Biolife
AN INTERNATIONAL QUARTERLY JOURNAL OF BIOLOGY & LIFE SCIENCES
5(4):557-563
ISSN (online): 2320-4257
www.biolifejournals.com
BIOLIFE ORIGINAL ARTICLE

Glycosylated hemoglobin (HBA1c) levels as follow-up for clinical outcome (cardiac events) after coronary artery stenting in diabetic patients

Suzy Fawzi

Critical Care Department, Faculty of Medicine, Cairo University, Egypt

Email: manalmanar@mail.com

ABSTRACT

Diabetes mellitus (DM) has been recognized to be a strong risk factor for cardiovascular disease (CVD) and has been proved to be an independent risk factor for in-stent restenosis. After stent implantation, restenosis remains the "Achilles' heel" of percutaneous coronary intervention (PCI) and diabetic patients compared to non-diabetics still have poorer clinical outcomes. Objective:(Aim of Work) is to evaluate whether the level of HbA1c - as an indicator for the glycaemic control in diabetic patient - is related to major cardiovascular events during the follow up in diabetic patients after percutaneous coronary intervention [(PCI) – stenting]. Methods: This self-controlled cohort study included hundred patients with diabetes, 72 patient on oral hypoglycemic agent and 28 patient on insulin at the time of the study. These patients included 71 male (71%) and 29 female (29%) with mean age 57+7.94 years. All patients were subjected to stress thallium at the end of follow-up period (24 month) or at the occurrence of the cardiac events. Follow-up HbA1c were performed before stenting and every 3 month till the end of follow-up period or at the occurrence of cardiac events. Results: Regarding the duration of diabetes mellitus (in years), patients who had cardiac events had longer duration of DM (12.46+6.6, 8.89+3.8 years with p-value=0.001). LDL level was lower in the patients who had no cardiac events than who did (104+19 mg/dl, 134+26 mg/dl with p-value<0.01). Patients who had cardiac events were on shorter duration of clopidogrel than those who did not (8.3+4.7 month, 18.6+6.6 month with p-value < 0.01). HbA1c in the patients with cardiac events was ≥ 7% while in the no cardiac events patients was ≤ 7% with p-value <0.01. HBA1c during stenting was higher than HBA1c during follow-up in the whole diabetic group (9.7+1.67%, 7.1+2.0% with p-value < 0.01). Conclusion: In diabetic patients undergoing coronary artery stenting, patients with HbA1c levels ≤ 7% may have lower risk of adverse cardiac events and have better clinical outcome after PCI at 2-year follow-up. Clopidogrel may reduce the risk of adverse cardiac events (restenosis) in diabetic patients who underwent coronary artery stenting when used for more than 12 month or more (12-24 month).

Key words: Diabetes mellitus, percutaneous coronary intervention (stenting), HbA1c, adverse cardiac events, Stress Thallium.

INTRODUCTION

Diabetes mellitus (DM) has been recognized to be a strong risk factor for cardiovascular disease (CVD) and has been proved to be an independent risk factor for in-stent restenosis (1).After stent implantation, restenosis remains the "Achilles' heel" of percutaneous coronary intervention (PCI) and diabetic patients compared to non-diabetics still have poorer clinical outcomes (2).

Glycemic control has been established to have an impact on the clinical outcome in DM patients after PCI. Glycosylated hemoglobin level (HbA1c) that reflects the average blood glucose concentrations over the preceding 2 to 3 months is a stable marker of long-term blood glucose control (3).

Several studies found that patients with major adverse cardiac events had significantly higher levels of HbA1c (> 7.3%) compared to those without (4-5). Thus, in DM patients in whom the optimal glycaemic control is defined as HbA1c ≤ 7% , HbA1c is potentially a better prognostic marker of long-term outcome than other glycometabolic parameters (6).

How to Site This Article:
Suzy Fawzi (2017). Glycosylated hemoglobin (HBA1c) levels as follow-up for clinical outcome (cardiac events) after coronary artery stenting in diabetic patients. *Biolife*. 5(4), pp 557-563. doi: 10.5281/zenodo.7393268

Received: 4 October 2017; Accepted; 25November2017; Available online : 4 December 2017

The present study evaluates whether the level of HbA1c as an indicator for the glycaemic control in diabetic patient is related to major cardiovascular events during the follow up in diabetic patients after percutaneous coronary intervention [(PCI) – stenting].

