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Original Research Article

Effect of atorvastatin combined with interventional therapy for acute myocardial infarction

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Abstract

Purpose: *To evaluate the coronary thrombolytic effect of atorvastatin plus percutaneous coronary intervention (PCI) for the treatment of acute myocardial infarction.*
Methods: *From April 2019 to October 2020, 88 patients with acute myocardial infarction who were treated in Zhangqiu District People's Hospital were randomly assigned to receive either PCI (conventional group) or PCI plus atorvastatin (combined group). Myocardial injury index, TnI, and creatine kinase isoenzyme (CK-MB) were used to determine myocardial injury, while serum cTnI was determined using enzyme-linked immunosorbent assay (ELISA). Creatine kinase isoenzyme (CK-MB) levels were determined by immunosuppression method. Cardiac ultrasound was used to measure and compare the left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), and left ventricular end-systolic diameter (LVESD) before and after treatment in the two groups. Blood lipid levels were determined before and after drug administration, respectively, while the levels of high-density lipoprotein cholesterol (HDL-C) were determined using a colorimetric method. Total cholesterol (TC) and triacylglycerol (TG) were assessed by an enzymatic method, while low-density lipoprotein cholesterol (LDL-C) was determined using a biochemical method. Serum B-type natriuretic peptide (BNP), c-reactive-protein (CRP), and interleukin (IL)-6 levels were evaluated in an automatic biochemical analyzer. The incidence of adverse reactions during treatment, including creatinine elevation, muscle pain, and gastrointestinal reactions and their frequencies were computed.*
Results: *The combined group exhibited significantly lower levels of myocardial injury indices when compared with the conventional group ($p < 0.05$). Atorvastatin plus PCI resulted in significantly higher left ventricular ejection fraction (LVEF), and lower left ventricular end-diastolic dimension (LVEDD) as well as left ventricular end-systolic diameter (LVESD) in patients when compared with PCI alone group ($p < 0.05$). After treatment, the combined group showed significantly healthier levels of low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) compared with the conventional group ($p < 0.05$).*
Conclusion: *Atorvastatin plus PCI mitigates myocardial injury and lowers cardiac function, lipid indices, serum B type natriuretic peptide (BNP), C-reactive-protein (CRP), and interleukin (IL)-6 levels. It also reduces the incidence of adverse events during treatment. Thus, this therapeutic strategy has potentials for application in the management of acute myocardial infarction.*

Keywords: *Atorvastatin, Percutaneous coronary intervention, Acute myocardial infarction, Coronary thrombolysis*

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INTRODUCTION

Acute myocardial infarction is a functional or structural abnormality of the cardiac coronary vessels. This results in blockage of the blood vessels of the myocardium and disruption of the blood supply to the innervated myocardium of the corresponding vessel and impairs myocardial function. The most common symptoms of myocardial infarction are crushing pain in the upper and middle chest, mostly accompanied by sweating and choking. A small portion of patients also experiences pain in the left shoulder or the left ring finger [1-4]. Acute myocardial infarction features an acute onset, and early thrombolytic therapy and percutaneous coronary intervention (PCI) are essential to quicken the recovery of myocardial perfusion and reduce the risk of death. Coronary embolism refers to the blockage of the lumen of the coronary arteries by abnormal insoluble substances [5-7]. PCI is one of the effective methods for the treatment of acute myocardial infarction that improves myocardial blood circulation by directly unblocking the affected vessels and improving myocardial blood perfusion. Some studies have shown that PCI significantly outperformed thrombolytic therapy in terms of revascularization rate. However, the invasiveness of PCI may trigger multiple complications such as vagal reflex, reperfusion injury, and coronary artery spasm. Contemporary pharmacodynamics has confirmed that statins significantly reduce lipid levels, protect vascular endothelial function, and inhibit thrombus formation in patients. Nevertheless, evidence on the effects and mechanisms of myocardial protection by statins after thrombolysis is limited [8,9]. Therefore, this study investigated the coronary thrombolytic effect of atorvastatin plus PCI for the treatment of acute myocardial infarction.

