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THE EFFECT OF PERCUTANEOUS CORONARY INTERVENTION (PCI) WITH DES ON ANTITHROMBIN-III (AT-III) AND THROMBIN ANTITHROMBIN COMPLEX (TAT) IN CORONARY HEART DISEASE PATIENTS AT HAJI ADAM MALIK GENERAL HOSPITAL

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Abstract
Introduction: Percutaneous coronary intervention (PCI) is currently the most commonly used invasive procedure in patients with coronary artery disease (CAD). PCI procedure can cause friction to the endothelium leading to the release and activation of thrombin. Thrombin activation increases the risk of restenosis. This study aims to determine the effect of PCI on AT-III and TAT levels in coronary artery disease (CAD) patients.
Methods: This study was conducted on CAD patients who will undergo PCI and have met the inclusion criteria. Blood samples were collected before and after PCI procedure and were examined for AT-III and TAT measurements. The value obtained is then analyzed based on changes in values before and after the PCI procedure, and is significant if the *p*-value <0.05.
Results: A total of 20 subjects, 17 males and 3 females. The mean of pre-PCI procedure for AT-III and TAT were 92.4 ± 7.17 and 6.1 ± 1.02 while the mean of post-PCI procedure for AT-III and TAT were 100.7 ± 12.78 and 5.17 ± 1.36, with a significant with the *p*-value <0.001
Conclusion: There is an increase level of AT-III and a decrease level of TAT in post-PCI CAD patients.

Introduction
Cardiovascular disease is considered a leading cause of death in developed countries and is increasing in many developing countries. Among these, coronary artery disease (CAD) is the most common cardiovascular disease and is associated with high rates of morbidity and mortality. It is estimated that by 2020, coronary artery disease will be the leading cause of death worldwide (1). Percutaneous coronary intervention (PCI) is currently the most commonly used invasive procedure in patients with CAD. Since the introduction of PCI by Gruentzig *et al.* in 1977, the technology has developed rapidly (2).

The PCI procedure can cause friction to the endothelium as when the catheter is directed retrograde through the blood vessel. Due to the friction of PCI on the surface of the endothelium, the endothelium will release and activate the thrombin contained therein (3). PCI involves a variety of events that cumulatively increase the risk of intra and post-procedure thrombosis (4). Thrombin activation is a major risk for complications of new thrombus formation and recurrent stenosis after PCI (3).

The blood itself contains a natural thrombin inhibitor called antithrombin III (often named antithrombin or abbreviated AT), which is the main inhibitor of thrombin, besides that AT also inhibits the plasma factors Xa, IXa, XIa and XIIa. Thrombin is neutralized by antithrombin, so the measurement of thrombin-antithrombin complex (TAT) is an in-vivo marker of thrombin formation (5). Thrombin generation in-vivo can be evaluated by measuring the thrombin-antithrombin (TAT) complex (6). AT and TAT test can be examination that determine the risk factors for thrombus/fibrin formation. So that the researchers were interested in examining the effect of PCI on AT-III and TAT levels in coronary artery disease (CAD) patients.

Method
This was a clinical quasi experimental study one group pretest - posttest analysis design. This study was carried out at H. Adam Malik Hospital Medan from November 2019 to November 2020. The inclusion criteria in this study were aged over 30 years and were patients with coronary artery disease who would undergo PCI. Exclusion criteria in this study were patients with sepsis, or were in an infectious condition and patients with malignancy. All subjects who meet the inclusion criteria were asked for consent to participate in this study.

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Baseline data were collected through history taking, physical examination and electrocardiography (ECG). The blood samples were taken twice, pre- and post-PCI procedure to be examined for AT and TAT levels. Blood samples were taken through the puncture vein from the median cubital vein and the blood was put into a vacutainer tube containing 0.2 ml of 3.2% sodium citrate anticoagulant until the blood stopped by itself (1.8 ml). Mix the blood with 3.2% sodium citrate by slowly turning the tube back and forth.

For AT-III examination, citrate blood with a ratio of 9: 1 immediately centrifuged for 15 minutes, at a rate of 1500 G then the plasma was transferred carefully into a closed plastic tube using a plastic pipette. then performed an examination of the level of AT-III activity. The examination of AT-III level was performed using the Chromogenic method using the Coatron A4 automatic device. For TAT examination, citrate blood with a ratio of 9: 1 immediately centrifuged for 15 minutes, at a rate of 1500 G and then the plasma were carefully collected and stored at -20 C or lower. TAT examination was performed using ab108907-Thrombin-Antithrombin Complex (TAT) Human Elisa KIT.

The AT-III and TAT values obtained before and after the action were carried out by the Shapiro-Wilk normality test, from this test it was found that the TAT values were normally distributed and the AT-III values were not normally distributed. Furthermore, to assess changes, the analysis was continued with the T dependent for TAT levels and Wilcoxon test for AT-III levels.