PATIENTS AND METHODS

A total of hundred diabetic patients (100psts) in the period between March 2012 and March 2014 were enrolled in this prospective cohort study. All patients were scheduled for elective PCI at the critical care department, Faculty of Medicine (Al Kasr El Aini), Cairo University.

All patients were on oral clopidogrel 75mg/day after PCI. Inclusion criteria were: age between 30-80 years, either sex, diabetic patients on oral hypoglycemic drugs or insulin, and patients with bare-metalor drug eluted stenting. All patients were known to be ischemic before stenting either complaining of unstable angina or myocardial infarction.

Exclusion criteria were: refusal to complete follow-up, severe liver disease, renal disease, malignancy, anemia, patients on conservative treatment of ischemia or requiring coronary bypass. Ethical approval was obtained from Ethics Committee of the Faculty of Medicine. All patients provided their consent prior to participation in the current study.

All patients were subjected to detailed medical history and physical examination. Routine labs and followed up when needed in form of: complete blood count, liver function tests, urea, creatinine, fastening blood sugar, postprandial blood sugar, HbA1c (before and after stenting and every 3 month till occurrence of cardiac events or till end of follow-up period), and compete lipid profile (cholesterol, triglycerides, LDL, HDL).

All patients were subjected to stress thallium at end of follow-up period (24 month) or at the occurrence of cardiac events. Follow-up HbA1c were performed before stenting and every 3 month after stenting till the end of follow-up period or at the occurrence of cardiac events. The optimal glycaemic control is defined as HbA1c ≤ 7% (6).

End point in the study: either the patient completed the 24 months of follow-up without cardiac events or at any time during follow-up period the patient developed cardiac event in form of unstable angina or infarction.

RESULTS

This study included hundred diabetic patients with mean age of 57+7.94 years. Out of the hundred patients enrolled in the study, 71 (71%) were males and 29 (29%) were females. Patients were classified into two groups according to occurrence of cardiac events: no cardiac

Table-1. Data of both no events group and cardiac events group in studied population

		No events	Cardiac events	P value
Sex (M/F)	Count	52/20	19/9	0.66
Smoker	No (%)	30 (42%)	14 (50%)	0.451
Age	mean±SD	58.78±8.05	55.06±7.03	0.26
Duration of DM (years)	mean±SD	8.89±3.83	12.46±6.65	0.001(S)
Duration before any event (month)	mean±SD	22.08±5.59	8.50±3.17	<0.01 (S)
Glycosylated Hb % on stenting	mean±SD	9.44±1.69	10.50±1.14	0.003 (S)
Glycosylated Hb% follow up	mean±SD	6.32±1.14	9.32±1.02	<0.01 (S)
Cholesterol mg/dl	mean±SD	194±22	219±39	<0.01 (S)
LDL mg/dl	mean±SD	104±19	134±26	<0.01 (S)
Clopidogrel duration (months)	mean±SD	18.69±6.6	8.31±4.7	<0.01 (S)
Length stent	mean±SD	18.74±4.26	18.06±4.56	0.430

Patients with cardiac events showed longer duration for DM, higher HBA1C, cholesterol, LDL and longer duration of clopidogrel.

Table-2. Association between type of stent and occurrence of cardiac events

Groups	**Cardiac Events Groups**		**Total**
Stent Type	No Cardiac Events	Cardiac Events	
Bare Metal Stent	19	21	**40**
Drug-eluted Stent	53	7	**60**
Total	**72**	**28**	**100**

Bare metal stent type is significantly associated with cardiac events while patients with no cardiac events used drug- eluted stent (P<0.01 (S)

events (no events) group and cardiac events group (Table-1).

In Table-1, the cardiac events group had longer duration of diabetes, higher HbA1c on stenting and follow-up (FUP), higher cholesterol, higher LDL, and shorter duration on clopidogrel than those with no cardiac event group with significant statistical difference (P=0.001, 0.003, <0.01, <0.01, <0.01, and <0.01 respectively).

Figure-1 shows that patients with no cardiac events had more decline in HbA1c on follow-up compared to cardiac events patients with significant statistical difference (P=< 0.01).

In relation to the type of stent in the cardiac events group and no cardiac events group, patients who had drug-eluted stent had lower cardiac events compared to patients with bare metal stent with statistical significant difference (P= <0.01) (Table 2).

