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Prognostic Value of Hemoglobin A1c Levels in Postmenopausal Diabetic Patients Undergoing Percutaneous Coronary Intervention (PCI) for Acute Coronary Syndrome

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Background: The purpose of our study was to analyze the clinical value of glycosylated hemoglobin A1c (HbA1c) levels in postmenopausal women with acute coronary syndrome (ACS) and diabetes following percutaneous coronary intervention (PCI).





Material/Methods: A total of 173 consecutive postmenopausal patients with comorbid diabetes underwent PCI for primary ACS were enrolled in this study. Serum HbA1c levels were measured prior to PCI, and baseline clinical characteristics of all patients were collected. All patients were followed up at regular intervals for major adverse cardiovascular events (MACEs) during the first year after PCI. MACEs included cardiac death, non-fatal myocardial infarction, and target vessel revascularization (TVR).

Results: At the endpoint of this study, 29 (16.8%) patients out of all 173 patients had MACEs. According to the effect of glycemic control (as indicated by HbA1c levels), all patients were stratified into a well-controlled group (HbA1c $\leq 7.0\%$, N=72) and a poorly-controlled group (HbA1c $> 7.0\%$, N=101). The incidence rate of MACEs and TVR in poorly-controlled diabetics was prominently higher than that in well-controlled diabetics (10.8% vs. 21.8%, $p=0.04$). In multivariable COX regression analysis, after adjustment for potential confounders, HbA1c $\geq 7.0\%$ remained an independent risk predictor of MACE (HR, 2.17; 95%CI, 1.13–5.65; $p<0.01$).

Conclusions: In postmenopausal ACS patients with comorbid diabetes, a high level of HbA1c is associated with a higher MACE rate after PCI, which is mainly driven by a higher rate of TVR.

MeSH Keywords: **Acute Coronary Syndrome • Diabetes Mellitus • Hemoglobin A, Glycosylated • Percutaneous Coronary Intervention • Postmenopause**

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Background

Cardiovascular disease is the leading cause of death worldwide, with coronary artery disease (CAD) accounting for the largest proportion of these deaths [1–3]. Diabetes mellitus (DM) is a major risk factor for CAD, and patients with DM have worse outcomes after acute coronary syndrome (ACS) [4,5]. Moreover, DM appears to have an even greater influence on cardiovascular disease risk in women than in men, especially for postmenopausal women, due to decreasing estrogen level [6,7]. Although the development of treatment has brought benefits to ACS patients in recent decades, the long-term prognosis of ACS following percutaneous coronary intervention (PCI) remains unsatisfactory, mainly due to in-stent restenosis or thrombosis [8–11]. When DM is coexisting, ACS in postmenopausal patients is characterized by diffuse and erosive lesions in small vasculature, with greater risk of in-stent restenosis or thrombosis after PCI [12,13]. Therefore, identification of adverse risk factors of PCI, stratification of the patients according to risk level, and early intensive treatment are crucial for improving clinical efficacy of PCI in postmenopausal ACS patients with comorbid DM.

The higher rates of restenosis after stent implantation in DM patients might be partly caused by aggressive neointimal proliferation in the setting of hyperinsulinemic and hyperglycemic status [14]. Therefore, optimal glycemic control may decrease the incidence of adverse complications after PCI. Glycosylated hemoglobin (HbA1c) is an indicator of mean serum glucose levels over the preceding 2 to 3 months, which also is significantly associated with progression of coronary narrowing in postmenopausal women with DM [15–17]. However, the significance of HbA1c level in prediction of outcome of PCI in postmenopausal ACS patients with comorbid DM has not been fully elucidated. Hence, in this study, we assessed the predictive value of HbA1c in severity of coronary lesion and prognosis evaluation for postmenopausal DM patients who underwent PCI for ACS

