Evaluation of the Effect of Preoperative HbA1c Value on Development of Postoperative Atrial Fibrillation in Diabetic Patients with On-Pump Coronary Artery Bypass Graft.

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Abstract

Background: We aimed to determine the relationship between HbA1c levels and the development of postoperative atrial fibrillation (PoAF) . **Methods:** 288 patients diagnosed with diabet and undergoing on-pump coronary bypass were included in the study. Those with serum HbA1c levels between 5.5-7.0% were defined as Group 1, those with serum HbA1c levels between 7.1-8.9% were defined as group 2, while those with serum HbA1c levels 9.0% and above formed Group 3. Data between groups were compared. The predictive values of the independent variables for the development of PoAF were measured. **Results:** We did not found difference between groups in terms of development PoAF (p=0.170). Presence of hypertension was determined as an independent predictor for the development of PoAF (p=0.003) but not HbA1c levels (p=0.134). There was 50.5% sensitivity and 61.1% specificity for HbA1c values of 9.06% and above to predict PoAF (AUC: 0.571, p=0.049) **Conclusions:** HbA1c levels were not an independent predictor of PoAF development. However, we think that high HbA1c levels may be a risk factor for the development of PoAF.

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Running Title: HbA1c and Postoperative Atrial Fibrillation

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Abstract

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Methods: 288 patients diagnosed with diabet and undergoing on-pump coronary bypass were included in the study. Those with serum HbA1c levels between 5.5-7.0% were defined as Group 1, those with serum HbA1c levels between 7.1-8.9% were defined as group 2, while those with serum HbA1c levels 9.0% and above formed Group 3. Data between groups were compared. The predictive values of the independent variables for the development of PoAF were measured.

Results: We did not found difference between groups in terms of development PoAF (p=0.170). Presence of hypertension was determined as an independent predictor for the development of PoAF (p=0.003) but not HbA1c levels (p=0.134). There was 50.5% sensitivity and 61.1% specificity for HbA1c values of 9.06% and above to predict PoAF (AUC: 0.571, p=0.049)

Conclusions: HbA1c levels were not an independent predictor of PoAF development. However, we think that high HbA1c levels may be a risk factor for the development of PoAF.

Key words: Diabetes mellitus, HbA1c, postoperative atrial fibrillation, coronary artery bypass grafting

INTRODUCTION

Diabetes mellitus (DM) is a chronic condition with dysfunction in insulin secretion that associated with systemic atherosclerosis, such as stroke, ischemic heart disease, and lower extremity arterial disease.[1] In 2015, the International Diabetes Federation reported that 8.8% of the world's population suffers from DM.[2]

Hyperglycemia could increase mortality by causing renal and lung adverse events in diabetic patients undergoing cardiac surgery and may also increase the incidence of postoperative atrial fibrillation (PoAF).[3] PoAF is the most common arrhythmic complication of coronary artery bypass grafting (CABG) surgery. Various studies have reported that the incidence of PoAF varies between 10% and 45%, depending on the type of cardiac surgery.[4,5] There are many risk factors for the development of PoAF, such as advanced age, obesity, abnormal heart rate, hyperglycemia, hypertension, increased left atrial size, statin withdrawal, and the presence of atrial fibrillation (AF).[6] Diabetes-induced endothelial dysfunction, abnormal renin-angiotensin-aldosterone system, acceleration of atherogenesis, angiogenesis and abnormal hemostasis eventually lead to atrial remodeling, one of the mechanisms that may be responsible for the formation of AF.[7-9] In other words, diabetes can cause structural, electrical, electromechanical and autonomic remodeling in the

atrium.[10]However, it is not entirely known whether DM plays a role in the development of AF by affecting only the atrial tissue or by involving different pathways such as hypertension, coronary artery disease and abnormal activity of the autonomic nervous system.

Hemoglobin A1c (HbA1c) reflects the average blood glucose level over the previous 3 months for glycemic management in patients with diabetes and has been a well-accepted biomarker over the past few decades.[11] There are studies showing that high HbA1c levels are associated with increased cardiovascular risks, such as myocardial infarction and AF, in patients with and without diabetes.[12] However, the data on the effect of HbA1c, which is determined as a marker of preoperative glycemic control and the degree of hyperglycemia, on the development of PoAF are insufficient and its predictive value has not yet been understood.