On a multivariate regression analysis, incidence of cardiac events was significantly associated with elevated glycosylatedHb on stenting, elevated glycosylated Hb on follow-up (FUP), and elevated LDL (P=0.04, 0.01, and 0.08 respectively). Also, cardiac events occurrence probability decreased significantly with longer duration on clopidogrel (P=0.01) (Table 3).

ROC curve (figure-2) revealed glycosylated HB more than 9.5% on stenting is predictor for occurrence of cardiac events. This cutoff has sensitivity 82% and specificity 62%, positive predictive value 35% and negative predictive value 86%.

On follow up; HBA1C more than 7.1% is predictor for occurrence of cardiac events. This cutoff has sensitivity 93% and specificity 95%, positive predictive value 87% and negative predictive value 97%.

It appears that HBA1C on follow-up is more predictive for occurrence of cardiac events rather than HBA1C on stenting (P value for the difference in the two ROC curves <0.01).

From Figure-3, Cholesterol more than 205mg/dl is predictor for occurrence of cardiac events. This cutoff has sensitivity 54% and specificity 77%, positive predictive value 43% and negative predictive value 81%.

LDL more than 105mg/dl is also a predictor for occurrence of cardiac events. This cutoff has sensitivity 82% and specificity 77%, positive predictive value 51% and negative predictive value 92%.

It appears that no significant difference between ROC curves of cholesterol and LDL (P=0.10 NS)

DISCUSSION

Diabetes mellitus (DM) is known as a well-established risk factor for cardiovascular disease (CVD). Diabetic patients admitted with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI) are more likely to develop major adverse cardiovascular events including stent restenosis and have worse clinical outcomes compared with non-diabetics undergoing PCI (1).

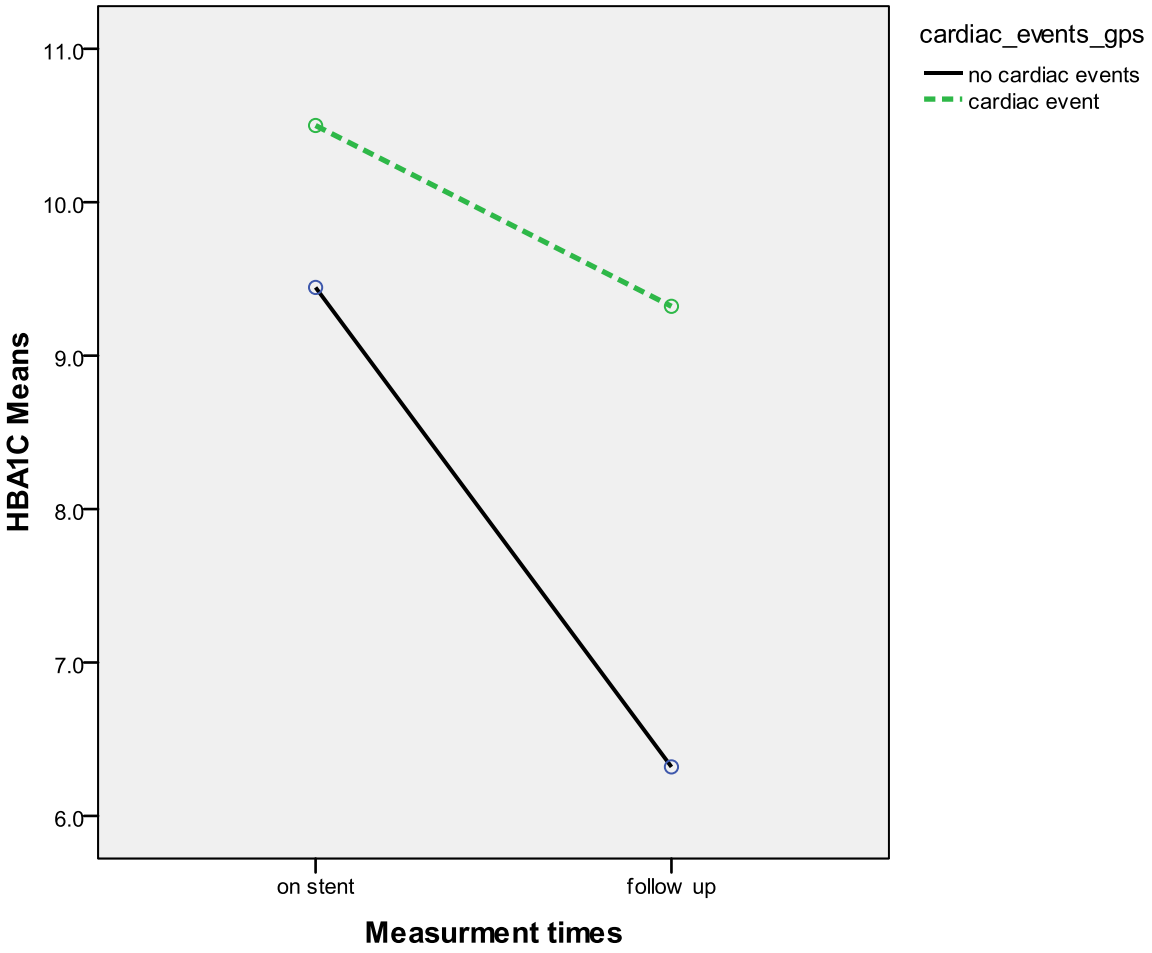
HbA1c is potentially a better and stable prognostic marker of long-term outcome and blood glucose control in DM patients (3). The use of Hb1Ac levels for the prognosis of patients with diabetes have been the focus of many studies (7-8). High HbA1c levels can increase

