International Journal of PharmTech Research

CODEN (USA): IJPRIF, ISSN: 0974-4304, ISSN(Online): 2455-9563
Vol.11, No.02, pp 119-128, 2018

ST-Segment Depression as a Predictor of three vessel disease in Non-ST-Segment elevation Acute Coronary Syndromes with Diabetes Mellitus Patients

M.Nasri*[1], Z.Safri[2], C.A.Andra[2], H.Hasan[2], Z.Mukhtar[2], A.H.Raynaldo[2]

[1]Faculty of Medicine, University of Sumatera Utara, Medan, Indonesia;
[2]Department of Cardiology and Vascular Medicine, Haji Adam Malik General Hospital, Medan, Indonesia

Abstract : Background: Electrocardiogram (ECG) is a simple, non-invasive modality widely used for diagnostic and prognostic tools in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). Early identification of three-vessel disease (3-VD) in ECG findings in NSTE-ACS with diabetes mellitus (DM) patients is important, due to consideration of prognosis and revascularization modalities. Previous studies that compare 3-VD incidence based on ST-segment-depression were not specified for NSTE-ACS with DM patients. Especially with our current national insurance system, it can be a guide for healthcare providers in terms of management strategies so that NSTE-ACS with DM patients get optimal management and revascularization. The objective of this study was to assess the predictive value of ST-segment depression for the incidence of 3-VD in NSTE-ACS with DM patients. **Methods:** 67 NSTE-ACS with DM patients that hospitalized from January 2015-December 2017 in Haji Adam Malik General Hospital were analyzed retrospectively. Patients were divided into two group based on ST-segment depression on admission ECG. Bivariate and multivariate analysis was performed to study the association between ST-segment depression and 3-VD, p- value < 0.05 was considered statistically significant. **Results:** Bivariate analysis shows that 3-VD incidence was higher in NSTE-ACS with DM patient accompanied by ST-segment depression compared to without ST-segment depression (80.6% vs 19.4 %, p <0.001). On multiple logistic regression analysis, patients with ST-segment depression had a 27.3 fold increased the risk for 3-VD compared to patients without ST-segment depression [OR 27.3 (6.117 – 121.851), p=0.000]. **Conclusion:** The presence of ST-segment depression on admission ECG in NSTE-ACS with DM patients was associated with a higher incidence of 3-VD and was the strongest independent predictor of 3-VD. In clinical practice, it may serve as a simple non-invasive tool for predicting 3-VD in NSTE-ACS with DM patients.

Keywords : ST-segment Depression, NSTE-ACS, DM, 3-VD.

International Journal of PharmTech Research, 2018,11(2): 119-128.

DOI: http://dx.doi.org/10.20902/IJPTR.2018.11210

Introduction:

Acute Coronary Syndrome (ACS) is a main cardiovascular problem due to the high hospital admission and high mortality cases.[1] Almost half of the cardiovascular death is caused by the acute myocardial infarction (AMI) (Departemen Kesehatan Republik Indonesia, 2008). IMA is a 30% cause of death in people with Diabetes Mellitus (DM).[2] ACS is caused by disturbances of flow to coronary due to the atherosclerosis plaque as well as worsening of thrombus closing the lumen. A progression of plaque formation and a tearing of plaque can trigger a thrombus formation which progressing to the further coronary stenosis. DM is related to both of process, which are the plaque formation and intraluminal thrombus which causing infarction and worsened the cardiovascular condition.[3] Some researchers are showing a diabetic pattern of CAD such as a significant number of stenosis, more spreading stenosis, and a multivessel.[4,5] Factors on DM patient that can increase ACS risk are atherosclerosis acceleration, prothrombic state, and autonomic disfunction.[6] While 20–30% of European patients with NSTE-ACS have known diabetes mellitus, a similar proportion may have undiagnosed diabetes or impaired glucose tolerance.[7-10]

Coronary angiography has an important role in ACS-NSTE intervention.[11] Coronary angiography pattern on ACS-NSTE is various from normal to the worse and diffuse artery disease. Almost 20% of SKA-NEST patients found no epicardial lesions or non-obstructive epicardial lesions, and about 40-80% with 3-VD.[11] Multiessel diseases is a predictor of Major Acute Cardiovascular Event (MACE) on CAD patient after a long follow up monitoring.[12] All patients with diabetes and complex multivessel disease should be discussed within a Heart Team. Overall, the threshold for CABG should be lower in patients with diabetes than in individuals without diabetes mellitus, and in low surgical risk patients with the multivessel CAD, CABG should be favored over PCI, especially in the setting of complex disease.[13,14,15]