Material and Methods

Patients

This was a post hoc analysis of a prospective registry, performed according to the principles of the Declaration of Helsinki and corresponding guidelines, and was approved by the Institutional Review Board of the Zhong Shan Hospital of Sun Yat-sen University (No. C20160321). All subjects were signed a written informed consent. We enrolled 156 consecutive postmenopausal patients presenting with ACS and DM, undergoing PCI between January 2016 and July 2017 at the Zhong Shan Hospital of Sun Yat-sen University. The inclusion

criteria were ACS with a comorbidity of DM on admission. The ACS was diagnosed according to European Society of Cardiology guidelines in 2015 [18], including ST-segment elevation myocardial infarction, none-ST-segment elevation myocardial infarction, and unstable angina pectoris, while the diagnosis of comorbid DM was based on the Standards of Medical Care in Diabetes in 2016 [19]. The exclusion criteria included previous coronary artery bypass grafting, organic heart disease (e.g., heart failure, cardiomyopathy, and valvulopathy), abnormal liver and kidney functions, poor compliance to long-term antiplatelet and anticoagulant treatments, and unavailable and unreliable clinical and laboratory data. Patients with acute and severe preoperative infection or who had comorbidity of malignant conditions were also excluded. Patients who underwent only old plain balloon angioplasty (POBA) or coronary angiography without stent deployment were excluded. All PCIs with drug-eluting stent were performed according to the standard approach, and in the setting of Thrombolysis in Myocardial Infarction Flow (TIMI) grade 3 and residual stenosis less than 10%, PCI procedural was considered successful. The perioperative and postoperative appropriate treatments and management were administrated at the discretion of the attending cardiologist. Demographic, clinical, and laboratory data of all patients were collected from the hospital information system, including demographic, laboratory test, and PCI-related data. SYNTAX score was calculated according to the corresponding American revascularization guidelines[20].

Laboratory analysis

Sterile peripheral venous blood specimens were collected from each patient after 10-h overnight fasting. Serum HbA1c level was measured according to immunoturbidimetric methods using a SIEMENS 1650 analyzer (Siemens Medical, Tarrytown, USA). Routine laboratory tests of lipids, glucose level, and hepatic and renal functions were performed using the standardized methods at Zhong Shan Hospital. Left ventricular ejection fractions (LVEF) and left atrial diameter (LAD) were evaluated by echocardiography prior to PCI.

Follow-up and clinical evaluation

All patients were regularly followed up at 1-month intervals after discharge. Follow-up data was obtained by telephone communication or face-to-face clinic visiting with the patients or their family members. A well-trained research cardiologist in our team conducted the follow-up examinations according to a structured protocol. The primary endpoint of interest was assessed as 12-month major adverse cardiovascular events (MACEs). MACE included non-fatal myocardial infarction, cardiovascular death, and revascularization procedures. Revascularization of the target vessel was considered to be necessary if there was evidence of ischemia and angina. If the

patients did not have angina symptoms, a functional stress test was performed during a clinic visit to reveal silent ischemia. Repeat PCI was performed for recurrent symptoms or objective evidence of ischemia with provocative testing. According to the glycemic control assessed by HbA1c levels before PCI, patients with a HbA1c level $\leq 7\%$ were defined as “well-controlled”, whereas HbA1c $> 7\%$ was defined as “poorly-controlled”.

Statistical analysis

Statistical analyses were performed using SPSS 20.0 (IBM, USA). $P < 0.05$ (2-sided) was considered as statistically significant. Normally-distributed data were evaluated by Kolmogorov-Smirnov test. Continuous variables are expressed as mean \pm SD and were compared using ANOVA, whereas comparisons of categorical variables were conducted by using chi-square or Fisher's exact test presented as frequencies and percentages. The univariate analyses of association of clinical variables with MACEs were conducted using the log-rank test, and an event-free survival curve was drawn based on the Kaplan-Meier method. Cox multivariate analysis was used to evaluate the independent predictors of MACEs.

Results

Baseline characteristics

Baseline characteristics of 173 postmenopausal patients with DM and ACS enrolled in this study are shown in Table 1. There were 101 (58.4%) poorly-controlled and 72 (41.6%) well-controlled diabetic patients, with average age 58.7 ± 8.6 years. Patients in the well-controlled group had significantly lower levels of TC, TG, and HbA1c (all $p < 0.05$, Table 1) as compared to the poorly-controlled group. Furthermore, patients in the well-controlled group had lower SYNTAX scores and higher LVEF than that of the poorly-controlled group (all $p < 0.05$, Table 1). There were no significant differences between the well-controlled and poorly-controlled group regarding the other clinical, laboratory, and PCI-related variables (Table 1).