Table-3. On multivariate regression analysis, incidence of cardiac events was significantly associated with elevated glycosylated HB on stenting and follow-up, elevated LDL, longer duration of clopidogrel.

Variant	P value	OR	95.0% CI for OR	
			Lower	Upper
Sex	0.777	1.512	0.086	26.554
Age	0.14	0.76	0.53	1.1
Duration of DM years	0.696	1.045	0.837	1.306
Glycosylated Hb on stenting	0.004	9.989	2.071	48.182
LDL mg/dl	0.008	1.127	1.031	1.232
Duration of clopidogrel (months)	0.005	0.619	0.445	0.863
Stent type (drug –eluted)	0.158	6.769	0.477	96.080
Glycosylated Hb on follow-up	0.01	31	2.2	449

- *Elevated of HBA1C on stenting increase probability of cardiac eventsoccurring more than patients with low HBA1C (P=0.004 significant)*
- *High LDL increase probability of cardiac events occurring more than patients with low LDL (P=0.008 significant)*
- *Longer duration of clopidogrel decrease probability of cardiac eventsoccurring (P=0.01)*
- *Elevated of HBA1C on follow-up increase probability of cardiac eventsoccurring more than patients with low HBA1C (P=0.01 significant).*

Figure-1. The relation of HbA1c between cardiac and no cardiac events on stenting and on follow –up..



P value within groups <0.01 i.e. all pts with or without cardiac events showed decline in HBA1C, P value between groups <0.01 i.e. pts with no cardiac events showed more decline in HBA1C.

coronary heart disease incidence and adversely affect its prognosis (4).

The relationship between coronary heart disease and HbA1c prognosis remains controversial. The prognostic potential of HbA1c levels in diabetic patients after PCI have been investigated in few studies and reported results are inconclusive and conflicting. Therefore, the optimal HbA1c target in diabetic patients is an ongoing controversy subject that may be especially important for DM patients with PCI. The general follow-up duration in most studies is short, ranging from 9 months and 1 year (6).

In our study, DM patients with high level of HbA1c had adverse long-term outcome (cardiac events) compared to those with lower level of HbA1c (who had no cardiac events) (HbA1c: 9.32+1.02% and 6.32+1.1%, P-value:<0.01).

Kowalczyk et al..(3) found that acute myocardial infarction (AMI) patients with higher levels of HbA1c were associated with worse long-term outcome. Also, Zheng etal. (6) revealed a significant correlation between higher HbA1c levels and non-fatal myocardial infarction (MI) and the risk of target vessel revascularization (TVR) (OR 2.47, 95% CI 1.38 – 4.4,OR 1.36, 95% CI 1.03 – 1.82, respectively).

Geng et al.(9) in their data found that elevated HbA1c level is associated with long term MI and mortality , but not with early deaths in non-diabetic patients with CAD, thus, DM patients with CAD have excess risk for developing adverse outcomes resulting from long-term insulin resistance, leading to hypercoagulability ,inflammation, dyslipidemia, and subsequent cardiovascular events.