Electrocardiogram (ECG) on admission can be an early marker of risk.[16] Besides of a diagnostic need, ECG can also be used for assessing prognosis on patients with ischemic symptoms. ECG on admission can give an important information and risk stratification on ACS.[16,17,18] ECG findings of ST-segment depression can be a strong predictor for a worse outcome.[16,18,19,20,21] On substudy of FRISC II ECG can be found that an ST-segment depression on unstable angina pectoris patient is related to the increase of 100% 3-VD/Left main disease and this also can explain an increased risk of MACE.[20] Other modalities such as echocardiography, nuclear scintigraphy, or computed tomographic coronary angiography may provide additional diagnostic and prognostic information, but it may not necessarily be available in health services and may take a long time.[21]

Predicting 3-VD is an important thing in relation to the care or referral of ACS-NSTE because not all center, especially on a referral hospital in Indonesia, have an angiography coronary facility or a Heart Team which consisted of the interventionist cardiologist, noninvasive cardiologist, cardiothoracic surgeon, and other multidisciplinary teams to make a decision. An especially on National Healthcare System by this day, this procedure can be made as a protocol and guideline so the ACS-NSTE with DM can have an optimal intervention or revascularization.

Methods

This was a single-center, retrospective cohort study on ACS-NSTE with DM patients on Haji Adam Malik General Hospital (HAM Hospital) Medan. The sampling method for this research is a nonprobability sampling, which is consecutive sampling. Observers were taking all the subjects with ACS-NSTE with DM until the minimal sample is reached. This study was held by data taking from the medical record from January 2015 to December 2017. Inclusion criteria are ACS-NSTE with DM who were hospitalized on HAM Hospital and undergone coronary angiography on admission without the history of valvular heart disease, congenital heart disease, cardiomyopathy or other cardiac disease and without history of taking digitalis medicine. Exclusion criteria are the ACS-NSTE with DM patients with bundle branch block, left ventricular hypertrophy, pacemaker rhythm and hypokalemia.

An observer was checking a medical record of the ACS-NSTE patient to see anamneses, physical examination, ECG, thorax x-ray and cardiac enzyme and other laboratory findings, and also coronary angiography. All these data would be collected systematically. From this data, the ECG findings will be divided into the two group. The first group is the ACS-NSTE with DM with ST-segment depression and the other group is the ACS-NSTE with DM without ST-segment depression on admission. From each group, the coronary angiography data were collected to assess the 3-VD. All data were analyzed the significancies by statistical

analysis to compare the 3-VD occurrence by ECG on ACS-NSTE with DM. CAD 3-VD would also be assessed as a predictor by a multivariate analysis.

Descriptive statistics was used to represent characteristics at the entry of the study. The data were assessed for normality of distribution and transformed as appropriate. Results were expressed as frequencies and percentages for categorical variables, mean, standard deviation (SD) for normally distributed variables and median for non-normally distributed variables. The normality test of numerical variables on all subjects using Shapiro Wilk. Chi-Square test were used to determine the categorical variable on ST-segment depression. *Fisher exact* dan *Mann Whitney* test was used to assessed bivariate and comparing means of the ST-segment depression based on 3-VD and non 3-VD. Significant variables on univariate analysis were further analyzed on multivariate analysis by logistic regression on the categorical variable and linear regression on numerical variable. Interobserver variability test was assessed using Kappa test. The clinical outcome was presented as frequency, percentage, odds ratio, and 95% confidence interval. The significant p-value was below 0.05

Results

Total subjects of this study were 67 samples by the first group with ST-segment depression of 30 samples, and with the second group without ST-segment depression. Characteristics of research subjects can be seen in Table 1. From Table 1 can be seen the group with ST-segment depression has more cardiovascular risk factors such as hypertension, dyslipidemia, and CAD family history. Hypertension history was found in 27 samples (90%) in ST-segment depression group and 19 samples (51.4%) in without ST-segment depression group with a significant p-value of 0.001. Dyslipidmeia history was also higher in ST-segment depression group which was 12 samples (40%) and 6 samples (16.2%) in the group without ST-segment depression with a significant p-value of 0.029. CAD family history was also higher in ST-segment depression group which was 15 samples (50%) and 4 samples (10.8%) in the without ST-segment depression group, with a significant p-value of <0.001. No significant differences were found for smoking history in both groups. But it can be seen that more than half of both groups are smokers. On the physical examination were found that blood pressure and heart rate on admission were not significantly different.

Based on laboratory findings, there were significant differences on an increasing of troponin on both groups. On group with ST-segment depression, were found that higher troponin with mean 1.78 ± 3.93 as compare of 0.77 ± 1.64 on the group without ST-segment depression with the significant p-value of 0.018. Random blood glucose, fasting blood glucose and 2-hour postprandial were seen to be higher than normal but not significantly different on both groups. On both group were seen that HbA1C was higher from the standard for DM. HbA1C was seen higher on the group with ST-segment depression but not statistically significant. On the group with ST-segment depression, HbA1C was 8.6 ± 1.6, while 8.14 ± 1.93 on the group without ST-segment depression with the significant p-value of 0.313. Lipid profile finding was seen higher on the group with ST-segment depression but not statistically significant. There were no statistical significances on the lipid profile. On the group with ST-segment depression, creatinine was higher 1.37 ± 0.39 and 0.98 ± 0.28 on the group without ST-segment depression with the significant p-value < 0.001.

