 17; 97(10): 996-1001.
51. Giorgino F, Leonardini A, Laviola L. Cardiovascular disease and glycemic control in type 2 diabetes: now that the dust is settling from large clinical trials. Annals of the New York Academy of Sciences, 2013 Apr; 1281(1): 36.
52. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. Diabetes Care, 2008 Nov 1; 31(11): 2086-91.
53. Malouf R, Brust JC. Hypoglycemia: causes, neurological manifestations, and outcome. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 1985 May; 17(5): 421-30.