Saleem et al. (10) showed that HbA1c was an independent factor influencing the coronary artery disease severity demonstrated by coronary angiography, and that coronary artery disease severity was, also, correlated with duration of DM and poor control of diabetes as shown by higher levels of HbA1c. Also, Timmer et al.(11) found that increased HbA1c level reflects long-term glycol-metabolic derangement and probably cardiovascular risk in this mechanism. Kowalczyk et al. (3) revealed also in their study, that

diabetic patients with elevated HbA1c> 7% are prone to worse outcome.

Similarly, our study revealed that patients who developed cardiac events had longer duration of diabetes than those without cardiac events (12.46+6.6 years and 8.89+3.8 years respectively with P=0.001). Also, HbA1c in those with cardiac events was higher than those without (9.32+1.0% and 6.32+1.1% respectively with P value < 0.01).

In the present study, HbA1c level in patients with no cardiac events showed significant decline from the time of PCI till the end of follow-up period (24 months) (9.4+1.6 - 6.3+1.1% respectively, P-value < 0.01) compared to the HbA1c level in patients with cardiac events from the time of PCI till the occurrence of cardiac event (10.5+1.1% - 9.3+1.0% respectively, P-value <0.01). Ray et al. (12) reported that a 0.9% decline in HbA1c level was associated with 17% decrease in major adverse cardiovascular events (MACE) during acute coronary syndrome in diabetic patients. In another study, patients with high HbA1c (≥6.8%) or low HbA1c (≤5.9%) had a risk of major adverse cardiovascular events of target lesion revascularization (TLR) than patients with moderate HbA1c (6.8%). Low HbA1c due to severe hypoglycemia might lead to higher mortality in this study (13).

In our study, patients with high follow-up HbA1c experienced cardiac events more than patients with low-follow-up HbA1c (9.32+1.0% and 6.32+1.1% respectively with P-value <0.01). Similarly, Hwang et al (14) had similar observations in which they concluded that reduced rate of adverse events, especially repeated revascularization, was associated with HbA1c <7.0% measured 2 years after PCI.

In this present study, multivariable logistic regression showed that elevated LDL, HbA1c on stenting and on follow-up were significant predictor for cardiac events (OR: 1.1, 9.9, 31; 95% CI: 1.0 – 1.2, 2.0–48, 2.2 – 449; P-value: 0.008, 0.004, 0.01 respectively).

This present study strongly suggests that high level of HbA1c (either pre or post procedural) might be a potential risk factor and a follow-up marker for adverse cardiac events in DM patients after PCI. This may have several explanations: increased HbA1c is a measurement of poor glycemic control for the previous metabolic memory where diabetic cardiovascular disease had been established. Also, vascular endothelial cell proliferation or damage could be induce by chronic hyperglycemia. In addition, poor cardiovascular outcomes might be increased by dyslipidemia (6-15).

The novel aspect of this study was in addition to pre-procedural HbA1c which reflects the glycemic control 2-3 months before procedure, we measured the post-procedural HbA1c levels as a glycemic control marker for twenty four months after PCI and related them to adverse outcome.

Figure-2. ROC Curve for HbA1c in cases with and without cardiac events on stenting and on follow-up. Area under the curve (AUC) 0.68 for HBA1C on sending and 0.96 on follow up.