On echocardiography examination were seen the significant difference in the decreased left ventricular ejection fraction (LVEF). In group with ST-segment depression, LVEF <50% were 22 samples (73.3%) and LVEF >50% were 8 samples (26.7%). In Group without ST-segment depression, LVEF <50% were 12 (32.4%) samples and LVEF >50% were 25 (67.6%) with the significant p-value of 0.001. In ST-segment depression group were seen that ACS-NSTE with DM had a worse TIMI and GRACE score which describe more risk factors or other comorbidities in ST-segment depression group.

On Table 2 were seen that ECG was having a relationship with 3-VD on coronary angiography. 3-VD was found in 25 samples (80.6%) in ST-segment depression group and 6 samples (19.4%) in without ST-segment depression group. Meanwhile, non 3-VD was found over 5 (13.9%) samples in ST-segment depression group and 31 (86.1%) samples in without ST-segment depression group with OR (odds ratio) of 25.8 with the significant p-value <0.001.

Table 1. Sample Baseline Characteristic

Parameter	ST-segment Depression (n=30)	Without ST-segment Depression (n=37)	P
Sex (%)			
• Male	20 (66.7)	29 (78.4)	0.282
• Female	10 (33.3)	8 (21.6)	
Age (years ± SD)	56.6 ± 6.3	57.57 ± 9.	0.662
Systolic BP (mmHg ± SD)	137 ± 20	130 ± 21	0.202
Heart rate	85.3 ± 21.37	84.3 ± 22	0.574
Risk Factor			
Hypertension (%)	27 (90)	19 (51.4)	0.001
Dyslipidemia (%)	12 (40)	6 (16.2)	0.029
Family history of CAD (%)	15 (50)	4 (10.8)	< 0.001
Smoking (%)	18 (60)	21 (51.68)	0.789
LABORATORY FINDING			
Troponin	1.78 ± 3.93	0.74 ± 1.64	0.018
Random Blood Glucose	223 ± 100	263 ± 155	0.348
Fasting Blood Glucose	157.9 ± 59.7	143 ± 53.9	0.325
Two hour after meal Blood Glucose	212.8 ± 77.9	200.8 ± 67	0.504
HbA1C	8.6 ± 1.8	8.14 ± 1.93	0.313
Total Cholesterol	209.1 ± 73.69	194.6 ± 61.84	0.528
LDL	169 ± 43	132 ± 53	0.001
HDL	37.43 ± 11.73	43.5 ± 29.9	0.865
Trigliseride	151.8 ± 87.3	130.92 ± 50.28	0.504
Ureum	37.8 ± 18.2	44.77 ± 32.83	1
Creatinine	1.39 ± 0.4	1.08 ± 0.28	< 0.001
Hemoglobin	12.89 ± 1.9	13.02 ± 3.8	0.151
ECHOCARDIOGRAPHY			
LVEF(%)			
≥50	8 (26.7)	25 (67.6)	0.001
< 50	22 (73.3)	12 (42.4)	
CLINICAL STRATIFICATION			
TIMI Score			
Moderate + High	26 (86.7)	22 (59.6)	0.014
Low	4 (13.3)	15 (40.5)	
GRACE Score			
Moderate + High	25 (83.3)	20 (54.1)	0.011
Low	5 (16.7)	17 (45.9)	

Table 2. Association between ECG (With ST-segment Depression and Without ST-segment Depression) and The Incidence of 3-VD

ECG		Coronary Angiography		OR	p
		3-VD	Non 3-VD		
With ST-segment Depression	N (%)	25 (80.6)	5 (13.9)	25.8	< 0.001
Without ST-segment Depression	N (%)	6 (19.4)	31 (86.1)		
Total	N (%)	30 (100)	37 (100)		

From the bivariate analysis based on 3-VD grouping from Table 3 were found that besides ST-segment depression, family history, troponin value, creatinine value, LVEF, TIMI score, GRACE score was having a relationship with the 3-VD incidence. On 3-VD group, CAD family history risk factor was found in 13 samples (41.9%) and on non 3-VD was 6 (16.7%) samples with p-value 0.022. Troponin value was also higher in the 3-VD group which was 1.74 + 3.9 while on the non 3-VD group 0.27 + 1.7 with p-value 0.017. Creatinine value was also higher on 3-VD group with value was 1.27 + 3.6 mg/dL compare to non 3-VD group with value of 1.05 + 0.38 mg/dL with p-value 0.01. LVEF on the 3-VD group was seen to be lower. On 3-VD group were found that 22 (73.3%) sample had LVEF <50% while on non 3-VD with 12 (32.4%) samples with p-value 0.001. GRACE score and TIMI score were also higher on 3-VD. These described that other risk factors were also higher on 3-VD. Multivariate analysis on table 4 was also shown that ST-segment depression was the strongest predictor of 3-VD [OR 27.3 (6.117 – 121.851), p=0.000].

