ORIGINAL ARTICLE

APPROACH OF WITHHOLDING P2Y12 INHIBITORS FOR URGENT CORONARY ARTERY BYPASS GRAFTING IN DIABETIC PATIENTS WITH ACUTE CORONARY SYNDROME

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Objectives: To compare angiographic findings between diabetic and non-diabetic patients with acute coronary syndrome (ACS) along with feasibility of P2Y12 inhibitors withholding approach for urgent coronary artery bypass grafting (CABG) in diabetic (DM) patients with severe lesions.

Methodology: Consecutive ACS patients were included. P2Y12 inhibitors was hold in a certain number of diabetic patients with either left main (LM) or multi-vessel disease (MVD) on baseline angiogram, at the discretion of primary physician. Angiographic diseases severity was compared between diabetic and non-diabetics. The clinical management and outcomes of diabetic patients were further compared based on the deferred P2Y12 inhibitors approach.

Results: Out of 205 patients, 149 were males and 40.9% were diabetic. Involved vessel was LM in 19.8% vs. 16.6%; p=0.566, left anterior descending artery (LAD) in 62.8% vs. 39.3%; p=0.001, and right coronary artery in 27.3% vs. 45.2%; p=0.008 with MVD in 42.1% vs. 28.6%, p=0.047 of the diabetic and non-diabetic patients, respectively. P2Y12 inhibitors was hold in 59 diabetic patients who undergone urgent CABG with hospital stay of <5 days. In remaining 62 diabetic patients, 50 undergo coronary intervention and 12 undergo delayed CABG with hospital stay of >5 days due to P2Y12 administration.

Conclusion: The presence of DM showed a significant association with the involvement of the LAD artery. Most participants showed presence of MVD. By holding P2Y12 inhibitors reduces the perioperative bleeding and hospital stay.

Keywords: diabetes mellitus, three vessel disease, acute coronary syndrome, P2Y12 inhibitors, CABG

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INTRODUCTION

Diabetes mellitus (DM) is a sequel of complications as uncontrolled blood sugar levels over the course of several years affecting multiple organ systems. It is divided into two types: type I (juvenile) and type II (adult onset) diabetes. Globally, most of the cases are classified as type II DM. Important risk factors contributing to the onset of type II DM includes being older than 65 years of age, female, obese, having a family history of diabetes, hypertension, smoking and sedentary life-style .[1]

In 2015, five million deaths were due to DM and recently in February 2019, the readings of HbA1c of type II DM in Pakistan were estimated to be 16.98%. Above all, the IDF (International Diabetes Federation) has documented that by the year 2025, 11.5 million people living in Pakistan will be with diabetes, ranking Pakistan on the fifth position in IDF of diabetes populations.[1,2] Thus, in our region the quantification of DM is highlighted as the future complications for diabetics. As noted, complications are not only confined to a particular organ system but it involves multiple systems, with in all a common pathogenesis involving all vascular abnormalities which may represent into multiple clinical complicated scenarios.

It is noted that sudden cardiac death is one of the most common cause of mortality mainly in diabetics and 70% of all current hospitalizations

in diabetics are mainly due to vascular diseases and may demand multidisciplinary therapies. Mainly, type 2 diabetes affects all types of large and small size vessels. Consequently, it induces micro-angiopathies such as nephropathy, diabetic retinopathy and macro-angiopathies and neuropathy including coronary and peripheral artery disease. Moreover, pre-diabetes and type 2 diabetes are independently associated with the development of sub-clinical myocardial injury.[3] Hence, it does not come as a surprise when it is approximated that one-quarter majority of patients presenting for angiography following an acute coronary syndrome (ACS) are diabetics with a complex pattern of coronary artery disease (CAD) involving a diffuse plaque extending into multiple mid and distal arterial branches which require urgent coronary artery bypass grafting (CABG).[4] Therefore, if a person is going for an emergent CABG, there is increased risk of transfusion and bleeding and therefore leading to reopening/re-surgery. Keeping in view the coronary complications that DM imposes, in a study conducted in Brazil based on angiographic findings it was concluded that age, chronic renal failure and diabetes were the strongest predictors of multi-vessel CAD.[5]

We believe that although CAD and DM have been documented as having a proportional relationship with respect to severity and prognosis, there remains a scarcity of literature from Pakistan. As diabetes is usually associated with multi vessel disease (MVD) and these patients have to undergo coronary artery bypass grafting (CABG) either in same admission or elective basis. ACS patients usually receive dual antiplatelet before undergoing coronary angiogram, which mandates to delay bypass surgery at least 5-7 days, as wash out period before surgery, we believe by holding P2Y12 inhibitors will help to reduce hospitalization and delay in surgery.