Clinical outcomes following PCI

The 12-month outcomes after PCI are summarized in Table 2. During the 12-month follow-up of all 173 patients, there were 29 (16.8%) MACEs, which included 17 (9.8%) TVRs, 8 (4.6%) non-fatal MIs, and 4 (2.3%) cardiac-related mortalities. Patients in the well-controlled group had significantly lower MACEs incidence than in the poorly-controlled group (10.8% vs. 21.8%, $p = 0.04$, Table 2), of which TVR was a main contributor (2.8% vs. 14.9%, $p < 0.01$, Table 2). Figure 1 shows the Kaplan-Meier curve for MACEs-free survival according to glycemic control assessed by HbA1c levels, and there was a significant difference

between groups ($P = 0.04$, Figure 1). No significant difference was observed between groups regarding cardiac mortality and non-fatal MI.

Predictive significance of HbA1c level for MACE

In univariate analyses, we found that HbA1c $> 7\%$ was significantly associated to MACEs risks following PCI (HR, 1.61; 95% CI: 1.18–3.65; $p = 0.01$, Table 3). After adjustment for potential confounding factors, poor glycemic control (HbA1c $> 7\%$) was also an independent predictive indicator of MACEs (HR, 2.17; 95% CI, 1.13–5.65; $p < 0.01$, Table 3) in diabetic patients. The confounding factors included age, BMI, hypertension, hyperlipidemia, insulin therapy, ACEIs/ARBs use, statin use, SYNTAX score (HR, 2.68; 95% CI, 1.12–8.35; $p = 0.04$), and LVEF (HR, 0.82; 95% CI, 0.76–0.93; $p = 0.02$) (Table 3).

Discussion

Diabetes mellitus is a significant risk predictor for subsequent cardiovascular events and specific mortality in patients with ACS following PCI, especially for postmenopausal women [13,21,22]. In the present study, we found that glycemic control was significantly associated with 12-month clinical outcomes in postmenopausal diabetic patients undergoing PCI with stenting. We also showed that postmenopausal diabetic patients with poor glycemic control are at higher risk of developing MACEs compared to those with good glycemic control. Furthermore, the higher MACEs incidence in the poorly-controlled diabetes group was mainly due to the higher rate of TVR. The results of our study suggest that glycemic control reflected by HbA1c level can be used as an independent predictor for clinical outcome in postmenopausal patients with DM and ACS following PCI with stenting.

Diabetic patients are generally characterized by hyperglycemia, hyperinsulinemia, abnormal platelet function, and insulin resistance, which may chronically promote vascular neointimal hyperplasia after stent placement, thereby resulting in development of in-stent restenosis following interventional treatment with stent implantation [23–26]. The results of this study showed that the high rate of TVR is a main contributor to high MACEs incidence in diabetic patients after PCI with stent implanting, and this is confirmed by the significant association between in-stent restenosis risk and DM. Chronic hyperglycemia induces vascular endothelial cell injured, and further causes vasomotor dysfunction, with increased extracellular matrix formation and aggressive cellular proliferation [27]. Hyperinsulinemia has been considered a predisposing factor of stent restenosis, which mainly results from the atherogenic effect of the exogenously administered insulin in diabetic patients [28,29]. Insulin resistance promotes the progression of

Table 1. Baseline characteristics of 173 patients enrolled in current study.

| | Well-control DM (n=72) | Poor-control DM (n=101) | P |
|----------------------------|---------------------------|----------------------------|-------|
| General data | | | |
| Age, years | 58.2±8.1 | 59.3±8.4 | 0.39 |
| Age at menopause, years | 52.5±3.1 | 53.2±3.5 | 0.17 |
| BMI, kg/m ² | 25.8±3.1 | 26.1±3.8 | 0.58 |
| Hypertension | 61 (84.7%) | 87 (86.1%) | 0.79 |
| Hyperlipidemia | 56 (77.8%) | 80 (79.2%) | 0.82 |
| Insulin | 31 (43.1%) | 53 (52.5%) | 0.22 |
| OHA | 19 (26.4%) | 32 (31.7%) | 0.45 |
| ACEIs/ARBs | 29 (40.3%) | 43 (42.6%) | 0.76 |
| Statins | 64 (88.9%) | 87 (86.1%) | 0.59 |
| Beta-blockers | 17 (23.6%) | 27 (26.7%) | 0.64 |
| Laboratory tests | | | |
| LDL-C, mmol/l | 3.08±0.92 | 3.16±0.74 | 0.53 |
| HDL-C, mmol/l | 0.96±0.25 | 0.94±0.23 | 0.59 |
| TC, mmol/l | 4.63±0.87 | 5.16±1.32 | <0.01 |
| TG, mmol/l | 2.61±1.63 | 3.11±1.26 | 0.02 |
| FPG, mmol/l | 7.22±1.45 | 9.46±1.89 | <0.01 |
| HbA1c, % | 6.62±0.24 | 8.66±1.13 | <0.01 |
| Cr, μmol/l | 78.11±13.01 | 75.86±17.81 | 0.36 |
| PCI related data | | | |
| Number of stents, per case | 1.71±0.72 | 1.73±0.74 | 0.86 |
| Total length of stents, mm | 34.76±13.37 | 35.52±16.72 | 0.75 |
| SYNTAX score | 21.62±9.98 | 25.53±10.21 | 0.01 |
| SYNTAX score >23% | 20 (27.8%) | 45 (44.6%) | 0.02 |
| LVEF, % | 54.23±3.15 | 52.62±3.85 | <0.01 |
| LAD, mm | 33.41±2.62 | 34.52±4.62 | 0.07 |