Table 3. Univariate Analysis of Factors Related to The 3-VD

Parameter	3-VD n = 31	NON 3-VD n = 36	P
Sex (%)			
• Male	23 (74.2)	26 (72.2)	0.856
• Female	8 (25.8)	10 (27.8)	
Age (years ± SD)	57 ± 6	57 ± 9	0.874
Systolic BP (mmHg ± SD)	134 ± 19	132 ± 22	0.636
Heart rate	84 ± 21	85 ± 21	0.860
Risk Factor			
Hypertension (%)	24 (77.4)	22 (61.1)	0.151
Dyslipidemia (%)	10 (32.7)	8 (22.2)	0.355
Family history of CAD (%)	13 (41.9)	6 (16.7)	0.022
Smoking (%)	21 (67.7)	18 (50)	0.142
ECG			
ST-segment Depression	25 (80.6)	5 (13.9)	<0.001
LABORATORY FINDING			
Troponin	1.74 ± 3.85	0.74 ± 1.71	0.017
Random Blood Glucose	220 ± 98	266 ± 157	0.324
Fasting Blood Glucose	158 ± 60	143 ± 53	0.454
Two hour after meal Blood Glucose	200 ± 64	211 ± 78	0.674
HbA1C	8 ± 1.76	8.4 ± 1.9	0.485
Total Cholesterol	195 ± 72	205 ± 62	0.346
LDL	140 ± 54	137 ± 59	0.646
HDL	37 ± 10	44 ± 30	0.743
Trigliseride	140 ± 73	139 ± 67	0.706
Ureum	41.6 ± 24	41.8 ± 30.2	0.521
Creatinine	1.27 ± 0.36	1.05 ± 0.4	0.01
Hemoglobin	12.8 ± 1.4	13.5 ± 2.42	0.097
ECHOCARDIOGRAPHY			
LVEF(%)			
≥50	8 (26.7)	25 (67.6)	0.001
< 50	22 (73.3)	12 (32.4)	
CLINICAL STRATIFICATION			
TIMI Score			
Moderate + High	26 (83.9)	22 (61.1)	0.039
Low	5 (16.1)	14 (38.9)	
GRACE Score			
Moderate + High	27 (87.1)	18 (50)	0.001
Low	4 (12.9)	18 (50)	

Tabel 4. Multivariate Analysis on 3-VD on ACS-NSTE with DM

	VARIABLES	P	OR	95% C.I.for EXP(B)	
				Lower	Upper
STEP 1	Hypertension	,211	,291	,042	2,008
	CAD Family History	,592	,587	,084	4,105
	Smoking	,128	3,479	,699	17,318
	ST-segment Depression	**,000**	**71,621**	**7,037**	**728,896**
	Troponin	,643	1,092	,752	1,585
	Creatinin	,628	,552	,050	6,099
	GRACE Score	,089	5,324	,773	36,663
	TIMI Score	,826	1,233	,191	7,951
	LVEF	,923	,922	,178	4,763
	Constant	,966	,857		
STEP 2	Hypertension	,212	,293	,043	2,012
	CAD Family History	,563	,574	,087	3,781
	Smoking	,122	3,518	,716	17,292
	ST-segment Depression	**,000**	**74,100**	**8,032**	**683,659**
	Troponin	,645	1,090	,754	1,577
	Creatinin	,622	,548	,050	5,984
	GRACE Score	,082	5,413	,809	36,210
	TIMI Score	,809	1,254	,201	7,834
	Constant	,963	,848		
STEP 3	Hypertension	,220	,304	,045	2,037
	CAD Family History	,591	,605	,097	3,786
	Smoking	,119	3,547	,721	17,463
	ST-segment Depression	**,000**	**75,610**	**8,236**	**694,132**
	Troponin	,664	1,083	,757	1,548
	Creatinin	,595	,526	,049	5,606
	GRACE Score	,069	5,663	,877	36,590
	Constant	,981	,919		
STEP 4	Hypertension	,221	,305	,046	2,039
	CAD Family History	,667	,678	,115	3,995
	Smoking	,113	3,606	,740	17,582
	ST-segment Depression	**,000**	**77,300**	**8,254**	**723,928**
	Creatinin	,566	,502	,048	5,297
	GRACE Score	,061	5,755	,920	35,995
	Constant	,986	,941		
STEP 5	Hypertension	,215	,302	,046	2,001
	Smoking	,117	3,540	,730	17,167
	ST-segment Depression	**,000**	**68,247**	**8,025**	**580,388**
	Creatinin	,548	,483	,045	5,188
	GRACE Score	,063	5,624	,912	34,697
	Constant	,947	,790		
STEP 6	Hypertension	,167	,270	,042	1,730
	Smoking	,101	3,710	,774	17,779
	ST-segment Depression	**,000**	**51,065**	**7,937**	**328,531**
	GRACE Score	,057	5,726	,948	34,598
	Constant	,620	,235		
STEP 7	Smoking	,070	3,978	,893	17,715
	ST-segment Depression	**,000**	**27,301**	**6,117**	**121,851**
	GRACE Score	**,030**	**5,597**	**1,181**	**26,517**
	Constant	,000	,026		

