Long Period and High Level of D-Dimer after Coronary Artery Bypass Grafting Surgery

Zanxin Wang,1 MD, Zhaoyang Qian,3 MD, Jing Ren,2 MD, Jianlong Men,2 MD, Junmin Wen,1 MD and Minxin Wei,1 MD

Summary

Hyper-coagulation after off-pump coronary artery bypass grafting (OPCAB) is one of the main reasons for graft thrombosis. D-dimer is closely linked to the activation of coagulation. Few studies have reported the variation range and long-term abnormal coagulation after OPCAB in the Chinese population. Our study aimed to determine the characteristics and value of D-dimer after OPCAB.

In this prospective study, 265 patients who underwent OPCAB for the first time were recruited from 2011 to 2012. The D-dimer level of the patients was tested before surgery and on the 1st, 4th, and 14th day, and 1st, 2nd, and 3rd month after surgery. Clinical data in the perioperative period and during the one-year follow-up period were recorded.

D-dimer level increased from day 4 after OPCAB ([1321.9 ± 36.4] μg/L), peaked at 1 month ([2839.7 ± 101.4] μg/L), and decreased to the baseline ([370.3 ± 260.2] μg/L) 3 months after surgery. No death occurred, but 25 (10%) patients suffered recurrent angina in the one-year follow-up. They had significantly higher D-dimer level at one month after OPCAB than those of patients who did not suffer from angina. Preoperative ejection fraction <50% and D-dimer level >2915 μg/L at one month after surgery were significantly associated with the recurrent angina.

After OPCAB, patients have a higher level of D-dimer. And this lasts for a long period (about 3 months). It may reflect a certain degree of hypercoagulable and hyperfibrinolytic state after OPCAB.

(Key words: Cardiac surgery, Angina pectoris, Coagulation)

Coronary artery bypass grafting (CABG) surgery has become the major surgical therapeutic method for coronary diseases. Off-pump CABG (OPCAB) prevents the harmful effects of extracorporeal circulation and reduces the consumption of coagulation products.1-3 However, shortly after the operation, patients are in a relatively hyper-coagulative state, which contributes to a high incidence of thrombotic events.4,5 According to previous studies, hyper-coagulation and hyperfibrinolysis after OPCAB usually peak on the fourth day after the operation.6,7 However, few studies have reported the range of variation and long-term abnormal coagulation status in patients after OPCAB. In addition, the time limit for the anti-coagulation and anti-platelet therapy has not yet been established. Therefore, to obtain prompt and accurate knowledge about the risks of thrombosis in patients after OPCAB and to introduce the targeted anticoagulant therapy, it is important to ease the hyper-coagulable state of patients and reduce the incidence of adverse events.

D-dimer is a marker that is closely related to the activation of coagulation and fibrinolysis,8 and is especially significant for the activation of thrombosis. Increased level of D-dimer indicates a state of hyper-coagulation, or the formation of fresh thrombosis and increased fibrinolysis.9 Patients with coronary diseases, especially those with angina pectoris and myocardial infarction, show higher D-dimer levels than those observed in normal individuals.10 In patients suffering from chest pain, plasma D-dimer level > 5000 μg/L has an independent diagnostic value for myocardial infarction. Further, emerging evidence endorses a 'predictive' role of increased D-dimer level, since its measurement provides prognostic data for a variety of conditions, including cardiovascular diseases, venous thromboembolism, and thrombosis (especially thrombus in grafts).11,12 However, few studies have reported the long-term D-dimer levels after CABG.
**Table 1. Clinical and Surgical Characteristics of Patients**