DM – diabetes mellitus; BMI – body mass index; OHA – oral hypoglycemic agent; ACEIs – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; FPG – fasting plasma glucose; TC – total cholesterol; TG – triglycerides; Cr – creatinine; LVEF – left ventricular ejection fractions; LAD – left atrial diameter.

coronary atherosclerotic plaques and endothelial dysfunction, which also is associated with traditional risk factors of ACS, such as serum levels of cholesterol or triglycerides, hypertension, and obesity [30,31]. Plasma HbA1c level is a routine indicator reflecting mean plasma glucose levels over the preceding 8 to 12 weeks [15]. It has been revealed that high HbA1c levels are significantly associated with hyperglycemia, dyslipidemia,

hypercoagulability, and insulin resistance, which also are confirmed as risk factors of ACS [32,33]. Several studies showed that HbA1c ≤7% was a cutoff level of optimal glycemic control in diabetic patients [34,35]. Therefore, in the present study, we used 7% as the optimal cutoff level of HbA1c, reflecting glycemic control.

Table 2. MACE characteristics of all 173 patients during follow-up.

| | Well-control DM (n=72) | Poor-control DM (n=101) | P |
|---------------|---------------------------|----------------------------|-------|
| Total MACE | 7 (10.8%) | 22 (21.8%) | 0.04 |
| Cardiac death | 2 (2.8%) | 2 (2.0%) | 0.73 |
| Non-fatal MI | 3 (4.2%) | 5 (4.9%) | 0.81 |
| TVR | 2 (2.8%) | 15 (14.9%) | <0.01 |

MACE – major adverse cardiovascular events; MI – myocardial infarction; TVR – target vessel revascularization.

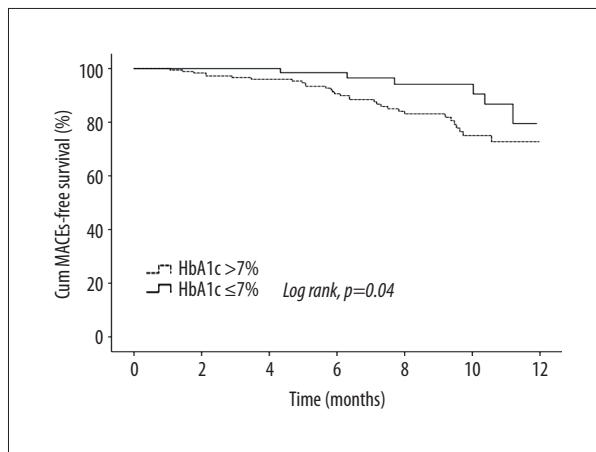


Figure 1. Kaplan-Meier event-free survival curves. The prognostic analysis revealed that the well-controlled diabetes group (HbA1c ≤7.0%, N=72) had a better 12-month MACEs-free survival than in the poorly-controlled group (HbA1c >7.0%, N=101) (P=0.04).