Discussion

On this study, there were two groups of samples which were samples on the group with ST-segment depression and without ST-segment depression. ST-segment depression group had more risk factors such as CAD family history, hypertension, dyslipidemia, and higher creatinine. The previous study was also shown the similar results. Jin et al described that ST-segment depression group had more comorbidities and older than without ST-segment depression.[22] FRISC II ECG study was as well shown that unstable angina pectoris on ECG with ST-segment depression was having more risk factors such as hypertension, older age, history of angina and infarction when compared to without ST-segment depression. On baseline characteristic table was

ST-segment depression.[22] FRISC II ECG study was as well shown that unstable angina pectoris on ECG with ST-segment depression was having more risk factors such as hypertension, older age, history of angina and infarction when compared to without ST-segment depression. On baseline characteristic table was shown that random blood glucose, fasting blood glucose and 2-hour post meal glucose and HbA1C were higher ST-segment depression group although it was not significantly differenced statistically. On those sample group, all those values were higher than normal limit value, showing that this population was suitable for uncontrolled DM. In ST-segment depression group, the HbA1C value was 8.6 ± 1.6 while in the group without ST-segment depression was 8.14 ± 1.93. This was similar to the previous study that on DM patients, plaque tearing was common.[23] DM was related to the worsening of plaque formation and intraluminal thrombosis that could cause infarction and cardiovascular deprivation.[3] Troponin value was also seen to be higher in ST-segment depression group. troponin value was higher in with ST-segment depression group. On group with ST-segment depression were seen the increasing of troponin higher with the mean value of 1.78 ± 3.93 compared to the group without ST-segment depression which had mean value 0.74 ± 1.64 with significant p-value 0.018. This similar explanation was shown previous literature. The presence of ST-segment depression was needed worse ischaemic condition than normal ECG or inversion of T wave.[24] If the ischaemic were worse, the myocardial necrosis would have happened (myocardial infarction).[25] These findings were similar to the study held previously by Kaul et al on 2003 and Jin et al on 2016.[22,26] Creatinine was also seen to be higher in ST-segment depression group. This probably was caused by the other risk factors on the group with ST-segment depression such as hypertension and the more reduced LVEF. More samples on ST-segment depression group were also seen to had LVEF <50% which was on 22 samples (73.3%) while on the group without ST-segment depression of 12 samples (32.4%) with significant p-value 0.001. These findings were also supported by the previous study held by Ghaffari in 2010 that described that ACS-NSTE with ST-segment depression had a more decreased LVEF. On group with ST-segment depression, LVEF found were 42.35 ± 9.47% while in without ST-segment depression group had a mean value of 50.42 ± 8% with the significant p-value of 0.001.21 A lower LVEF in ST-segment depression group could be caused by an ischemic condition which worsens and also the involvement more coronary artery. Hypertension and decreasing LVEF were also explained in the previous study which can cause a deprivation of renal function.[27,28] The assessment of risk stratification such as TIMI and GRACE score was higher in ST-segment depression group. This probably was caused by the more risk factor in ST-segment depression group besides the ST-segment depression which already added a score on this stratification.

This study was shown the significant incidence 3-VD between ST-segment depression group and without ST-segment depression group with OR 25.8 with the significant p-value 0.001. This study was also supported by the previous study. The 3-VD incidence on STEMI was significant (>50%) and could be up to 80%.[29] Similar prevalence also happened on ACS-NSTE.[30,31,32] Almost half of the patients were proved to had a significant multivessel stenosis.33 On study held by Diderholm showed that the ST-segment depression on unstable angina pectoris patients was related to the increasing 100% on 3-VD incidence.[20] The study held by Jin et all on 2016 was shown the higher occurrence of 3-VD in ST-segment depression group which was 53.5%.22 Ghaffari et all in 2010 were shown that ACS-NSTE with ST-segment depression had 58.3% 3-VD occurrence if compare to without ST-segment depression group.21 In this study, 3-VD on group with ST-segment depression was 24 samples (80.6%) while on the group without ST-segment depression was 6 samples (19.54%). This value was relatively higher than the previous study by Morgan 2004 than shown the diabetic pattern of the CAD with the significant stenosis, more spreading disease and the multivessel involvement.[4] Some studies were shown that DM patient had multivessel incidence which was higher.[34,35,36,37,38] On angiography result or autopsy, a patient with diabetes had 2-VD or 3-VD incidence higher than the non-DM patient.[39,40] On one big autopsy study were found that adult diabetecian had 83% chances of 2-VD or 3-VD.[41]