| Characteristic | Value |
|---------------|-------|
| Gender (male/female) | 167/98 |
| Age (years) | 63.3 ± 8.4 |
| Height (cm) | 169.1 ± 6.8 |
| Weight (kg) | 74.2 ± 11.4 |
| BMI (kg/m²) | 25.9 ± 3.0 |
| FEV₁ (L) | 2.4 ± 0.7 |
| BNP (g/mL) | 147.9 ± 14.3 |
| ACT Pre-OP (s) | 174.2 ± 41.1 |
| TG (mmol/L) | 1.6 ± 0.7 |
| TC (mmol/L) | 4.5 ± 1.2 |
| No. of diseased vessel | 3.0 ± 0.2 |
| LVEF (%) | 54.9 ± 11.6 |
| LVEDD (mm) | 53.6 ± 7.2 |
| Smoking, n (%) | 135 (51%) |
| Hypertension, n (%) | 170 (64%) |
| Diabetes, n (%) | 114 (43%) |
| Aspirin withdrawal pre-op (days) | 7.3 ± 1.8 |
| Clopidogrel withdrawal pre-op (days) | 7.3 ± 1.4 |
| Surgery time (minutes) | 275.2 ± 47.1 |
| Heparin dosage in Operation (mg) | 116.2 ± 28.5 |
| Protamine dosage in Operation (mg) | 107.4 ± 34.3 |
| No. of grafting | 3.8 ± 0.5 |
| Blood loss (mL) | 594.9 ± 221.7 |
| Ventilation time (hours) | 20.4 ± 23.5 |

Data are presented as mean ± SD or numbers. BMI indicates body mass index; FEV₁, forced expiratory volume in one second; BNP, B-type natriuretic peptide; ACT, activated clotting time; TG, triglyceride; TC, total cholesterol; LVEF, left ventricular ejection fraction; and LVEDD, left ventricular end-diastolic dimension.

The present study was designed to find out the characteristics and change of D-dimer after OPCAB.

**Methods**

**Study population:** In this observational and prospective study, 265 patients who underwent elective OPCAB for the first time were recruited from August 2011 to April 2012 in Tianjin Medical University General Hospital (Tianjin, China). The local ethics committee of the hospital approved the study protocol. Written informed consent was obtained from all participants. This study was in compliance with the principles outlined in the Declaration of Helsinki. All patients met the indications for CABG. Patients with a history of cardiac surgery, those who underwent emergency surgery, those in an inflammatory reaction state (infection, active arthritis, malignant tumor, etc.) before surgery, those on hormones and other anti-inflammatory drugs before surgery, those with preoperative respiratory insufficiency or coagulation dysfunction, those suffering from serious neurological disease, those with chronic hepatic and renal insufficiency, and those in whom CABG was combined with other cardiac surgery were excluded from the study.

**Surgical procedure:** All operations were performed by the same group of surgeons. OPCAB was performed via median sternotomy with the internal thoracic artery, radial artery, and/or saphenous vein as the conduit. A U-shaped stabilizer (Octopus®; Medtronic Inc., Minneapolis, MN, USA) was used to dampen the movement of the beating heart and, consequently, to isolate the region for anastomosis. Proximal anastomosis of the aorta was performed using tangential clamping. Heparin (1.5 mg/kg) was administered to achieve an activated clotting time > 300 seconds. At the end of the grafting procedure, the effect of heparin was reversed by protamine administration (1:1 ratio) to achieve an ACT of approximately 150-170 seconds.

**Peri- and postoperative management:** Aspirin and clopidogrel were discontinued 3-5 days prior to surgery and replaced by low-molecular-weight heparin until the day before surgery. Postoperative treatment in the ICU was standardized. Low-molecular-weight heparin therapy was begun at night of the surgery day (body weight < 60 kg, 0.4 mL, twice a day; body weight > 60 kg, 0.6 mL, twice a day). Aspirin (100 mg) was administered one day after the surgery. Double anti-platelet therapy was prescribed for one year.

**Sample and data collection:** Peripheral blood samples were taken before surgery and on day 1, 4, 14 and 1, 2, and 3 months after surgery. General clinical data of the patients such as gender, age, weight, height, time of surgery, number of bypass grafts, ventilation time, drainage volume, postoperative left ventricular ejection fraction, and cardio-cerebro-vascular complications in the perioperative period were recorded.

**Laboratory inspection:** A dot immune gold filtration assay was used to test patient serum to detect D-dimer levels. Nyco Card READER II U2 DOT Read meter (Norway Axis-Shield PoC AS, Oslo, Norway) was used to inspect the intensity of the red color of the membrane, which was proportional to the D-dimer concentration. The normal range of D-dimer is 0–500 μg/L.⁹

The clinical and biochemical indices were detected in the hospital laboratory.