Table 3. Univariate and multivariate analyses of the predictive factors of MACE after PCI.

| | Univariate | | | Multivariate | | |
|----------------------------|------------|-----------|------|--------------|-----------|-------|
| | HR | 95%CI | p | HR | 95%CI | p |
| Age, years | 1.02 | 0.89–1.22 | 0.15 | | | |
| Age at menopause, years | 0.52 | 0.31–0.89 | 0.02 | | | |
| BMI, kg/m ² | 0.98 | 0.88–1.36 | 0.64 | | | |
| Hypertension | 1.01 | 0.96–1.32 | 0.92 | | | |
| Hyperlipidemia | 0.86 | 0.53–1.21 | 0.42 | | | |
| Statin use | 0.92 | 0.61–1.51 | 0.75 | | | |
| Insulin | 1.71 | 0.83–4.57 | 0.19 | | | |
| ACEIs/ARBs use | 1.13 | 0.72–2.72 | 0.58 | | | |
| Number of stents, per case | 1.00 | 0.85–1.22 | 0.96 | | | |
| Total length of stents, mm | 1.01 | 0.98–1.14 | 0.26 | | | |
| SYNTAX score | 2.24 | 1.02–3.52 | 0.03 | 2.68 | 1.12–8.35 | 0.04 |
| LVEF, % | 0.79 | 0.77–0.82 | 0.02 | 0.82 | 0.76–0.93 | 0.02 |
| LDL-C, mmol/l | 1.01 | 0.97–1.02 | 0.51 | | | |
| HbA1c >7% | 1.61 | 1.18–3.65 | 0.01 | 2.17 | 1.13–5.65 | <0.01 |

MACE – major adverse cardiovascular events; PCI – percutaneous coronary intervention; HR – hazard ratio; 95%CI – 95% confidence interval; BMI – body mass index; ACEIs – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers; LVEF – left ventricular ejection fractions; LDL-C – low-density lipoprotein cholesterol.

Menopause is an independent predictor of subsequent cardiovascular events and mortality, with postmenopausal women having higher risk [36,37]. We similarly found that age at menopause of patients was significantly associated with the risk of MACEs. The underlying mechanism appears to be accelerating cardiovascular aging, loss of the vascular protective effect of estrogen, and the classical cardiovascular risk factors such as dyslipidemia and metabolic dysfunction resulting from decreasing estrogen levels [38,39]. The Women's Angiographic and Vitamin and Estrogen (WAVE) trial showed that the presence of clinical DM and higher baseline HbA1c levels were associated with significantly larger reductions in minimum luminal diameter and average luminal diameter of coronary vessels over a mean follow-up of nearly 3 years [40]. In the present study, we found that HbA1c >7% was significantly associated with 12-month events-free survival in postmenopausal diabetic patients after PCI, which was consistent with the WAVE trial.

SYNTAX score is an angiographic grading tool that does not consider clinical factors, which can reflect the complexity and severity of coronary lesions [41]. Several validation studies had proved SYNTAX score to be an independent predictor of outcome after PCI [42,43], which is consistent with results of our study. Moreover, we found that patients in the well-controlled diabetes group had significantly lower mean SYNTAX scores than that of the poorly-controlled group, suggesting worsening metabolic disturbance and severe coronary lesions in diabetic patients with poor glycemic control. Furthermore, we found that a high HbA1c level was significantly associated

with a low level of LVEF, indicating decreased cardiac function and adverse clinical outcome, which is consistent with a previous study [44]. We also analyzed the predictive significance of HbA1c level for MACEs in multivariable COX analysis enrolling all confounders, and further confirmed that high HbA1c level is an independent risk factor of post-PCI MACEs.

There were several potential limitations in this study. The single-center design and short follow-up duration may have influenced the generalization of results, so the implications of this study are limited. A large, multi-center, prospective study should be conducted to confirm our findings. Moreover, the cutoff level of HbA1c was based on a standard value from previous studies, and further meta-analyses should evaluate the optimal cutoff level of HbA1c for predicting clinical outcome after PCI. Finally, the results of this study should be interpreted cautiously due to its small sample size.

Conclusions

Our results demonstrate that postmenopausal diabetic patients with good glycemic control, as indicated by serum HbA1c levels $\leq 7\%$, have lower risk of restenosis and a better clinical outcome after coronary artery stenting during 12-month follow-up.

Conflicts of interest

None.