Our aim is to study the impact of diabetes mellitus as risk factor for severe coronary artery disease requiring urgent CABG and to evaluate the P2Y12 inhibitors withholding approach in such patients to reduce hospitalization and delays in CABG.

METHODOLOGY

It is a retrospective observational study that conducted at Civil Hospital Karachi, tertiary care referral center from September 2019 to March 2020. After approval from the institutional review board (IRB), data of patients with ACS undergone diagnostic angiography at the cath lab was extracted from hospital records. Diagnosis of ACS was initially made by electrocardiography (ECG) and troponin levels (cardiac biomarker levels) to check ST elevation, NSTEMI and unstable angina, while the number and type of vessel(s) involved was confirmed by coronary angiography. Loading P2Y12 inhibitor was hold in a certain number of diabetic patients with either left main (LM) or multi-vessel disease (MVD), on the discretion of primary physician. Coronary angiography conducted by an interventional cardiologist, and interpreted by two independent interventional cardiologists. The collected data includes: age, gender, presence of hypertension, smoking, family history of premature coronary artery disease (CAD), dyslipidemia, echo findings, and ECG findings. There were no restrictions regarding the demographic and socioeconomic details of the patient. Diagnosis of coronary artery disease and its severity was made on the number of coronary vessels involved and percentage of stenosis, those who had severe 3VD with or without LM was sent for emergent /urgent CABG without any delay. Patients above 18years of age and previously diagnosed acute coronary syndrome (ACS) were included in the study. Patients with previously diagnosed chronic kidney disease (CKD) (creatinine >2), chronic liver disease with child Pugh class C and D were excluded. Data was analyzed using SPSS version 25 (IBM Corp, Armonk, NY). Categorical variables were examined using the Fisher's Exact and Chi Square test. P value less than 0.05 was considered significant.

RESULTS

Our study comprised a total of 205 patients who were diagnosed with the ACS. A majority of patients were males (n=149/205; 72.7%). Most of them belonged to the age group of 55 years or more (92/205; 44.8%), followed by 80 (39%) patients belonging to the age group of 46-55 years. Type 2 diabetes mellitus (T2DM) was diagnosed in 121 (59%) of the patients, while hypertension was prevalent in 103 (50.2%) of the patients (Table 1). Out of the total patients, 39.5% (81) had ST-elevation myocardial infarction (STEMI), 51.2% (105) had non-STEMI (NSTEMI), while the remaining 9.3% (19) had unstable angina (Table 1). Involved vessel was LM in 19.8% vs. 16.6%; p=0.566,

left anterior descending artery in 62.8% vs. 39.3%; p=0.001, and right coronary artery in 27.3% vs. 45.2%; p=0.008 with MVD in 42.1% vs. 28.6%, p=0.047 of the diabetic and non-diabetic patients, respectively (Table 1).

Table 1: General clinical characteristics and angiographic findings of non-diabetics vs. diabetic patients

	Non-diabetics	Diabetics	P-value
Total (N)	**84**	**121**	**-**
Age (years)			
15-25	1.2% (1)	0% (0)	0.028
26-35	17.9% (15)	5% (6)	
36-45	11.9% (10)	13% (16)	
46-55	33.3% (28)	43% (52)	
>55	35.7% (30)	39% (47)	
Gender			
Male	69% (58)	75.2% (91)	0.330
Female	31% (26)	24.8% (30)	
Risk factors			
Hypertension	58.3% (49)	44.6% (54)	0.054
Smoking	35.7% (30)	26.4% (32)	0.155
Family history of premature CAD	41.7% (35)	30.0% (36)	0.078
Dyslipidemia	58.3% (49)	42.1% (51)	0.023
Diagnosis			
STEMI	42% (35)	41.3% (50)	0.844
NSTEMI	50% (42)	50.4% (61)	
Unstable angina	8.3% (7)	8.2% (10)	
LV Dysfunction	36.9% (31)	32.2% (39)	0.488
LV ejection fraction			
>55%	48.8% (41)	51.2% (62)	0.941
44.45	11.9% (10)	13.2% (16)	
34.55	28.6% (24)	24.8% (30)	
<35%	10.7% (9)	10.7% (13)	
Normal Sinus rhythm on admission	91.7% (77)	88.4% (107)	0.663
Abnormal Sinus rhythm on admission			
Atrial fibrillation	1.2% (1)	5% (6)	
Ventricular tachycardia	2.3% (2)	2.5% (3)	
Atrial flutter	3.6% (3)	2.5% (3)	
Other	1.2% (1)	1.7% (2)	
Type of myocardial infarction			
ST Elevation	42% (35)	41.3% (50)	0.961
Anterior wall	18% (15)	22% (27)	0.045
Lateral wall	6% (5)	8.2% (10)	
Inferior wall	2.4% (2)	5.7% (7)	
Multiple walls	15% (13)	4.9% (6)	
ST depression	58% (49)	57% (71)	0.961
Number of diseased vessels			
Single vessel disease	71.4% (60)	57.9% (70)	0.047
Two vessel disease	17.9% (15)	16.5% (20)	0.804
Three vessel disease	10.7% (9)	25.6% (31)	0.008
Coronary involvement			
Left anterior descending artery	39.3% (33)	62.8% (76)	0.001
Right coronary artery	45.2% (38)	27.3% (33)	0.008
Left circumflex artery	16.7% (14)	18.2% (22)	0.779
Left main	16.7% (14)	19.8% (24)	0.566