**Follow-up:** All patients were followed up one year after surgery in the outpatient department of our hospital. The clinical data was recorded by a cardiologist.

**Statistical analysis:** Statistical analysis was performed using SPSS/Win (Version 22.0, Chicago, IL, USA). Data are presented as median (quartiles) or mean ± standard deviation. The χ² test was used to analyze the relationship between categorical variables. Nonparametric Mann-Whitney U test and Kruskal-Wallis test, as appropriate, were used to compare the different outcomes between subgroups. An exploratory evaluation for additional cut points of different variables was performed using the receiver operating characteristic (ROC) curve analysis. COX regression was used to analyze the risk factors of outcome with hazard ratios and the 95% confidence interval (CI). The survival curve during the one-year follow-up to assess the D-dimer level was analyzed using the Kaplan-Meier method, and statistical assessment was performed using the log-rank test. F-values < 0.05 were considered statistically significant.

**Results**

All patients completed the study, and no deaths or major complications (such as cerebral complications, renal, and hepatic dysfunction) were reported. The average...
duration of surgery was (275.17 ± 47.13) minutes. No incidence of perioperative myocardial infarction was reported. The general clinical and surgical data are detailed in Table I. Perioperative liver and renal functions of the patients were within the normal range.

The preoperative D-dimer basal level was (222.2 ± 58.8) μg/L; it continued to increase from day 4 after OPCAB ([1321.9 ± 36.4] μg/L) and peaked at 1 month after the surgery ([2839.7 ± 101.4] μg/L). Thereafter, it decreased to the basal level at 3 months after surgery ([370.3 ± 260.2] μg/L). The perioperative change in D-dimer level is demonstrated in Figure 1A.

At the one-year follow-up, no patient died. Twenty-five (10%) patients suffered from recurrent angina pectoris, most of the symptoms of which could be relieved after dual anti-platelet therapy, β-blockers, and nitrate consumption. All the 25 patients received coronary computed tomography angiogram (CTA) examination. The LIMA was well, but some vein grafts were narrow at the distal anastomosis or aorta anastomosis. One of them is displayed in Figure 2. The CTA revealed a normal left mammary artery to left anterior descending artery (Figure 2A). The radial artery to the diagonal branch was also filled (Figure 2B). However, the vein graft to the posterior descending artery showed diffuse lesions (Figure 2C). Only one patient suffered from unstable angina. Coronary angiography (CAG) showed a normal left mammary artery to left anterior descending (Figure 2D). The saphenous veins to the diagonal branch and left circumflex branch were filled well (Figure 2E). However, the right coronary artery, which was mild stenosis one year ago, had severe stenosis (Figure 2F). After PCI, it was filled well (Figure 2G).

These patients had significantly higher levels of D-dimer at one month after OPCAB than the D-dimer levels of patients without angina ([3256.4 ± 154.7 μg/L versus 1816.8 ± 64.6 μg/L, \(P = 0.001\)], Figure 1B). ROC curves explored the relation between D-dimer level one month after OPCAB and angina pectoris at one-year follow-up. Area under the curve was 0.844 (95% CI: 0.746–0.943). The D-dimer cut-off level of > 2915 μg/L predicted angina with a sensitivity of 85.7% and a specificity of 66.0% (Figure 1C). Kaplan-Meier curve for the cumulative event indicated that a D-dimer level > 2915 μg/L was also associated with recurrent angina pectoris (\(\chi^2 = 11.498, P = 0.001\); Figure 1D). When patients were stratified according to the cut-off D-dimer level of 2915 μg/L, the recurrence of angina pectoris was significantly higher in patients with D-dimer level above 2915 μg/L compared to those with D-dimer level below this cut-off (\(\chi^2 = 11.498, P = 0.001\); Figure 1D).