References:

- Dauerman HL: Five years of coronary artery disease. *Coron Artery Dis*, 2018; 29(5): 366–67
- Waldeyer C, Brunner FJ, Braetz J et al: Adherence to Mediterranean diet, high-sensitive C-reactive protein, and severity of coronary artery disease: Contemporary data from the INTERCATH cohort. *Atherosclerosis*, 2018; 275: 256–61
- Zhang C, Liu P, Xia K et al: Association of serum prealbumin with angiographic severity in patients with acute coronary syndrome. *Med Sci Monit*, 2017; 23: 4041–49
- Naito R, Miyauchi K: Coronary artery disease and type 2 diabetes mellitus. *Int Heart J*, 2017; 58(4): 475–80
- Srinivasan MP, Kamath PK, Bhat NM et al: Severity of coronary artery disease in type 2 diabetes mellitus: Does the timing matter? *Indian Heart J*, 2016; 68(2): 158–63
- Di Carli MF, Afonso L, Campisi R et al: Coronary vascular dysfunction in premenopausal women with diabetes mellitus. *Am Heart J*, 2002; 144(4): 711–18
- Boukhris M, Tomasello SD, Marza F et al: Coronary heart disease in postmenopausal women with type II diabetes mellitus and the impact of estrogen replacement therapy: A narrative review. *Int J Endocrinol*, 2014; 2014: 413920
- Wang Y, Ping Yen Yan B et al: Clinical and economic analysis of lipid goal attainments in Chinese patients with acute coronary syndrome who received post-percutaneous coronary intervention. *J Atheroscler Thromb*, 2018 [Epub ahead of print]
- Tscharre M, Herman R, Rohla M et al: Uric acid is associated with long-term adverse cardiovascular outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Atherosclerosis*, 2018; 270: 173–79
- Pang Z, Zhao W, Yao Z: Cardioprotective effects of nicorandil on coronary heart disease patients undergoing elective percutaneous coronary intervention. *Med Sci Monit*, 2017; 23: 2924–30
- Zhang F, Tongo ND, Hastings V et al: ST-segment elevation myocardial infarction with acute stent thrombosis presenting as intractable hiccups: An unusual case. *Am J Case Rep*, 2017; 18: 467–71
- Selvin E, Coresh J, Golden SH et al: Glycemic control and coronary heart disease risk in persons with and without diabetes: the atherosclerosis risk in communities study. *Arch Intern Med*, 2005; 165(16): 1910–16
- Mellen PB, Cefalu WT, Herrington DM: Diabetes, the metabolic syndrome, and angiographic progression of coronary arterial disease in postmenopausal women. *Arterioscler Thromb Vasc Biol*, 2006; 26(1): 189–93
- Kornowski R, Mintz GS, Kent KM et al: Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia. A serial intravascular ultrasound study. *Circulation*, 1997; 95(6): 1366–69
- Dunn PJ, Cole RA, Soeldner JS, Gleason RE: Reproducibility of hemoglobin A1c and sensitivity to various degrees of glucose intolerance. *Ann Intern Med*, 1979; 91(3): 390–96
- Nathan DM, Singer DE, Hurxthal K, Goodson JD: The clinical information value of the glycosylated hemoglobin assay. *N Engl J Med*, 1984; 310(6): 341–46
- Ahmad S, Xue Z, Silverman A, Lindsay J: Complexity of the relation between hemoglobin A1C, diabetes mellitus, and progression of coronary narrowing in postmenopausal women. *Am J Cardiol*, 2013; 111(6): 793–99