CAD: coronary artery disease, STEMI: ST elevation myocardial infarction, NSTEMI: non-ST elevation myocardial infarction, UA: unstable angina, LV: left ventricular

P2Y12 inhibitors was hold in 59 diabetic patients who undergone urgent CABG with hospital stay of <5 days. In remaining 62 diabetic patients, 50 undergo coronary intervention and 12 undergo delayed CABG with hospital stay of >5 days due to P2Y12 administration (Table 2).

Table 2: Clinical characteristics and management of diabetic patients based on withholding status of P2Y12 inhibitors

	P2Y12 Inhibitors Given	P2Y12 Inhibitors Withhold	P-value
Total (N)	**62**	**59**	**-**
Age (years)			
15-25	0% (0)	0% (0)	0.002
26-35	9.7% (6)	0% (0)	
36-45	25.8% (16)	6.8% (4)	
46-55	24% (15)	50.8% (30)	
>55	40% (25)	42% (25)	
Gender			
Male	66% (41)	81.4% (48)	0.058
Female	33.9% (21)	18.6% (11)	
Diagnosis			
STEMI	35.5% (22)	47.5% (28)	0.004
NSTEMI	61.3% (38)	35.6% (21)	
Unstable angina	3.2% (2)	16.9% (10)	
Management			
PCI	80.6% (50)	0% (0)	<0.001
Urgent CABG	0% (0)	100% (59)	
Delayed CABG	19% (12)	0% (0)	
^Coronary involvement			
Two vessel disease	41.7% (5)	25.4% (15)	0.019
Three vessel disease	41.7% (5)	44.1% (26)	
Left main	16.7% (2)	30.5% (18)	
^Hospital Stay post CABG			
<5 days	0% (0)	100% (59)	-
>5 days	100% (12)	0% (0)	

STEMI: ST elevation myocardial infarction, NSTEMI: non-ST elevation myocardial infarction, UA: unstable angina, PCI: percutaneous coronary intervention, CABG: Coronary artery bypass graft

^Based on patients who undergone CABG

DISCUSSION

The present study aims to assess type 2 diabetes mellitus (DM) as risk factor for the development of multi-vessel disease in patients with ACS.[1] To our knowledge, this has not thoroughly been analyzed from our part of the region which is overburdened with multiple adverse factors including poverty, poor infrastructure, illiteracy, and neglected health care facilities. Our results analyzed the angiography findings of patients with ACS and DM to assess the involvement of severe coronary vessel disease which

mandates coronary artery bypass surgery for further management.

Diabetes mellitus is characterized by insulin resistance and the dysfunction of islet B-cells owing to various factors notably obesity, sedentary lifestyle, aging and family history.[6] According to the International Diabetes Federation (IDF), the incidence of DM will rise to 642 million people worldwide by 2040, which has imposed serious implications for health care advisors.[7] It is an established risk factor for the development of cardiovascular adverse events, due to accelerating the progress of atherosclerosis and thus, increases the risk of an acute coronary syndrome (ACS).[6] Birkner K et al.[6] has reinforced the increased risk of ACS as due to a dysfunction in the platelets of patients with diabetes which leads to an increase in their reactivity. Thus, they exhibit a role not only in increasing the risk of myocardial infarction but also in worsening the prognosis for patients with concurrent diabetes.[6] This pathogenicity has been clinically demonstrated in a study by Radomska E et al.[15] in which data of 26,035 STEMI patients were collected between 1 June 2005 and 31st May 2006 from 456 hospitals in Poland. From this data, type 2 DM occurred in 20.5% of the patients out of which majority (28%) was women.[15] Women with diabetes yielded worse clinical profiles including hypercholesteremia, obesity, hypertension and a history of myocardial infarction.[7] Majority of female patients with type 2 diabetes, admits usually more frequently with cardiogenic shock and pulmonary edema. Such patents had the highest in-hospital, 6-month, and 1-year mortality rates. So, the multi-variate analysis highlighted that type, 2 diabetes was a significant independent risk factor for in-hospital and 1-year mortality in women with STEMI.[8]