Figure 1. A: Perioperative changes in D-dimer levels. Data are presented as mean ± SD. * \(P < 0.001\) as compared to the baseline. B: Perioperative D-dimer levels in different patient groups (those suffering from recurrent angina and those without angina). Data are presented as mean ± SD. * \(P < 0.001\) as compared to the group of patients without angina. C: Receiver operating characteristic (ROC) curves of D-dimer levels for predicting recurrent angina one year after OPCAB. D: Kaplan-Meier curve for the cumulative event of recurrent angina pectoris per D-dimer level above and below the cut-off value (2915 μg/L).
2915 μg/L, no significant differences were observed between them (Table II). There was no difference in medication between patients with D-dimer ≤ 2915 μg/L and > 2915 μg/L, either.

COX regression was used to analyze the predictors of angina one year after OPCAB. In univariate analysis, preoperative brain natriuretic peptide (HR = 1.002, 95% CI: 1.001–1.004), troponin T (HR = 2.983, 95% CI: 1.518–5.862), EF < 50% (HR = 2.387, 95% CI: 1.078–5.285), postoperative left ventricular end-diastolic diameter (HR = 1.152, 95% CI: 1.049–1.265), postoperative EF < 50% (HR = 3.443, 95% CI: 1.475–8.034), and D-dimer level > 2915 μg/L at one month (HR = 5.308, 95% CI: 1.781–15.819) were significantly associated with angina one year after OPCAB (Table III). When multivariate COX regression was applied, preoperative EF < 50% (HR = 3.311,
thrombotic events. Previous research has shown that and hyper-fibrinolysis, which increases the incidence of circulation on blood cells. However, in a short time after one month after surgery (HR = 5.694, 95% CI: 1.894~8.026) and D-dimer level > 2915 μg/L at one month after OPCAB; patients usually suffered from delayed hyper-coagulation after OPCAB; the concentration of D-dimer starts increasing on the first day, and is considerably high on day 4 after the operation. However, most studies have reported D-dimer levels in the first two weeks after surgery, while longer-term clinical observations have rarely been reported. Our results demonstrated that within one month after OPCAB, D-dimer level showed a continuous increase till it reached a peak, after which it reduced to baseline until the third month after OPCAB. In the first month after the operation, patients are still in the thrombotic and thrombolytic phase. As the specific degradation product of fibrin, D-dimer is the major marker of thrombosis and thrombolytic activity. As the specific degradation product of fibrin, D-dimer is the major marker of thrombosis and thrombolytic activity.17) These symptoms were reported to persist for weeks to months.18-20)

Discussion

OPCAB reduces the harmful effects of extracorporeal circulation on blood cells. However, in a short time after the operation, patients are in a state of hyper-coagulation and hyper-fibrinolysis, which increases the incidence of thrombotic events. Previous research has shown that compared with extracorporeal circulation, patients usually suffered from delayed hyper-coagulation after OPCAB; the concentration of D-dimer starts increasing on the first day, and is considerably high on day 4 after the operation. However, most studies have reported D-dimer levels in the first two weeks after surgery, while longer-term clinical observations have rarely been reported. Our results demonstrated that within one month after OPCAB, D-dimer level showed a continuous increase till it reached a peak, after which it reduced to baseline until the third month after OPCAB. In the first month after the operation, patients are still in the thrombotic and thrombolytic phase. As the specific degradation product of fibrin, D-dimer is the major marker of thrombosis and thrombolysis.13-16) Elevated concentration of D-dimer in peripheral blood indicates hyper-coagulation or formation of fresh thrombus and increased fibrinolysis.15) These symptoms are also likely related to the formation and coagulation of

Table II. Comparison of Clinical Data among Patients with a D-Dimer Level Cut-Off Level of 2915 μg/L at One Month after OPCAB