18. Roffi M, Patrono C, Collet JP et al: [2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)]. *G Ital Cardiol (Rome)*, 2016; 17(10): 831–72 [in Italian]
19. American Diabetes Association: Standards of medical care in diabetes – 2016 abridged for primary care providers. *Clin Diabetes*, 2016; 34(1): 3–21
20. Patel MR, Calhoun JH, Dehmer GJ et al: ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Nucl Cardiol*, 2017; 24(5): 1759–92
21. Lee MG, Jeong MH, Ahn Y et al: Additive impact of diabetes mellitus on patients with metabolic syndrome and acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Int J Cardiol*, 2012; 157(2): 283–85
22. Sweeny JM, Angiolillo DJ, Franchi F et al: Impact of diabetes mellitus on the pharmacodynamic effects of ticagrelor versus clopidogrel in troponin-negative acute coronary syndrome patients undergoing ad hoc percutaneous coronary intervention. *J Am Heart Assoc*, 2017; 6(4): pii: e005650
23. Indolfi C, Torella D, Cavuto L et al: Effects of balloon injury on neointimal hyperplasia in streptozotocin-induced diabetes and in hyperinsulinemic nondiabetic pancreatic islet-transplanted rats. *Circulation*, 2001; 103(24): 2980–86
24. Nabati M, Taghavi M, Saffar N et al: Alterations in echocardiographic left ventricular function after percutaneous coronary stenting in diabetic patients with isolated severe proximal left anterior descending artery stenosis. *Indian Heart J*, 2017; 69(2): 146–50
25. Tran HA, Barnett SD, Hunt SL et al: The effect of previous coronary artery stenting on short- and intermediate-term outcome after surgical revascularization in patients with diabetes mellitus. *J Thorac Cardiovasc Surg*, 2009; 138(2): 316–23
26. Germing A, von Dryander S, Bojara W et al: Coronary artery stenting in diabetes mellitus – unfavourable clinical outcome due to increased rate of myocardial ischemia and percutaneous interventions. *Eur J Med Res*, 2002; 7(6): 265–70
27. Marso SP, Mak KH, Topol EJ: Diabetes mellitus: Biological determinants of atherosclerosis and restenosis. *Semin Interv Cardiol*, 1999; 4(3): 129–43
28. Genuth S: Exogenous insulin administration and cardiovascular risk in non-insulin-dependent and insulin-dependent diabetes mellitus. *Ann Intern Med*, 1996; 124(1 Pt 2): 104–9
29. Feinglos MN, Bethel MA: Therapy of type 2 diabetes, cardiovascular death, and the UGDP. *Am Heart J*, 1999; 138(5 Pt 1): 5346–52
30. Caccamo G, Bonura F, Bonura F et al: Insulin resistance and acute coronary syndrome. *Atherosclerosis*, 2010; 211(2): 672–75
31. Barazzoni R, Aleksova A, Armellini I et al: Adipokines, ghrelin and obesity-associated insulin resistance in nondiabetic patients with acute coronary syndrome. *Obesity*, 2012; 20(12): 2348–53
32. Lerstad G, Brodin EE, Enga KF et al: Hyperglycemia, assessed according to HbA1c, and future risk of venous thromboembolism: The Tromso study. *J Thromb Haemost*, 2014; 12(3): 313–19
33. Droumaguet C, Balkau B, Simon D et al: Use of HbA1c in predicting progression to diabetes in French men and women: Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR). *Diabetes Care*, 2006; 29(7): 1619–25
34. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*, 1993; 16(2): 434–44
35. Kassaian SE, Goodarzynejad H, Boroumand MA et al: Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. *Cardiovasc Diabetol*, 2012; 11: 82
36. van der Schouw YT, van der Graaf Y, Steyerberg EW et al: Age at menopause as a risk factor for cardiovascular mortality. *Lancet*, 1996; 347(9003): 714–18
37. Muka T, Oliver-Williams C, Kunutsor S et al: Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: A systematic review and meta-analysis. *JAMA Cardiol*, 2016; 1(7): 767–76
38. Mendelsohn ME: Protective effects of estrogen on the cardiovascular system. *Am J Cardiol*, 2002; 89(12A): 12E–17E; discussion 17E–18E
39. Kok HS, van Asselt KM, van der Schouw YT et al: Heart disease risk determines menopausal age rather than the reverse. *J Am Coll Cardiol*, 2006; 47(10): 1976–83
40. Hsia J, Bittner V, Tripputi M, Howard BV: Metabolic syndrome and coronary angiographic disease progression: the Women's Angiographic Vitamin & Estrogen trial. *Am Heart J*, 2003; 146(3): 439–45
41. Sianos G, Morel MA, Kappetein AP et al: The SYNTAX Score: An angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*, 2005; 1(2): 219–27
42. Chakravarty T, Buch MH, Naik H et al: Predictive accuracy of SYNTAX score for predicting long-term outcomes of unprotected left main coronary artery revascularization. *Am J Cardiol*, 2011; 107(3): 360–66
43. Caixeta A, Genereux P, Palmerini T et al: Prognostic utility of the SYNTAX score in patients with single versus multivessel disease undergoing percutaneous coronary intervention (from the Acute Catheterization and Urgent Intervention Triage Strategy [ACUITY] trial). *Ame J Cardiology*, 2014; 113(2): 203–10
44. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ*, 1998; 317(7160): 703–13 [Erratum in: *BMJ* 1999; 318(7175): 29]