This result was shown that on ACS-NSTE with DM who had ST-segment depression on ECG had a 3-VD incidence higher than without ST-segment depression. Multivariate analysis was shown that ST-segment depression was the strongest predictor of 3-VD (OR 27.3 (6.117 – 121.851), p=0.000]. This also was supported by the previous study by Misumida, et al in 2015. ST-segment depression was found to be the strongest predictor of LM and or 3-VD on an ACS-NSTE patient with relative risk of 2.98 with the significant p-value of 0.001.[42]

Based on the results of data analysis obtained in this study can be concluded that the presence of ST-segment depression on admission ECG in NSTE-ACS with DM patients was associated with a higher incidence of 3-VD and was the strongest independent predictor of 3-VD.

Conflict of interest: None declared. Richard M.Jacoby , Richard W.Nesto.

References:

1. Irmalita, Juzar DA, Andrianto, et al. PedomanTatalaksanaSindromKoronerAkut. EdisiKetiga. 2015. Jakarta: PerhimpunanDokterSpesialisKardiovaskular Indonesia.
2. Barrett-Connor, E., & Orchard, T. J. (1985). Insulin-dependent diabetes mellitus and ischemic heart disease. *Diabetes Care*, 8(Supplement_1), 65–70. doi:10.2337/diacare.8.1.S65.
3. Jacoby, R. M., & Nesto, R. W. (1992). Acute Myocardial Infarction in the Diabetic Patient: Pathophysiology,Clinical Course and Prognosis. *Journal of the American College of Cardiology*, 20(3), 736–744. doi:10.1016/0735-1097(92)90033-J.
4. Morgan, K. P., Kapur, A., & Beat, K. J. (2004). Anatomy of coronary disease in diabetic patients: an explanation for poorer outcomes after percutaneous coronary intervention and potential target for intervention. *Heart (British Cardiac Society)*, 90(7), 732–738. doi:10.1136/hrt.2003.021014.
5. Wu, T., & Wang, L. (2003). Angiographic characteristics of the coronary artery in patients with type 2 diabetes. *Experimental and Clinical Cardiology*, 7(4), 199–200.
6. Soelistijo, S. A., Novida, H., Rudijanto, A., Soewondo, P., Swastika, K., Manaf, A., Konsensus Pengelola and anpencegahan Diabetes melitustipe 2 Di indonesia. 1st ed. 2015. PB PERKENI
7. Giraldez RR, Clare RM, Lopes RD, et al. (2013). Prevalence and clinical outcomes of undiagnosed diabetes mellitus and prediabetes among patients with high-risk non-ST-segment elevation acute coronary syndrome, *American Heart Journal*, 165, 918–925.
8. Conaway, D. G., O'Keefe, J. H., Reid, K. J., & Spertus, J. (2005). Frequency of undiagnosed diabetes mellitus in patients with acute coronary syndrome. *The American Journal of Cardiology*, 96(3), 363–365. doi:10.1016/j.amjcard.2005.03.076.
9. Norhammar, A., Tenerz, A., Nilsson, G., Hamsten, A., Efendíc, S., Rydén, L., & Malmberg, K. (2002). Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet*, 359(9324), 2140–2144. doi:10.1016/S0140-6736(02)09089-X.
10. Bartnik, M., Ryden, L., Malmberg, K., Ohrvik, J., Pyorala, K., Standl, E., & Soler-Soler, J. (2007). Oral glucose tolerance test is needed for appropriate classification of glucose regulation in patients with coronary artery disease: a report from the Euro Heart Survey on Diabetes and the Heart. *Heart (British Cardiac Society)*, 93(1), 72–77. doi:10.1136/hrt.2005.086975.