Result

A total of 20 patients with CAD who met the inclusion criteria. From this study, 17 subjects were male and 3 were female. The mean patient age was 40-59 years old (70%). The majority of subjects were diagnosed with ST-Elevation Myocardial Infarction (STEMI) (65%) and with most common comorbid were Diabetes and hypertension as shown in Table 1.

Of the 20 subjects of this study, it was reported that the mean AT-III value pre-PCI and post-PCI procedure were 92.4 ± 7.17 and 100.7 ± 12.78 respectively. After the PCI procedure, there was a significant increase in the AT-III value with a *p*-value <0.001 as seen in Table 2.

In this study, the mean TAT value pre-PCI and post-PCI procedure were reported 6.1 ± 1.02 and 5.17 ± 1.36. A significant decrease of TAT levels was reported with a p value <0.001 as seen in the table 3.

Table 1. Subjects Characteristics

Characteristics		n	%
Sex	Male	17	85.0
	Female	3	15.0
Age	< 40 years old	2	10.0
	40-59 years old	14	70.0
	≥ 60 years old	4	20.0
Diagnosis	STEMI	13	65.0
	NSTEMI	3	15.0
	UAP	2	10.0
	APS	2	10.0
Smoking	Yes	12	60.0
	No	8	40.0
Hypertension	Yes	14	70.0
	No	6	30.0
Diabetes Mellitus	Yes	10	50.0
	No	10	50.0
Total		20	100.0

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Table 2. AT-III levels pre- and post-PCI procedure

	Mean +/- SD	Median (Min - Max)	p value
Pre-	92.4 ± 7.17	93.1 (81 - 105.1)	<0.001*
Post-	100.7 ± 12.78	98.6 (84.3 - 143.2)	

Table 2. TAT levels pre- and post-PCI procedure

	Mean +/- SD	Median (Min - Max)	p value
Pre-	6.1 ± 1.02	6.15 (3.9 - 7.6)	<0.001*
Post-	5.17 ± 1.36	5 (3.2 - 7.4)	

Discussion

Our study reported a total of 20 CAD patient underwent PCI procedure with 85% of them were male. The high number of male sufferers of CAD is associated with the fact that the high prevalence of male smokers (62.9%) at the age of over 15 years and was 16 times higher than female (4.8%) (7). Smoking is considered one of the main risk factors for CAD, especially in ST-elevation myocardial infarction (STEMI) patients (8).

In our study, we also found that ST-segment elevation myocardial infarction STEMI was the most common diagnosis (65%) of patients underwent PCI, in which the restoration of coronary blood flow with PCI is an effective procedure for STEMI patients. Primary PCI is the evidence-based standard of care for STEMI patients within 12 hours of time symptom onset (9). The study conducted by Chen *et al.* (2019) also reported STEMI was the main diagnosis of CAD for PCI (10). The same thing was also reported by Miyachi *et al.* (2016) where STEMI was the most common diagnosis in their study (11).

In our study, TAT levels was found higher in pre-PCI procedure. CAD patients during ischemia with ST segment changes characterization on the ECG were reported to have a higher TAT levels compared to CAD patients without ST segment changes (12). In vivo thrombin generation, assessed by TAT, has been found to be increased in symptomatic coronary artery disease (13), and TAT were also reported to be increased in patients with recurrent coronary events (14).

AT-III is the most important type of antithrombin, and its activity is often used as a laboratory indicator for assessing anticoagulant levels and the detection of a thrombotic disease (15). Lu *et al.* (2018) reported that AT-III levels were associated with the severity of coronary artery obstruction (16). A predecessor study by Dewi (2012) found that AT-III levels in PCI with the Drug Eluting Stent (DES) and Bare Metal Stent (BMS), both shown an improvement in post-PCI samples. However, the AT-III level in PCI with DES were reported slightly higher level compared to PCI with BMS but the difference was not significant.

A lower level of AT-III level in pre-PCI patients were reported in our study. This could be due to an increased risk of thromboembolism in individuals with relative low AT-III level, especially in CAD patients (17). Antithrombin deficiency was associated with a 16x increased risk of venous thromboembolic events (18). Arterial thrombosis, as in myocardial infarction and stroke, is different from venous thrombosis, such as deep vein thrombosis (DVT) and pulmonary embolism (PE) (19). Arterial and venous thrombosis have different pathophysiology and treatment, but the risk factors are overlap (20). An inverse relationship was found between antithrombin levels and arterial thromboembolism (21). The incidence of CAD when associated with AT-III levels was related to AT-III deficiency, whereas the frequency of AT-III activity below <75% was reported in 23.3% of CAD patient compared to patients without CHD (22).

Conclusion

There was an increase of AT-III level and a decrease of TAT level in post-PCI patients, where the change was statistically significant with *p*-value <0.001

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