| Variables               | Univariate COX HR (95% CI) | P     | Multivariate COX HR (95% CI) | P     |
|-------------------------|-----------------------------|-------|-----------------------------|-------|
| Age (years)             | 63.8 ± 7.2                  | 62.9 ± 7.0 | 0.571                       |       |
| Gender (male, %)        | 113 (64%)                   | 54 (61%) | 0.611                       |       |
| BMI (kg/m²)             | 27.0 ± 1.9                  | 24.1 ± 5.4 | 0.584                       |       |
| Diabetes (n, %)         | 73 (41%)                    | 41 (46%) | 0.760                       |       |
| Hypertension (n, %)     | 104 (59%)                   | 66 (74%) | 0.299                       |       |
| BNP (pg/mL)             | 110.9 ± 15.5                | 224.9 ± 26.5 | 0.060                       |       |
| TG (mmol/L)             | 1.4 ± 0.9                   | 2.2 ± 0.7 | 0.730                       |       |
| TC (mmol/L)             | 4.6 ± 2.1                   | 4.5 ± 1.6 | 0.924                       |       |
| LVEF (%)                | 56.5 ± 10.5                 | 52.8 ± 12.2 | 0.161                       |       |
| LVEDD (mm)              | 50.9 ± 5.2                  | 54.2 ± 6.8 | 0.061                       |       |
| Surgery time (minutes)  | 273.0 ± 42.4                | 264.3 ± 50.1 | 0.437                       |       |
| Blood loss (mL)         | 420 ± 246                   | 375 ± 153 | 0.137                       |       |
| No. of grafting         | 3.9 ± 0.9                   | 3.5 ± 0.9 | 0.734                       |       |
| Atrial fibrillation     | 16 (9%)                     | 11 (12%) | 0.647                       |       |

Data are presented as mean ± SD or numbers. BMI indicates body mass index; BNP, B-type natriuretic peptide; TG, triglyceride; TC, total cholesterol; LVEF, left ventricular ejection fraction; and LVEDD, left ventricular end-diastolic dimension.

Table III. Univariate and Multivariate COX Regression for Angina Pectoris One Year after OPCAB

| Variables               | Univariate COX HR (95% CI) | P     | Multivariate COX HR (95% CI) | P     |
|-------------------------|-----------------------------|-------|-----------------------------|-------|
| Gender (male)           | 0.897 (0.302–2.666)         | 0.846 |                            |       |
| Age                     | 1.009 (0.939–1.084)         | 0.816 |                            |       |
| BMI                     | 0.880 (0.648–1.196)         | 0.414 |                            |       |
| Hypertension            | 0.947 (0.632–1.420)         | 0.793 |                            |       |
| Diabetes                | 0.638 (0.376–1.083)         | 0.096 |                            |       |
| Smoking                 | 0.722 (0.220–2.374)         | 0.592 |                            |       |
| Drinking                | 0.706 (0.207–2.409)         | 0.578 |                            |       |
| No. of grafting         | 1.158 (0.408–3.289)         | 0.783 |                            |       |
| Surgery time            | 0.987 (0.974–1.001)         | 0.062 |                            |       |
| BNP Pre-OP              | 1.002 (1.001–1.004)         | 0.003 | 1.004 (0.999–1.009)        | 0.119 |
| CKMB Pre-OP             | 1.004 (0.996–1.013)         | 0.333 |                            |       |
| TrT Pre-OP              | 2.983 (1.518–5.862)         | 0.025 | 7.702 (0.982–4.993)        | 0.058 |
| LVEDD Pre-OP            | 1.049 (0.960–1.146)         | 0.288 |                            |       |
| LVEF Pre-OP < 50%       | 2.387 (1.076–5.285)         | 0.005 | 3.311 (1.366–8.026)        | 0.018 |
| LVEDD Post-OP           | 1.152 (1.049–1.265)         | 0.020 | 1.208 (0.871–1.675)        | 0.258 |
| LVEF Post-OP < 50%      | 3.443 (1.475–8.034)         | 0.017 | 12.108 (0.984–49.010)      | 0.052 |
| D-dimer > 2915 μg/L     | 5.308 (1.781–15.819)        | 0.001 | 5.694 (1.894–15.117)       | 0.001 |

HR indicates hazard ratio; CI, confidence interval; BMI, body mass index; BNP, B-type natriuretic peptide; CKMB, creatine kinase MB; TrT, troponin T; LVEDD, left ventricular end-diastolic dimension; and LVEF, left ventricular ejection fraction.
fibrin in blood vessels and unstable atherosclerotic plaque activities. The risks of thrombosis at bypass anastomosis should be considered first for OPCAB. In addition, the large chest wound created by the operation and long cuts in the legs indicate a longer bleeding period and thrombosis after operation, which is another reason for the slow decrease in D-dimer levels.