The aim of this study was to investigate the relationship between preoperative HbA1c and PoAF development in diabetic patients who underwent isolated on-pump CABG in our center.

METHODS

The Patients

All procedures were performed in accordance with the Declaration of Helsinki. This retrospective observational clinical study was conducted on 447 consecutive patients over 18 years of age diagnosed with Diabetes Mellitus who underwent on-pump CABG in the Department of Cardiovascular Surgery of Bursa Yüksek İhtisas Training and Research Hospital between January 2018 and December 2020. This study was approved by the local institutional Ethical Committee of University of Health Sciences - Turkey (Approval number: 2011- KAEK-25 2021/04-05). All procedures were performed in accordance with the Declaration of Helsinki.

Patients who were randomized according to the exclusion criteria were included in the study. All data to be analyzed were obtained from the patients' medical files. Preoperative clinical conditions such as atrial fibrillation/flutter, heart valve disease, chronic obstructive pulmonary disease, patients receiving hemodialysis for end-stage renal disease, serum creatinine $>$ 2.0 mg/dl, clinical conditions such as combined surgery (CABG + carotid surgery, CABG + heart valve surgery, CABG + aortic surgery), emergency coronary bypass, redo bypass, preoperative inotropic or mechanical support, bleeding revision, and prolonged (more than ten days) intensive care unit (ICU) stay were accepted as exclusion criterias. After these exclusion criteria, 288 diabetic patients who underwent isolated on-pump CABG were included in the study (Figure 1). The patients included in the study were divided into three groups according to their serum HbA1c levels. Those with serum HbA1c levels between 5.5-7.0% were defined as Group 1, those with serum HbA1c levels between 7.1-8.9% were defined as group 2, while those with serum HbA1c levels 9.0% and above formed Group 3.

All data including age, gender, history of hypertension, presence of peripheral arterial disease, previous cerebrovascular accident, preoperative drug use (beta-blockers, statins, ACE /ARB inhibitors, antidiabetic treatment), ejection fraction, left atrial diameter (LAD), body mass index (BMI), development of PoAF, number of anastomosis, aortic X-clamp time, total cardiopulmonary bypass (CPB) time, duration of intensive care unit (ICU) stay, and discharge time from hospital were added to the records. Laboratory parameters were also studied from venous blood sample before the surgery.

Anesthesia and Surgical Procedure

The same anesthesia and surgical method were applied to all patients. Fentanyl (Talinat®; Vem, Istanbul, Turkey) 1-2 µg/kg and pentothal (Pental® Sodium, Istanbul, Turkey) 5-7 mg/kg and rocuronium bromide (Curon®, Mustafa Nevzat, Istanbul, Turkey) 0.6 mg/kg iv was used for induction. Anesthesia was maintained with midazolam, fentanyl and rocuronium.

For extracorporeal circulation, membrane oxygenator and non-pulsatile roller pump were used ((Maquet, Getinge group, Restalt, Germany) and mild hypothermia (32°C) was applied. The mean arterial blood pressure was kept in the range of 60-80 mmHg. Following the completion of the surgery, patients were taken to the cardiovascular surgery intensive care unit. Standard postoperative care was given to all the patients.

Insulin management

Insulin infusion was initiated at blood glucose levels above 200 mg/dL and blood glucose levels between 120-150 mg/dL were targeted. Insulin infusion dose "(Unit/hour) = (Blood sugar-60) × insulin sensitivity coefficient (0.03-0.05)" was calculated according to the formula. Blood glucose measurements were made every 20 minutes in the operating room, every hour for the first 6 hours in the intensive care unit, and every 2 hours thereafter.

Diagnosis of PoAF

All patients were followed up in ICU by monitoring continuous heart rhythm and invasive blood pressure. In addition, a 12-lead electrocardiography (ECG) was also obtained daily during the ICU stay. A 12-lead ECG was taken when patients complained of palpitations, shortness of breath or angina in the postoperative inpatient service. AF was verified by a 12-lead ECG and diagnosed according to the guidelines of the European Society of Cardiology. An AF episode that lasted longer than 5 minutes was considered as PoAF. Standard medical cardioversion therapy was performed with a 30-minute amiodarone (5 mg/kg) infusion followed by a maintenance dose of 900 mg/day. AFs that developed until the day the patients were discharged from the operation were recorded.