The analysis data in our study yielded significant association of DM with variable degrees of atherosclerosis. The presence of diabetes showed a significant association with the involvement of three vessel disease the predominant artery was left anterior descending artery (LAD). Our secondary findings include significant associations between diabetes mellitus and other risk factors such as hypertension (p-value =0.054), smoking (p-value: 0.115) and hyperlipidemia (p-value < 0.023). This is in line with the results of previous large-scale studies.[9] Thus, they are independent risk factors for multi-vessel coronary artery disease.

The association between diabetes and hypertension could be due to the fact that there are several risk factors that are common to both. Consuming an inappropriate diet, physical inactivity and the subsequent possibility of development of obesity are all common factors in the etiology of both diseases.[10]

Smoking shares a strong involvement with incident diabetes. Smoking can be linked to changes in insulin secretion by the pancreas through oxidative damage to β-cells and can also affect insulin resistance, which may cause impaired glucose metabolism leading to diabetes. Furthermore, smoking may induce endothelial dysfunction which may precipitate the development of microvascular complications in diabetics.[11]

Previous studies, such as the Prospective Cardiovascular Münster (PROCAM) study,[12] has shown that elevated lipid levels are a typical finding in diabetic patients. In this study, the lipid levels of patients afflicted with both hypertension and diabetes were analyzed, which showed that 40.8 % of men and 34.0 % of women evaluated had large impairments in combined lipid levels. Raised triglyceride levels were associated with low levels of HDL cholesterol, which itself is a risk factor for cardiovascular disease.[12] Diabetes, hypertension, dyslipidemia and central obesity often coexist as components of the metabolic syndrome. As obesity is often the foundation for further development of the other components of metabolic syndrome, weight loss may be useful to prevent the development of the metabolic syndrome, hypertension, diabetes and consequently cardiovascular disease.[10] Thus, our results highlight the role of diabetes and its risk factors in the pathogenesis of MVD in STEMI patients.[13] Diabetes is usually associated with multi vessel disease and these patients have to undergo bypass surgery either in same admission or elective basis.

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12-receptor antagonist plays a critical role in secondary prevention after an ACS. The use of DAPT lowers recurrent ischemic events, including stent thrombosis.[16] Hence, ACS patients usually receive dual antiplatelet before undergoing coronary angiogram, which mandates to delay bypass surgery (in needed) at least 5-7 days, as wash out period before surgery, our study shows by holding P2Y12 inhibitors help to reduce post-operative hospital stay and delay in surgery and reduce cost burden on public hospitals.[14,17]

Limitations: This study has some epidemiologic limitations. As it is a retrospective study, selection bias may play a role. Therefore, this study may be further supported by conducting a prospective study with a

larger sample size. We classified diabetes mellitus as patients with known diabetic status on admission based on their history and current use of medications for diabetes. However, patients could have been misclassified as they may have undetected diabetes mellitus. Also, we were unable to evaluate blood glucose levels or hemoglobin A1C levels. Therefore, we could not assess the effect of the actual glycemic levels which may have more value than simply having diabetic status. Finally, this study concerns results of a single center with tertiary cardiac catheterization facilities and the results may be not applicable for smaller centers which do not have this facility.

CONCLUSION

Our study highlights association of varying degrees of atherosclerosis of the left anterior artery and left main coronary artery disease being more prevalent in patients with DM which mandates early/urgent bypass surgery. Additionally, smoking, dyslipidemia, hypertension and a family history of coronary artery disease was also linked to be significantly associated with a worse prognosis. Most diabetic participants showed presence of 3VD followed by 2VD. By holding P2Y12 inhibitors reduces the time delay for surgery, hospital stay and perioperative as current guidelines suggest to hold P2Y12 inhibitors 5-7 days before surgery hence it reduces the post-operative bleeding as well as economic burden on society and public health sectors.

AUTHORS' CONTRIBUTION

GAS and MNL: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. GAS, FA, AAS, SDASA, FA, S, and MNL: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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