To our knowledge, few studies conducting long-term follow-up of D-dimer levels with adverse outcomes after OPCAB have been reported. Our findings revealed that during follow-ups, 10% of patients suffered recurrent angina pectoris one year after operation. The D-dimer levels in this group of patients were obviously higher than those in patients without angina pectoris, and were most significant in the first month after operation. D-dimer level > 2915 μg/L at one month after operation is an indicator of angina pectoris, and verifies endothelial acceleration following damage to the graft endothelium, neointimal formation, or atherosclerosis. Consequently, the platelets are activated to speed up coagulation, leading to the hypercoagulation state observed in patients. Dead cells stimulate the fibrinolytic system and promote the degradation of fibrin. Therefore, the concentration of D-dimer is remarkably increased. After OPCAB, patients are in a state of hyper-coagulation and hyper-fibrinolysis, and have a high risk of suffering from thrombus, especially in grafts, which affects the long-term patency of grafts and impacts the long-term fractional survival of patients. The predictive role of D-dimer in patients at a risk of venous thrombosis was confirmed by a European study. Further, consistently high D-dimer levels after one month of anti-coagulation and anti-platelet therapy could suggest easy recurrence of thrombus. Hence, plasma D-dimer level could be a promising biomarker to identify patients at an increased risk for angina after OPCAB in a simple and rapid manner. These patients require special attention after surgery.

The present study also found that preoperative EF < 50% is another risk factor for recurrent angina. The causes may be that poor cardiac function before operation is reflected in serious coronary artery lesion. The symptoms are relieved shortly after the operation. However, due to poor vessel condition, the long-term efficacy of bypass will be inevitably affected, consequently increasing the risk for recurrence of angina pectoris. This finding differs from previous results. Inci, et al. showed that EF > 50% is an independent predictor for re-operation after CABG. This can be explained by the increased risk of recurrent angina in patients with a low preoperative EF. But it is possible that patients with low EF died before a re-do operation was needed or performed.

This study, however, had some limitations. Firstly, it was a single-center study with a relatively small sample size. And the patients we choose had good cardiac function without serious disease. This is our first stage research. We will evaluate D-dimer level in patients with poor health conditions and low cardiac output in a further study. Secondly, our results were limited to patients who underwent off-pump CABG and lack comparison with patients who undergo on-pump CABG and other cardiac surgeries. Therefore, further large-scale studies are warranted to confirm our findings.

In conclusion, after OPCAB, patients are in a relatively hyper-coagulation state, which lasts for a long period of time. Consecutive detection of D-dimer level may be a simple, easily available, and valuable method to reflect a certain degree of hypercoagulable and hyperfibrinolytic state after OPCAB.

Disclosures

Conflicts of interest: None declared.