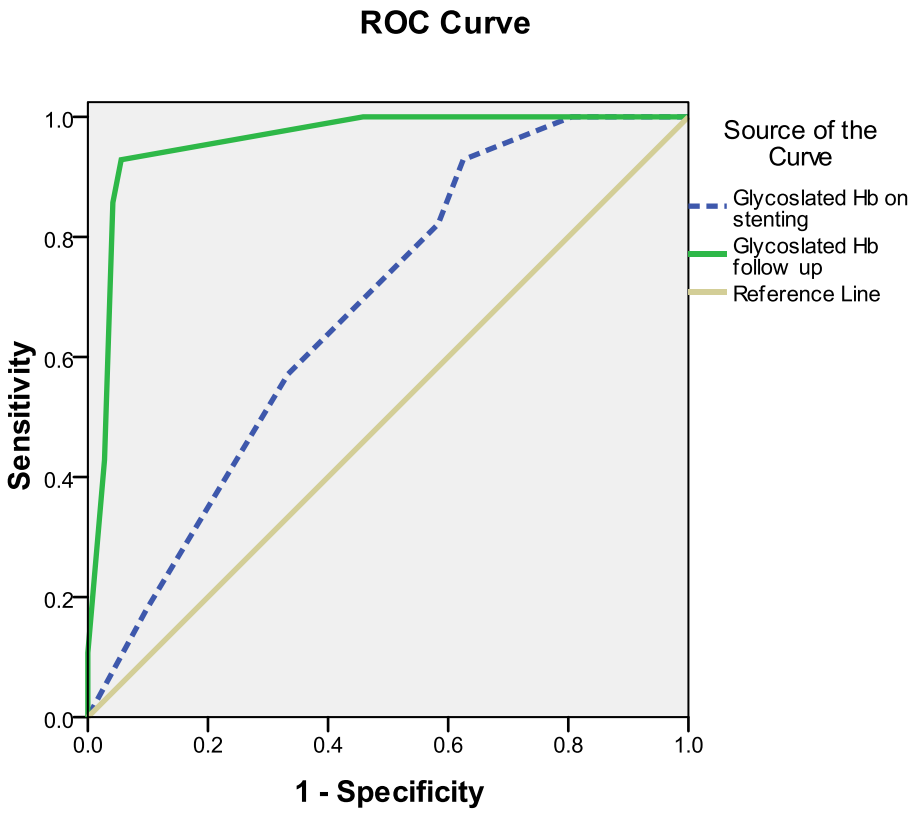
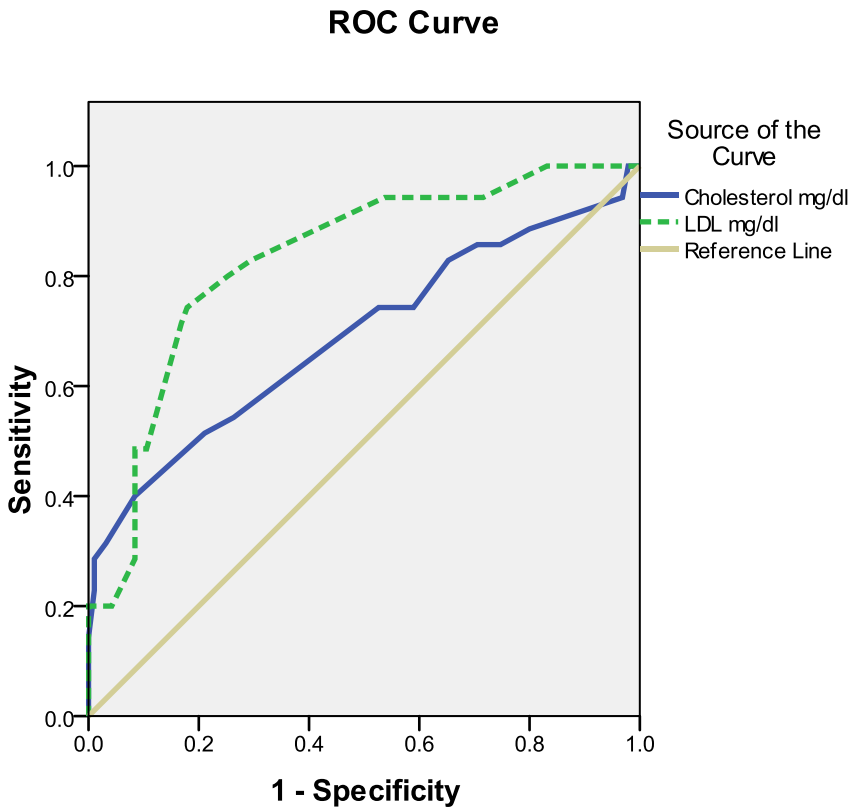


Figure-2. ROC Curve for cholesterol (AUC 0.69) and low density lipoproteins (LDL) (AUC 0.83) in cases with cardiac events.



Limitations

- There are several possible limitation in our study that could be mentioned. Firstly, in this study angiographic follow-up was not performed instead we performed stress perfusion study.
- Secondly, this study was a single-center experience. Thus, the studied number of patients were small.
- Thirdly, HbA1c measurements were done in different labs.
- Fourthly, in our study cardiac events were limited to unstable angina or myocardial infarction and this may be due to follow-up duration (24 months). Thus, longer duration of follow-up maybe advisable.

Conclusion

- HbA1c levels ≤7% may have better clinical outcome after PCI in diabetic patients in 2-year follow-up.
- Clopidogrel may reduce the risk of adverse clinical outcome (restenosis) in diabetic patients who underwent coronary artery stenting when used for more than 12 months (12-24 months).
- Low LDL may reduce the risk of adverse clinical outcome in DM patients after PCI.
- Our study supports the notion that HbA1c level, as a marker of long-term glycemic control, may reflect the prognosis of the clinical outcomes in DM patients undergoing PCI.

Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1]. Lee TT, Feinberg L, Baim DS, Holmes DR, Aroesty JM, Carrozza JP, Cohen DJ, Hokk. Five-year clinical outcomes after single-vessel coronary stenting (a pooled analysis of coronary stent clinical trials) Am J Cardiol. 2006; 98: 718-721.doi: 10.1016/j.amjcard.2006.03.059.

[2]. Dauerman HL. Percutaneous coronary intervention, diabetes mellitus, and death. J AM CollCardiol 2010; 55: 1076-1079.

[3]. Kowalczyk J, Mazurek M, Zielinska T, et al. Prognostic significance of HbA1c in patients with AMI treated invasively and newly detected glucose abnormalities. Eur J Prevent Cardiol 2015; 22: 798-806.

[4]. Ueda H, Mitsusada N, Harimoto K, Miyawaki M, Yasuga Y and Hiraoka H. Glycosylatedhemoglobin is a predictor of major adverse cardiac events after drug-eluting stent implantations in patients with diabetes mellitus. Cardiology 2010; 116: 51-57.

[5]. Kataska Y, Shao M, et al. Multiple risk factor intervention and progression of coronary atherosclerosis in patients with type 2 diabetes mellitus. Eur J PrevCardiol 2013; 20: 209-217.

[6]. Zheng J, Cherg J, Zhang Q, Qi C, Wang T, Xiao X. Association between glycosylated hemoglobin level and cardiovascular outcomes in diabetic patients after percutaneous coronary intervention. Medicine (Baltimore) 2016; 95: 19-28: e 3696.
[7]. Fatima N, Zaman M, Ishaq M, Baloch DJ, Bano M, et al. Impact of glycosylated hemoglobin (HBA1c) on the extent of perfusion abnormalities and left ventricular using gated myocardial perfusion imaging and clinical outcomes in diabetic patients. Nucl Med Commun2013; 34: 489-494.
[8]. Su G, Mi SH, Tao H, Li Z, Yang Hx, etal, Impact of admission glycemic variability, glucose, and glycosylated hemoglobin on major adverse cardiac events after acute myocardial infarction. Diabetes Care 2013; 36: 1026-1032.
[9]. Swapna Gurrapu and Estari Mamidala**.** Medicinal Plants Used By Traditional Medicine Practitioners in the Management of HIV/AIDS-Related Diseases in Tribal Areas of Adilabad District, Telangana Region. *The Ame J Sci & Med Res*. 2016:2(1):239-245. doi:10.17812/ajsmr2101.
[10]. Geng J, Zhang Y, Wang B, Xie J, Xu B, Li J.Glycosylated hemoglobin leveled clinical outcomes in non-diabetic patients with coronary artery disease. Medicine 2017; 96: 17 (e 6784).
[11]. Saleem T, Mohammad KH, Abdel-Fattah MM, et al. Association of glycosylated hemoglobin level and diabetes mellitus duration with the severity of coronary artery disease. DiabVasc Dis Res 2008; 5: 184-189.
[12]. Timmer JR, Hoekstra M, Nijsten M, et al. Prognostic value of admission glycosylated hemoglobin and glucose in non-diabetic patients with ST-segment elevation myocardial infarction treated with percutaneous coronary intervention. Circulation 2011; 124: 704-711.
[13]. Ray KK, Seshasai SR, Wijesuriya S et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. Lancet 2009; 373: 1765-1772.
[14]. Wang J, Yan G, Qiao Y, Wang D, Ma G, Tang C. Different levels of glycosylated hemoglobin influence severity and long-term prognosis of coronary heart disease patients with stent implantation. Experimental and Therapeutic Medicine 2015; 9: 361-366.
[15]. Hwang JK, Lee SH, Song YB, Ahn J, Carriere K, Tang MJ et al. Glycemic control status after percutaneous coronary intervention and long-term clinical outcomes in patients with type 2 diabetes mellitus. Circulation 2017; 10: e004157.
[16]. Kassaian SE, Goodarzyneiad H, Boroumand MA, Salarifar M, Masoudkabir F, Mohajeri-Tehrani MR et al. Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. CardiovascDiabetol 2012; 11: 82doi 10 1186/1475-2840-11-82.