METHODS

Baseline data

From April 2019 to October 2020, 88 patients with acute myocardial infarction admitted in Zhangqiu District People's Hospital, Jinan City, China were recruited. The patients were assigned to receive either PCI (conventional group) or PCI plus atorvastatin (combined group), with 44 patients in each group. All eligible patients had typical symptoms of ischemic chest pain and showed no changes after oral administration of nitroglycerin. Diagnosis was confirmed using a 12-lead electrocardiogram and laboratory tests, which met the diagnostic criteria of acute myocardial infarction. Patients with contraindications to drugs and thrombolysis, and those with blood pressure over 160/100 mmHg were excluded. The study was approved by the ethics committee of Zhangqiu District People's Hospital (approval no. 20100020), and the procedures were conducted in line with the guidelines of Declaration of Helsinki [9].

In the conventional (PCI) group, there were 21 males and 23 females, aged 49 – 70 (57.4 ± 5.6) years, including 19 cases of anterior interstitial and extensive anterior wall infarction, 11 cases of inferior posterior wall infarction, 7 cases of high lateral wall infarction, and 7 cases of inferior wall with right ventricular infarction. In the combined group, there were 22 males and 22 females, aged 49 – 70 (56.8 ± 5.4) years, including 15 cases of anterior interstitial and extensive anterior wall infarction, 12 cases of inferior posterior wall infarction, 9 cases of high lateral wall infarction, and 8 cases of inferior wall with right ventricular infarction. The patient characteristics between the two groups were comparable (P>0.05). (Table 1).

Table 1: Comparison of baseline data between the two groups (n[%])

Variable	Conventional group (n=44)	Combined group (n=44)	t or χ^2	*P*-value
Gender			0.045	0.831
Male	21	22		
Female	23	22		
Mean age	57.4 ± 5.6	56.8 ± 5.4	0.512	0.61
Infarction site			-	-
Anterior interstitial and extensive anterior wall infarction	19	15		
Inferior posterior wall infarction	11	12		
High lateral wall infarction	7	9		
Inferior wall with right ventricular infarction	7	8		

Drug administration

Before PCI, patients in both groups received 300 mg of aspirin-vitamin C enteric-coated tablets (Heilongjiang Rigel Pharmaceutical Co. Ltd, Guodianzhi H23023548) through oral administration, 300 mg of clopidogrel sulfate tablets (Nanjing Zhengda Tianqing Pharmaceutical Co. Ltd, State Pharmacopoeia H20203269) through oral administration, and 5 000 IU of sodium heparin (Jiangsu Wanbang Biochemical Pharmaceutical Group Co. Ltd., State Drug Administration H20020179) through intravenous injection, to maintain the activated clotting time of 250 - 350 s. All included patients underwent PCI. The puncture was performed via the radial artery route for stent placement, and 1 mg/kg of low-molecular-weight heparin sodium was administered every 12 h after the procedure. The patients also received 100 mg of aspirin vitamin C enteric-coated tablets and 75 mg of clopidogrel sulfate tablets once daily. The patients in the combined group additionally received 20 mg of oral atorvastatin (Pfizer Pharmaceutical Co., Ltd., National Drug Administration H20051408) once daily after dinner.

Evaluation of parameters/indices

Myocardial injury index

Serum eTnI and creatine kinase isoenzyme (CK-MB) were used as indices to determine myocardial injury, and serum cTnI was determined using ELISA method. The ELISA kit was purchased from the Cell Signaling Technology Co., Ltd., USA.

ELISA double antibody sandwich method: Roche IV reagents (Shanghai Roche Pharmaceutical Co. Ltd.) were used for ELISA assay. The test entailed the use of high-speed centrifugation (800 rpm) of the blood sample to be tested to isolate the serum, and the blood sample was tested according to the ELISA kit manufacturer's instructions.

Creatine kinase isoenzymes (CK-MB) levels

Creatine kinase isoenzymes were determined using the immunosuppression method, and the CK-MB test kit was purchased from Beijing Lidman Biochemistry Co. Ltd., and the mass method CK-MB test kit was produced by Dia Lebo Biotechnology Co. Venous blood (5mL) was collected from the patients and centrifuged to isolate the serum, and the concentrations of CK-MB were determined. The assay was performed in strict accordance with standard operating procedures and reagent instructions.