References

1. Bicer M, Senturk T, Yanar M, et al. Effects of off-pump versus on-pump coronary artery bypass grafting: apoptosis, inflammation, and oxidative stress. Heart Surg Forum 2014; 17: E271-6.
2. Men JL, Ren J, Ma R, Wang ZX. High level of von Willebrand factor in non-ST segment elevation myocardial infarction patients predicted cardiovascular ischemic events after off-pump coronary artery bypass surgery. Int Heart J 2015; 56: 298-302.
3. Vieira de Melo R, Hube W, Rezende P, et al. On-pump versus off-pump coronary artery bypass surgery in patients older than 60 years: five-year follow-up of MASS III trial. J Cardiothorac Surg 2014; 9: 136.
4. Nomura T, Suzuki N, Takamura S, Kyono H, Kozuma K. Three-year clinical and angiographic outcomes after everolimus-eluting stent implantation in patients with a history of coronary artery bypass grafting. Int Heart J 2016; 57: 158-66.
5. Scrascia G, Rotunno C, Nanna D, et al. Pump blood processing, salvage and re-transfusion improves hemoglobin levels after coronary artery bypass grafting, but affects coagulative and fibrinolytic systems. Perfusion 2012; 27: 270-7.
6. Paparella D, Galeone A, Venneri MT, et al. Activation of the coagulation system during coronary artery bypass grafting: comparison between on-pump and off-pump techniques. J Thorac Cardiovasc Surg 2006; 131: 290-7.
7. Yachi T, Watanabe G, Tonita S. Activation of coagulation and fibrinolysis after off-pump coronary artery bypass grafting with and without endotracheal general anesthesia. Innovations (Phila) 2010; 5: 444-9.
8. Raja SG, Akhtar S. Hypercoagulable state after off-pump coronary artery bypass grafting: evidence, mechanisms and implications. Expert Rev Cardiovasc Ther 2011; 9: 599-608.
9. Akgul O, Uyarul H, Pusuroglu H, et al. Predictive value of elevated D-dimer in patients undergoing primary angioplasty for ST elevation myocardial infarction. Blood coagul Fibrinolysis 2013; 24: 704-10.
10. Becattini C, Lignani A, Masotti L, Forte MB, Agnelli G. D-dimer for risk stratification in patients with acute pulmonary embolism. J Thromb Thrombolysis 2012; 33: 48-57.
11. Mahe I, Bergmann JF, Chassany O, dit-Sollier CB, Simoneau G, Drouet L. A multicentric prospective study in usual care: D-dimer and cardiovascular events in patients with atrial fibrillation. Thromb Res 2012; 129: 693-9.
12. Ay C, Dunkler D, Pirkner R, et al. High D-dimer levels are associated with poor prognosis in cancer patients. Haematologica 2012; 97: 1158-64.
13. Wen D, Du X, Dong JZ, Zhou XL, Ma CS. Value of D-dimer and C reactive protein in predicting inhospital death in acute aortic dissection. Heart 2013; 99: 1192-7.
14. Rodger MA, Le Gal G, Wells P, et al. Clinical decision rules and D-Dimer in venous thromboembolism: current controversies and future research priorities. Thromb Res 2014; 134: 763-8.
15. Kaireviciute D, Lip GY, Balkrishnan B, et al. Intracardiac expression of markers of endothelial damage/dysfunction, inflammation, thrombosis, and tissue remodeling, and the development
of postoperative atrial fibrillation. J Thromb Thrombost 2011; 9: 2345-52.

16. Shitrit D, Bar-Gil Shitrit A, Rudensky B, Sulkes J, Gutterer N, Zviony D. Role of ELISA D-dimer test in patients with unstable angina pectoris presenting at the emergency department with a normal electrocardiogram. Am J Hematol 2004; 77: 147-50.

17. Di Castelnuovo A, Agnoli C, de Curtis A, et al. Elevated levels of D-dimers increase the risk of ischaemic and haemorrhagic stroke. Findings from the EPICOR Study. Thrombo Haemost 2014; 112: 941-6.

18. Arnaud E, Barbalat V, Nicaud V, et al. Polymorphisms in the 5’ regulatory region of the tissue factor gene and the risk of myocardial infarction and venous thromboembolism: the ECTIM and PATHROS studies. Etude Cas-Temoins de l’Infarctus du Myocarde. Paris Thrombosis case-control Study. Arterioscler Thrombo Vasc Biol 2000; 20: 892-8.

19. Song J, Kweon TD, Song Y, Lee EY, Kim SJ, Park R. Analytical and clinical performance of a new point of care LABGEOIB D-dimer test for diagnosis of venous thromboembolism. Ann Clin Lab Sci 2014; 44: 254-61.

20. van der Hulle T, den Exter PL, Erkens PG, et al. Variable D-dimer thresholds for diagnosis of clinically suspected acute pulmonary embolism. J Thromb Haemost 2013; 11: 1986-92.

21. Kong XL, Zhang X, Zhang SJ, Zhang L. Plasma Level of D-dimer is an Independent Diagnostic Biomarker for Deep Venous Thrombosis in Patients with Ischemic Stroke. Curr Neurovasc Res 2016; 13: 100-6.

22. Inci S, Arslan S, Bakirci EM, Tas MH, Gundogdu F, Karakelleoglu S. Predictors of reintervention after coronary artery bypass grafting. Eur Rev Med Pharmacol Sci 2014; 18: 66-70.