Statistical Analysis

For statistical analysis, SPSS (IBM SPSS 21.0, Chicago, IL, USA) was used. Continuous variables were expressed as mean±standard deviation and nominal variables were expressed as frequency and percentage. Kolmogorov-Smirnov test was used to identify distribution of variables for normality analysis. Pearson chi-square test was used to compare two and three independent groups for nominal variables and in the event of the minimum expected count is less than 5 Fisher's Exact test was used. One-way ANOVA test was used for continuous data with normal distribution in independent more than two groups, while Kruskal Wallis test was used for continuous data that without normal distribution. To determine which group caused the statistical difference, Tukey HSD for One-way ANOVA and Dunn's -Bonferroni test for Kruskal Wallis test were used as post-hoc analyses. To evaluate whether there is a correlation between the development of PoAF and preoperative HbA1c levels , a Dual-Series Correlation test was performed, which correlates a dichotomy data with a continuously variable data. Preoperative and operative independent variables that may affect PoAF development were included in the logistic regression analysis for predictors of development of PoAF. Parameters with a p value < 0.25 in univariate logistic regression analysis were included in multivariate logistic regression analysis. Receiver-operating characteristic (ROC) curve was applied for the prediction of PoAF development in patients undergoing diabetic isolated CABG and the area under the curve was calculated for HbA1c levels and by measuring the cut-off value the sensitivity and specificity of the area under curve (AUC). For all tests, $p < 0.05$ was considered statistically significant.

RESULTS

Based on exclusion criteria, 288 of 447 diabetic coronary bypass patients were included in the study (Figure 1). The demographic findings of the patients according to the groups are shown in Table 1. While there was no statistical difference between the groups in terms of demographic data in general, the rate of not using any anti-diabetic drug in the group with high HbA1c was found to be statistically significantly higher than the other groups. Likewise, it was an expected finding that oral anti-diabetic drug use was less common in group 3 than in other groups (Table 1).

Comparison of laboratory variables is also shown in Table 1. It was a natural consequence of this study that HbA1c levels were different ($p < 0.001$) between groups in terms of laboratory parameters. In addition, although creatinine levels were within normal limits, they were found to be significantly lower in group 1 compared to other groups ($p=0.010$).

The perioperative and postoperative findings of the patients are summarized in Table 2. While the X-clamp time was shorter in Group 1, the length of stay in the ICU was longer in Group 2. These differences were statistically significant ($p=0.034$, $p=0.007$, respectively) (Table 2). Except those, when the groups were

compared, there was no significant difference in terms of development of PoAF, mortality and length of hospital stay (Table 2)(p=0.170, p=0.996, p=0.088, respectively)

We found a weak correlation between HbA1c levels and the development of PoAF in a Dual-Series Correlation analysis (r=-0.116, p=0.049, Spearman's correlation).

In this study, risk factors related with the development of PoAF were included in the univariate logistic regression analysis. In univariate logistic regression analysis, the PoAF was significantly correlated with only the presence of hypertension (OR [Odds Ratio]= 2.566, 95% CI [Confidence interval]: 1.388-4.742, p=0.003), but was not correlated with age, ejection fraction, LAD, BMI, C-reactive protein (CRP), creatinine, HbA1c levels and aortic X-clamp time (Table 3). Parameters with a p value < 0.25 in univariate logistic regression analysis were included in multivariate logistic regression analysis. Only the presence of hypertension (OR= .397, 95% CI: .214- .738, p=0.003) was identified as an independent predictor of PoAF development after CABG surgery in multivariate analysis (Table 3).

ROC curve analysis demonstrated that HbA1c values of 9.06% or above could predict development PoAF with 50.5% sensitivity and 61.1% specificity (AUC: 0.571, 95% CI: 0.502-0.640, log rank p=0.049)(Figure 2).