11. Bajraktari, G., & Henein, M. Y. (2016). Treatment Strategies of NSTEMI-ACS with Multivessel Disease. *International Cardiovascular Forum Journal*, 6, 3. doi:10.17987/icfj.v6i0.211.
12. Tsai, I., Wang, C. P., Lu, Y. C., Hung, W.-C., Wu, C.-C., Lu, L.-F., & Yu, T.-H. (2017). The burden of major adverse cardiac events in patients with coronary artery disease. *BMC Cardiovascular Disorders*, 17(1), 1. doi:10.1186/s12872-016-0436-7.
13. Farkouh, M. E., Domanski, M., Sleeper, L. A., Siami, F. S., Dangas, G., Mack, M., . . ., & Fuster, V. (2012). Strategies for multivessel revascularization in patients with diabetes. *The New England Journal of Medicine*, 367(25), 2375–2384. doi:10.1056/NEJMoa1211585.
14. Kappetein, A. P., Head, S. J., Morice, M. C., Banning, A. P., Serruys, P. W., Mohr, F.-W., & Mack, M. J. (2013). Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *European Journal of Cardio-Thoracic Surgery*, 43(5), 1006–1013. doi:10.1093/ejcts/ezt017.
15. Kapur, A., Hall, R. J., Malik, I. S., Qureshi, A. C., Butts, J., de Belder, M., . . ., & Beatt, K. J. (2010). Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDIA (Coronary Artery Revascularization in DIAbetes) trial. *Journal of the American College of Cardiology*, 55(5), 432–440. doi:10.1016/j.jacc.2009.10.014.
16. Savonitto, S., Ardissino, D., Granger, C. B., ... (1999). Prognostic value of the admission electrocardiogram in acute coronary syndromes. *Journal of the American Medical Association*, 281(8), 707–713. doi:10.1001/jama.281.8.707.
17. Damman, P., Holmvang, L., Tijssen, J. G. P., Lagerqvist, B., Clayton, T. C., Pocock, S. J., . . ., & de Winter, R. J. (2012). Usefulness of the admission electrocardiogram to predict long-term outcomes after non–ST-elevation acute coronary syndrome (from the FRISC II, ICTUS, and RITA-3 [FIR] Trials). *The American Journal of Cardiology*, 109(1), 6–12. doi:10.1016/j.amjcard.2011.08.002.
18. Cannon, C. P., McCabe, C. H., Stone, P. H., Rogers, W. J., Schactman, M., Thompson, B. W., . . ., & Braunwald, E. (1997, July). The Electrocardiogram Predicts One-Year Outcome of Patients With Unstable Angina and Non–Q Wave Myocardial Infarction: Results of the TIMI III Registry ECG Ancillary Study fn1fn1The TIMI III Clinical Centers are supported by Grant R01-HL42311 and the Data Coordinating Center by Grant R01-HL42428 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Additional support was supplied by Genentech, Inc., South San Francisco, California. *Journal of the American College of Cardiology*, 30(1), 133–140. doi:10.1016/S0735-1097(97)00160-5.
19. Hyde, T. A., French, J. K., Wong, C. K., Straznicky, I. T., Whitlock, R. M. L., & White, H. D. (1999). Four-year survival of patients with acute coronary syndrome without ST segment elevation and prognostic significance of 0.5 mm ST segment depression. *The American Journal of Cardiology*, 84(4), 379–385. doi:10.1016/S0002-9149(99)00319-7.
20. Diderholm, E., Andre'n, B., Frostfeldt, G., Genberg, M., Jernberg, T., & Lagerqvist, B. (2002). ST depression in ECG at entry indicates severe coronary lesions and large benefits of an early invasive treatment strategy in unstable coronary artery disease The FRISC II ECG substudy. *European Heart Journal*, 23(1), 41–49. doi:10.1053/euhj.2001.2694.