Cardiac function

Cardiac ultrasound was used to measure and compare the left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), and left ventricular end-systolic diameter (LVESD) before and after treatment in the two groups.

Lipid indices

Blood lipid levels were determined before and after drug administration in two groups, respectively. Morning fasting venous blood (3 - 5 mL) was collected from all eligible patients, and the levels of high-density lipoprotein cholesterol (HDL-C) were determined using the colorimetric method. The levels of total cholesterol (TC) and triacylglycerol (TG) were assessed with the enzymatic method, while low-density lipoprotein cholesterol (LDL-C) was determined using a biochemical method.

Inflammatory factors

Fasting venous blood (3Ml) was collected before and after treatment. Serum B-type natriuretic peptide (BNP), c-reactive-protein (CRP), and interleukin (IL)-6 levels of the two groups were evaluated using an automatic biochemical analyzer.

Adverse reactions

The incidence of adverse reactions during treatment includes creatinine elevation, muscle pain, and gastrointestinal reactions; their frequencies were computed.

Statistical analysis

SPSS 21.0 was used for data analyses and GraphPad Prism 8 was for image rendering. Measurement data are expressed as mean ± SD and processed using an independent sample t-test. Count data are expressed as the number of cases observed and analyzed using the chi-square test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Myocardial injury indices

In the conventional group, the peak cTnI concentration was 2.36 ± 0.21 ng/mL which required 79.74 ± 8.55 h to return a normal level,

and the peak CK-MB concentration was 157.34 ± 16.12 ng/mL, which took 31.12 ± 7.02 h to return a normal level. The combined group had significantly lower myocardial injury indices compared with the conventional group ($p < 0.05$) (Table 2).

Cardiac functions

The LVEDD of patients in the conventional group was 60.13 ± 3.08 before treatment and 56.37 ± 1.41 after treatment, LVEF was 48.44 ± 4.05 before treatment and 49.28 ± 1.24 after treatment, and LVESD was 58.32 ± 2.29 before treatment and 54.03 ± 1.27 after treatment. The LVEDD of patients in the combined group was 60.21 ± 3.15 before treatment and 53.01 ± 1.19 after treatment, LVEF was 48.21 ± 3.89 before treatment and 53.46 ± 1.19 after treatment, and LVESD was 58.39 ± 2.15 before treatment and 50.83 ± 0.63 after treatment. There were no significant differences in LVEDD, LVEF, and LVESD between the two groups of patients before treatment ($p > 0.05$). After treatment, LVEF increased in both groups, with higher LVEF in the combined group compared with the conventional group. The LVEDD and LVESD decreased in both groups, with lower LVEDD and LVESD observed in the combined group than in the conventional group ($p < 0.05$) (Table 3).

Blood lipid levels

The TC level of patients in the conventional group was 5.81 ± 0.52 before treatment and 4.47 ± 0.48 after treatment, the TG level was 2.02 ± 0.41 before treatment and 1.77 ± 0.35 after treatment, the LDL-C level was 3.65 ± 0.41 before treatment and 3.38 ± 0.51 after treatment, and the HDL-C level was 1.30 ± 0.33 after treatment was 1.47 ± 0.33. The TC level of patients in the combined group was 5.82 ± 0.50 before treatment and 3.51 ± 0.33 after treatment, the TG level was 2.01 ± 0.42 before treatment and 1.31 ± 0.22 after treatment, the LDL-C level was 3.66 ± 0.42 before treatment and 2.81 ± 0.61 after treatment, the HDL-C level was 1.28 ± 0.35 after treatment was 1.81 ± 0.36. No significant differences were found in the levels of LDL-C, TC, HDL-C, and TG between the two groups of patients before treatment ($p > 0.05$).