DISCUSSION

In our study, we evaluated the effect of HbA1c levels on the development of PoAF in patients diagnosed with diabetes mellitus and undergoing isolated on-pump CABG. In univariate and multivariate logistic regression analysis, we found that only the presence of hypertension was an independent variable predicting the development of PoAF. We could not find HbA1c levels as a predictor of PoAF development. But, we found that there was a weak correlation between HbA1c levels and the development of PoAF (r=-0.116, p=0.049, Spearman's correlation). Also, in the ROC curve analysis, we found that 9.06% or higher HbA1c values could predict the development of PoAF with 50.5% sensitivity and 61.1% specificity (AUC: 0.571, 95% CI: 0.502-0.640, log rank p=0.049). (Figure 2).

In a recently published meta-analysis involving 352,325 patients, the relationship between HbA1c and atrial fibrillation was investigated and demonstrated that high serum HbA1c levels are associated with an increased risk of AF in both diabetes and undiagnosed diabetes. It has been stated that for every 1% increase in HbA1c level, the risk of AF increases by 28%.[13] However, in the same meta-analysis, no relationship was found between HbA1c and PoAF in patients who had undergone CABG. In another study by Iguchi et al.[14] the effect of HbA1c on AF was investigated in 52,448 diabetic and non-diabetic patients and the authors stated that HbA1c levels above 6.5% may be associated with the prevalence of AF.

While no correlation was found between HbA1c and AF seen after coronary bypass in two studies investigating the relationship between PoAF and HbA1c.[15,16] Surer et al.[17] reported that high HbA1c levels may be a predictor of the development of PoAF in their study including off-pump coronary bypass patients. In their study which investigated the effect of glycosylated hemoglobin on outcomes after isolated CABG, Ramadan et al.[18] found more PoAF at HbA1c levels above 7%, but did not accept this as a predictor. Likewise, in a similar study, Arslan et al.[19] found statistically significantly more PoAF in the group with HbA1c level above 7%.

Contrary to these studies, Halkos et al.[20]found statistically significantly less PoAF in the group with HbA1c of 7% and above. Likewise, Kinoshita et al.[21]reported that higher preoperative HbA1c levels were independently associated with a lower risk of postoperative AF. They stated that the reason for this situation is that patients with high HbA1c need more insulin for postoperative blood sugar control and that these insulin applications reduce the risk of postoperative AF. In addition, Matsuura et al.[22] also detected more PoAF in the group with HbA1c below 6.5%.

Diabetes is associated with several metabolic defects including insulin resistance, impaired glucose tolerance, proinflammatory mediators, abnormalities of haemostasis, fibrinolysis, angiogenesis and extracellular matrix turnover.[23] With increased duration of DM, exposure to these metabolic abnormalities and hyperglycemia will be longer, and HbA1c is an indicator of this. In addition, DM is a chronic inflammatory process that

associated with systemic atherosclerosis, including coronary artery disease. An association between increased CRP levels and the prevalence of AF has been reported.[24] Hyperglycemia can regulate markers of chronic inflammation and contribute to increased generation of reactive oxygen species (ROS). Increased oxidative stress and inflammation can lead to insulin resistance and impaired insulin secretion.[25] Inflammation due to oxidative stress can cause atrial fibrosis. Animal studies have shown that interstitial fibrosis of the left atrium is a major trigger of AF in patients with diabetes by causing structural remodeling.[26] In a study, it was stated that hyperglycemia prolongs atrial transmission durations and P wave distribution in prediabetic patients.[27] Chao et al.[28] demonstrated that right and left atrial voltages were significantly reduced due to atrial electrical remodeling and atrial fibrosis in patients with diabetes and impaired glucose tolerance who underwent radiofrequency ablation for paroxysmal AF. In the light of all these explanations, it can be stated that inflammation, oxidative process, fibrosis, structural and electrical atrial remodeling caused by DM may play a role in the development of AF. Considering HbA1c as a measure of exposure to hyperglycemia, it can be said that high HbA1c levels are associated with the development of AF.[13,14] On the other hand, the relationship between the development of PoAF after CABG and high HbA1c levels is not clear, and there are even publications stating that it is inversely related.[20-22] This can be explained by the presence of many factors such as hypoxia, low EF, CPB duration, renal dysfunction and valve disease that may affect the development of PoAF in CABG patients. In addition, in the literature, AF has generally evaluated at HbA1c levels above 6.5% and 7%. In our study, the cut-off value of HbA1c was 9.06%, and in ROC analysis, 50.5% sensitivity and 61.1% specificity were found for this and higher levels (AUC: 0.571, p=0.049) (Figure 2). In our study, we could not find high HbA1c levels as an independent predictor for the development of PoAF in logistic regression analysis, but the 9.06% cut-off HbA1c level in our study was in the very high category, indicating mean blood glucose levels above 240 mg/dL. There is a risk of serious complications at these high blood glucose levels and together with other factors, may lead to the development of AF after coronary bypass surgery.