21. Ghaffari, S., Separham, A., & Pourafkari, L. (2010). Association of electrocardiographic changes with severity of coronary artery disease and short term outcome in patients with non-ST-segment elevation acute coronary syndromes. *Saudi Medical Journal*, 31(4), 400–440.
22. Jin Eun-Sun, Park Chang-Bum, Kim Dong-Hee, Hwang Hui-Jeong, Cho Jin-Man, et al. (2016). Comparative clinical implications of admission electrocardiographic findings for patients with non-ST-segment elevation myocardial infarction, *Medicine*, 95(37)(e4862) .
23. Davies, M. J. (2000). The pathophysiology of acute coronary syndromes. *Heart (British Cardiac Society)*, 83(3), 361–366. doi:10.1136/heart.83.3.361.
24. Jacoby, R. M., & Nesto, R. W. (1992). Acute Myocardial Infarction in the Diabetic Patient: Pathophysiology,Clinical Course and Prognosis. *Journal of the American College of Cardiology*, 20(3), 736–744. doi:10.1016/0735-1097(92)90033-J.
25. Luna, A. B. Electrocardiography normal and abnormalecgpatterns;electrocardiographic pattern of ischemia, injury and necrosis. 1st ed. 2007. Blackwell Futura.
26. Kaul, P., Fu, Y., Chang, W.-C., Harrington, R. A., Wagner, G. S., Goodman, S. G., & Armstrong, P. W. (2001, July). Prognostic value of ST segment depression in acute coronary syndromes: insights from PARAGON-A applied to GUSTO-IIb11Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON-A); Global Use of Strategies To Open occluded arteries in acute coronary syndromes (GUSTO-IIb). *Journal of the American College of Cardiology*, 38(1), 64–71. doi:10.1016/S0735-1097(01)01307-9.
27. Botdorf, J., Chaudhary, K., & Whaley-Connell, A. (2011). Hypertension in Cardiovascular and Kidney Disease. *Cardiorenal Medicine*, 1(3), 183–192. doi:10.1159/000329927.
28. Maile, M. D., Armstrong, W. F., Jewell, E. S., & Engoren, M. C. (2017). Impact of ejection fraction on infectious, renal, and respiratory morbidity for patients undergoing noncardiac surgery. *Journal of Clinical Anesthesia*, 36, 1–9. doi:10.1016/j.jclinane.2016.08.038.
29. Vlaar, P. J., Mahmoud, K. D., Holmes, D. R., Jr., van Valkenhoef, G., Hillege, H. L., van der Horst, I. C. C., & de Smet, B. J. G. L. (2011). Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease inpatients presenting with ST segment elevation myocardial infarction: a pairwise and network meta-analysis. *Journal of the American College of Cardiology*, 58(7), 692–703. doi:10.1016/j.jacc.2011.03.046.
30. Davies, M. J. (2000). The pathophysiology of acute coronary syndromes. *Heart (British Cardiac Society)*, 83(3), 361–366. doi:10.1136/heart.83.3.361.
31. Kastrati, A., Neumann, F. J., Mehilli, J., Byrne, R. A., Iijima, R., Büttner, H. J., . . ., & Schömig, A. (2008). Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *The New England Journal of Medicine*, 359(7), 688–696. doi:10.1056/NEJMoa0802944.
32. Thiele, H., Rach, J., Klein, N., Pfeiffer, D., Hartmann, A., Hambrecht, R., . . ., & Schuler, G. (2012). Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI Trial). *European Heart Journal*, 33(16), 2035–2043. doi:10.1093/eurheartj/ehr418.
33. Mehta, S. R., Granger, B. D., Boden, W. E., Steg, P. G., Bassand, J.-P., Faxon, D. P., & Yusuf, S. (2009). Early versus delayed invasive intervention in acute coronary syndrome. *The New England Journal of Medicine*, 360(21), 2165–2175. doi:10.1056/NEJMoa0807986.
34. Vigorita, V. J., Moore, G. W., & Hutchins, G. M. (1980). Absence of correlation between coronary arterial atherosclerosis and severity or duration of diabetes mellitus of adult onset. *The American Journal of Cardiology*, 46(4), 535–542. doi:10.1016/0002-9149(80)90500-7.
35. Dortimer, A. C., Shenoy, P. N., Shiroff, R. A., Leaman, D. M., Babb, J. D., Liedtke, A. J., & Zelis, R. (1978). Diffuse coronary artery disease in diabetic patients: fact or fiction? *Circulation*, 57(1), 133–136. doi:10.1161/01.CIR.57.1.133.
36. Melidonis, A., Dimopoulos, V., Lempidakis, E., Hatzissavas, J., Kouvaras, G., Stefanidis, A., & Foussas, S. (1999). Angiographic study of coronary artery disease in diabetic patients in comparison with nondiabetic patients. *Angiology*, 50(12), 997–1006. doi:10.1177/000331979905001205.
37. Waldecker, B., Waas, W., Haberbosch, W., Voss, R., Steen-Muller, M. K., Hiddessen, A., . . ., & Tillmanns, H. (1999). Type 2 diabetes and acute myocardial infarction: angiographic findings and results of an invasive therapeutic approach in type 2 diabetic versus nondiabetic patients. *Diabetes Care*, 22(11), 1832–1838. doi:10.2337/diacare.22.11.1832.
38. Natali, A., Vichi, S., Landi, P., Severi, S., L'Abbate, A., & Ferrannini, E. (2000). Coronary atherosclerosis in type II diabetes: angiographic findings and clinical outcome. *Diabetologia*, 43(5), 632–641. doi:10.1007/s001250051352.
39. Fein, F. S. (1982). Heart Diseases in diabetes. *Cardiovascular Reviews & Reports*, 3, 877–893.
40. Hamby, R., Sherman, L., Mehta, J., & Aintablian, A. (1976). Reappraisal of the role the diabetic state in coronary artery diseases. *Chest*, 70(2), 251–257. doi:10.1378/chest.70.2.251.
41. Waller, B. F., Palumbo, P. J., Lie, J. T., & Roberts, W. C. (1980). Status of the coronary arteries at necropsy in diabetes mellitus with onset after age 30 years. *The American Journal of Medicine*, 69(4), 498–506. doi:10.1016/S0149-2918(05)80002-5.
42. Misumida, N., Kobayashi, A., Fox, J. T., Hanon, S., Schweitzer, P., & Kanei, Y. (2016). Predictive Value of ST-Segment Elevation in Lead aVR for Left Main and/or Three-Vessel Disease in Non-ST-Segment Elevation Myocardial Infarction. *Annals of Noninvasive Electrocardiology*, 21(1), 91–97. Epub2015Apr17. doi:10.1111/anec.12272.

*****