In recent studies, it has been stated that oral antidiabetic drugs such as thiazolidinedione, dipeptidyl peptidase 4 inhibitor and dapagliflozin reduce the risk of developing atrial fibrillation in type-2 diabetic patients.[29-31] They explained the possible reason for this as its effects on inflammation, oxidative process and fibrosis. In our study, similar to the literature, we found the rate of development of PoAF to be lower in the group with a significantly higher rate of oral antidiabetic drug use (group 1) (p=0.002). At the same time, the rate of those who did not use any antidiabetic agent was statistically significantly higher in group 3 with high HbA1c levels (p=0.008). This finding explains the high HbA1c levels of patients in this group. Therefore, it can be said that the patients in this group have lower blood insulin levels. In addition, although it was not statistically significant, the incidence of PoAF was found to be higher in this group than in the other groups. In parallel with the statement of Kinoshita et al.[21] that adequate insulin levels reduce the risk of PoAF, according to our study it can be said that more PoAF was seen in the group exposed to less insulin before surgery.

Hypertension is a known cause of the development of AF, and in parallel, hypertension was detected as an independent predictor of the development of PoAF in our study. Although there was no correlation in univariate analysis, the age parameter was included in the multivariate analysis in our study since the role of advanced age in the development of AF has been shown in many studies.[32,33] But, we could not find age as an independent predictor for the development of PoAF. This may be because the mean age of the patients in our study was below 65 years of age and we did not evaluate the development of AF in patients over 65 years of age.

STUDY LIMITATIONS

There were several limitations of our study. Firstly, the sample size was relatively small and the study was retrospective and single-centered. Secondly, lack of a control group of non-diabetic patients in our study. Thirdly, our disregard for the doses of inotropes used that may have affected the occurrence of AF.

CONCLUSSION

Although more PoAF was seen in the high HbA1c (>9.0%) group in our study, we could not find HbA1c levels as an independent predictor for the development of PoAF. However, high HbA1c levels are indicative of high blood glucose levels. We think that this high hyperglycemic exposure may contribute to the development of PoAF after CABG by causing inflammation, oxidative process and metabolic disorders. Thus, we think it may be a risk factor.

Conflict of interest

The authors declared no conflict of interest.

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Author contributions

ŞY: Project administration, supervision, KKÖ: Project administration, formal analysis, writing, USS: Data collection, writing FT: Data collection, literature search, MÖ: Data collection, literature search, CE: Literature search, critical review. All authors read and approved the final manuscript.

References

1. Wang J, Luo X, Jin X, et al. Effects of Preoperative HbA1c Levels on the Postoperative Outcomes of Coronary Artery Disease Surgical Treatment in Patients with Diabetes Mellitus and Nondiabetic Patients: A Systematic Review and Meta-Analysis. J Diabetes Res. 2020 Feb 28;2020:3547491.
2. International Diabetes Federation, IDF Diabetes Atlas, International Diabetes Federation, Brussels, Belgium, 7th edition, 2015.
3. Giakoumidakis K, Nenekidis I, Brokalaki H. The correlation between peri-operative hyperglycemia and mortality in cardiac surgery patients: a systematic review. Eur J Cardiovasc Nurs. 2012 Mar;11(1):105-13.
4. Crystal E, Garfinkle MS, Connolly SS, et al. Interventions for preventing post-operative AF in patients undergoing heart surgery. Cochrane Database Syst Rev. 2004;18(4):CD003611.
5. Mathew JP, Fontes ML, Tudor IC, et al. Investigators of the Ischemia Research and Education Foundation; Multicenter Study of Perioperative Ischemia Research Group. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA. 2004;291:1720–1729.
6. Kaw R, Hernandez AV, Masood I, et al. Short- and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2011 May;141(5):1305-12.
7. Sun Y, Hu D. The link between diabetes and atrial fibrillation: cause or correlation? J Cardiovasc Dis Res 2010;1:10-1.
8. Tayebjee MH, Lim HS, MacFadyen RJ, et al. Matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 and -2 in type 2 diabetes: effect of 1 year's cardiovascular risk reduction therapy. Diabetes Care 2004;27:2049-51.
9. Lim HS, MacFadyen RJ, Lip GY. Diabetes mellitus, the renin-angiotensin-aldosterone system, and the heart. Arch InternMed 2004;164:1737-48.
10. Zhang Q, Liu T, Ng CY, Li G. Diabetes mellitus and atrialremodeling: mechanisms and potential upstream therapies. Cardiovasc Ther 2014;32:233-41.
11. John WG, Hillson R, Alberti SG. Use of haemoglobin A1c (HbA1c) in the diagnosis of diabetes mellitus. The implementation of World Health Organisation (WHO) guidance 2011. Practical Diabetes International. 2012; 29(1):12-a.
12. Santos-Oliveira R, Purdy C, M Pereira DS, et al. Haemoglobin A1c levels and subsequent cardiovascular disease in persons without diabetes: a metaanalysis of prospective cohorts. Diabetologia. 2011; 54(6):1327–34

13. Zhao H, Liu M, Chen Z, et al. Dose-response analysis between hemoglobin A1c and risk of atrial fibrillation in patients with and without known diabetes. PLoS One. 2020 Feb 18;15(2):e0227262.
14. Iguchi Y, Kimura K, Shibazaki K, et al. HbA1c and atrial fibrillation: a cross-sectional study in Japan. Int J Cardiol. 2012 Apr 19;156(2):156-9.
15. Abbaszadeh S, Shafiee A, Bina P, et al. Preoperative Hemoglobin A1c and the Occurrence of Atrial Fibrillation Following On-pump Coronary Artery Bypass Surgery in Type-2 Diabetic Patients. Crit Pathw Cardiol. 2017 Mar;16(1):37-41.
16. Durukan AB, Gürbüz HA, Salman N, et al. Evaluation of HbA1c Levels and Postoperative Atrial Fibrillation in Diabetic Patients. J Clin Anal Med 2013;4(3): 204-8.
17. Surer S, Seren M, Saydam O, et al. The relationship between HbA1c & atrial fibrillation after off-pump coronary artery bypass surgery in diabetic patients. Pak J Med Sci. 2016 Jan-Feb;32(1):59-64.
18. Ramadan M, Abdelgawad A, Elshemy A, et al. Impact of elevated glycosylated hemoglobin on hospital outcome and 1 year survival of primary isolated coronary artery bypass grafting patients. Egypt Heart J. 2018 Jun;70(2):113-118.
19. Arslan U, Memetoğlu ME, Kutlu R, et al. Preoperative Hba1c level in prediction of short-term morbidity and mortality outcomes following coronary artery bypass grafting surgery. Russian Open Medical Journal 2015; 4: e0204.
20. Halkos ME, Puskas JD, Lattouf OM, et al. Elevated preoperative hemoglobin A1c level is predictive of adverse events after coronary artery bypass surgery. J Thorac Cardiovasc Surg. 2008 Sep;136(3):631-40.
21. Kinoshita T, Asai T, Suzuki T, et al. Preoperative hemoglobin A1c predicts atrial fibrillation after off-pump coronary bypass surgery. Eur J Cardiothorac Surg. 2012 Jan;41(1):102-7.
22. Matsuura K, Imamaki M, Ishida A, et al. Off-pump coronary artery bypass grafting for poorly controlled diabetic patients. Ann Thorac Cardiovasc Surg 2009;15:18–22.
23. Dublin S, Glazer NL, Smith NL, et al. Diabetes mellitus, glycemic control, and risk of atrial fibrillation. J Gen Intern Med. 2010 Aug;25(8):853-8.
24. Abbaszadeh S, Shafiee A, Bina P, et al. Preoperative Hemoglobin A1c and the Occurrence of Atrial Fibrillation Following On-pump Coronary Artery Bypass Surgery in Type-2 Diabetic Patients. Critical Pathways in Cardiology. 2017; 16:37–41.
25. Luc K, Schramm-Luc A, Guzik TJ, et al. Oxidative stress and inflammatory markers in prediabetes and diabetes. J Physiol Pharmacol. 2019 Dec;70(6): 809-824.
26. Kato T, Yamashita T, Sekiguchi A, et al. What are arrhythmogenic substrates in diabetic rat atria? J Cardiovasc Electrophysiol. 2006 Aug;17(8):890-4.
27. Gudul NE, Karabag T, Sayin MR, et al. Atrial conduction times and left atrial mechanical functions and their relation with diastolic function in prediabetic patients. The Korean journal of internal medicine. 2017; 32(2):286–94.
28. Chao TF, Suenari K, Chang SL, et al. Atrial substrate properties and outcome of catheter ablation in patients with paroxysmal atrial fibrillation associated with diabetes mellitus or impaired fasting glucose. Am J Cardiol. 2010 Dec 1;106(11):1615-20.
29. Zelniker TA, Bonaca MP, Furtado RHM, et al. Effect of Dapagliflozin on Atrial Fibrillation in Patients With Type 2 Diabetes Mellitus: Insights From the DECLARE-TIMI 58 Trial. Circulation. 2020 Apr 14;141(15):1227-1234.
30. Chen HY, Yang FY, Jong GP, et al. Antihyperglycemic drugs use and new-onset atrial fibrillation in elderly patients. Eur J Clin Invest. 2017 May;47(5):388-393.
31. Liou YS, Yang FY, Chen HY, et al. Antihyperglycemic drugs use and new-onset atrial fibrillation: A population-based nested case control study. PLoS One. 2018 Aug 30;13(8):e0197245
32. Özsin KK, Sanrı US, Toktaş F, et al. Effect of Plasma Level of Vitamin D on Postoperative Atrial Fibrillation in Patients Undergoing Isolated Coronary Artery Bypass Grafting. Braz J Cardiovasc Surg. 2018 May-Jun;33(3):217-223
33. Wasmer K, Eckardt L, Breithardt G. Predisposing factors for atrial fibrillation in the elderly. J Geriatr Cardiol 2017; 14: 179–184.

Table 1. Demographic features and laboratory variables of the patients

	Group 1 ***HbA1c: 5.5-7.0*** **(n=83)**	**Group 2** HbA1c: 7.1-8.9 **(n=78)**	**Group 3** HbA1c: 9.0 [?] **(n=127)**	p value
Age(years)	63.5±8.7	64.1±9.5	63.5±9.3	0.870 *
Male gender, n (%)	55 (66.3)	63 (80.8)	92 (72.4)	0.116 #
Hypertension, n (%)	56 (67.5)	55 (70.5)	95 (74.8)	0.502 #
Previous CVA, n (%)	5 (6)	4 (5.1)	9 (7.1)	0.849 #
PAD, n (%)	7 (8.4)	8 (10.3)	22 (17.3)	0.123 #
Ejection fraction (%)	50.1± 8.3	52.0± 9.3	49.9± 10.5	0.187 ¶
LAD, (mm)	38.4± 4.4	37.6± 3.7	38.1± 4.0	0.151¶
BMI (kg/m^2)	28.0±4.3	27.3±4.0	28.3±4.1	0.404 ¶
Preoperative drugs				
Oral antidiabetics, n (%)	39 (47)	29 (37.2)	36 (28.3)	**0.022** #
Insulin, n (%)	39 (47)	46 (59)	71 (55.9)	0.272 #
No antidiabetic usage, n (%)	5 (6)	3 (3.8)	20 (15.7)	**0.008** #
Beta-blocker, n (%)	78 (94.0)	73 (93.6)	117 (92.1)	0.855 #
ACE-I/ARB, n (%)	56 (67.5)	55 (70.5)	95 (74.8)	0.502 #
Statin, n (%)	53 (63.9)	50 (64.9)	80 (63.0)	0.961 #
Laboratory data				
Hematocrit (%)	39.1±5.5	38.2±5.7	38.9±5.1	0.517*
Hemoglobin (g/dL)	12.9±1.8	12.7±2.0	12.9±1.9	0.755 *
HbA1c, (%)	6.5±0.5$^{\mathbf{b}}$	8.0±0.5$^{\mathbf{b}}$	10.6±1.2$^{\mathbf{b}}$	**< 0.001** ¶
Creatinine (mg/dL)	0.9±0.3$^{\mathbf{b}}$	1.0±0.3	1.1±0.3	**0.010** ¶
C Reactive protein (mg/dL)	8.9±7.2	8.3±6.5	9.5±8.6	0.801 ¶

CVA: Cerebrovascular accident, PAD: Peripheral arterial disease, LAD: Left atrium diameter, BMI: Body mass index, ACE-I: Angiotensin-converting enzyme inhibitör, ARB: Angiotensin-receptor blocker

* One-way ANOVA, # Pearson Chi- Suquare ,¶ Kruskal Wallis test.

Post-hoc test: [b] Dunn's -Bonferroni test

Table 2. Operative and postoperative parameters

	Group 1 ***HbA1c: 5.5-7.0*** **(n=83)**	**Group 2** HbA1c: 7.1-8.9 **(n=78)**	**Group 3** HbA1c: 9.0 [?] **(n=127)**	p value
Number of anastomosis	3.5±0.9	3.5±0.8	3.5±0.9	0.779 ¶
X-clamp time, (minute)	61.7± 20.0 [a]	70.2± 20.1	65.9± 21.3	**0.034** *
Total CPB time, (minute)	93.5± 29.3	95.3± 23.3	92.0± 28.5	0.703 *
PoAF, n (%)	22 (26.5)	24 (30.8)	49 (38.6)	0.170 #
ICU stay (day)	2.5±1.3	2.7±0.9 [b]	2.5±0.8	**0.007** ¶
Hospital stay (day)	6.9± 0.9	6.9± 2.1	6.5± 0.9	0.088 ¶
Mortality,n,(%)	2 (2.4)	2 (2.6)	3 (2.4)	0.996 #

CPB: Cardiopulmonary Bypass , PoAF: Postoperative atrial fibrillation, ICU: Intensive care unit

* One-way ANOVA, # Pearson Chi- Suquare ,¶ Kruskal Wallis test.

Post-hoc test: [a] Tukey HSD, [b] Dunn's -Bonferroni test

Table 3. Binary Logistic regression analysis to identify predictors of PoAF

Univariate analysis Multivariate analysis

Variables	**p**	**Exp(B) Odds Ratio**	**95% C.I. Lower Upper**	**p**	**Exp(B) Odds Ratio**	**95% C.I. Lower Upper**
Age	**0.229**	1.017	.990 - 1.045	0.227	1.017	.989 - 1.046
HT	**0.003**	2.566	1.388 - 4.742	**0.003**	.397	.214 – .738
EF	0.376	1.012	.986 - 1.039			
LAD	0.331	.970	.913 - 1.031			
BMI	0.611	1.015	.983 -1.077			
CRP		1.003	.972 - 1.036			
	0.836					
Creatinine	0.492	1.303	.612 - 2.776			
HbA1c	**0.079**	1.117	.987 - 1.264	0.134	1.101	.971 – 1.249
X-Clamp time	0.775	1.002	.990 - 1.014			

PoAF: Postoperative atrial fibrillation, , HT; Hypertension, EF; Ejection fraction, LAD: Left atrium diameter, BMI: Body mass index, CRP: C-reactive protein, CPB; Cardiopulmonary Bypass

Figure Legends

Figure 1. Flow chart of the patients included in the study

Figure 2. ROC curve and AUC for HbA1c for predicting PoAF. ROC: Receiver operation characteristic,

AUC: Area under the curve, PoAF: Postoperative atrial fibrillation