Table 2: Comparison of myocardial injury indices (mean ± SD, n = 44)

Group	cTnI		CK-MB	
	Peak concentration (ng/mL)	Return to normal (h)	Peak concentration (ng/mL)	Return to normal (h)
Conventional group	2.36 ± 0.21	79.74 ± 8.55	157.34 ± 16.12	31.12 ± 7.02
Combined group	1.77 ± 0.19	70.62 ± 8.10	121.75 ± 15.89	24.98 ± 6.57
T	13.819	5.136	10.43	4.236
P-value	<0.001	<0.001	<0.001	<0.001

Table 3: Comparison of cardiac function indices (mean ± SD, n = 44)

Group	LVEDD (mm)		LVEF(%)		LVESD(mm)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Conventional group	60.13 ± 3.08	56.37 ± 1.41	48.44 ± 4.05	49.28 ± 1.24	58.32 ± 2.29	54.03±1.27
Combined group	60.21 ± 3.15	53.01 ± 1.19	48.21 ± 3.89	53.46 ± 1.19	58.39 ± 2.15	50.83±0.63
t	-0.12	12.08	0.272	-16.133	-0.148	14.973
P-value	0.905	<0.001	0.786	<0.001	0.883	<0.001

Table 4: Comparison of serum levels of BNP, CRP, and IL-6 (mean ± SD, n = 44)

Group	BNP (pg/mL)		CRP(mg/L)		IL-6(ng/L)	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*
Conventional group	597.37 ± 88.34	246.44 ± 50.32	14.42 ± 3.58	7.68 ± 1.34	26.28 ± 4.21	25.35±4.17
Combined group	596.28 ± 89.20	181.33 ± 45.61	14.33 ± 3.54	4.23 ± 1.17	26.57 ± 4.15	21.07±3.13
t	0.058	6.359	0.119	12.864	-0.325	5.445
P-value	0.954	<0.001	0.906	<0.001	0.746	<0.001

After treatment, the two groups of patients had increased HDL-C levels and lower levels of LDL-C, TC, and TG, with higher HDL-C levels and lower levels of LDL-C, TC, and TG in the combined group than the conventional group ($p < 0.05$; Figure 1).

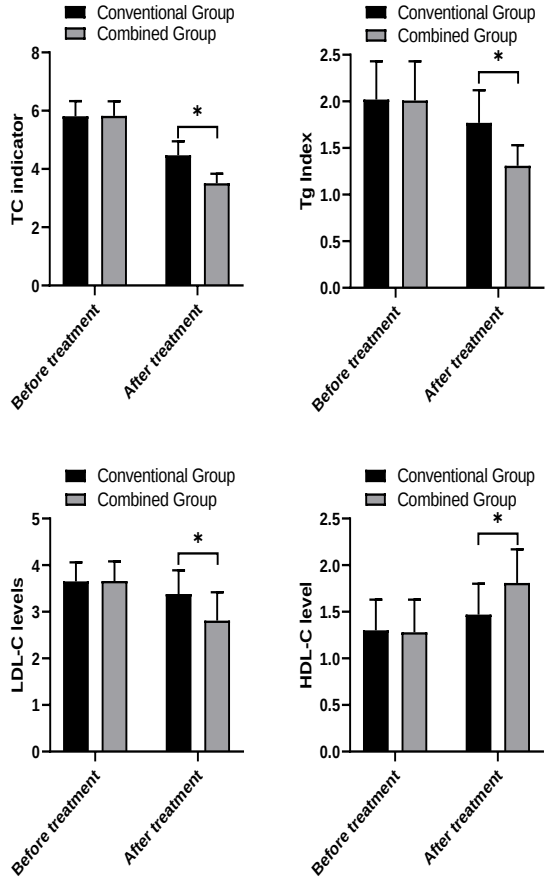

Figure 1: Comparison of blood lipid indices (mean ± SD, n = 44, mmol/L); indicates; $p < 0.001$

Serum levels of BNP, CRP, and IL-6

The BNP levels of patients in the conventional group were 597.37 ± 88.34 before treatment and 246.44 ± 50.32 after treatment, CRP levels were 14.42 ± 3.58 before treatment and 7.68 ± 1.34 after treatment, and IL-6 levels were 26.28 ± 4.21 before treatment and 25.35 ± 4.17 after treatment. The BNP levels of patients in the combined group were 596.28 ± 89.20 before treatment and 181.33 ± 45.61 after treatment, CRP levels were 14.33 ± 3.54 before treatment and 4.23 ± 1.17 after treatment, IL-6 levels were 26.57 ± 4.15 before treatment and 21.07 ± 3.13 after treatment. Before treatment, the two groups showed similar levels of the above indices ($p > 0.05$). The serum levels of BNP, CRP, and IL-6 decreased in both groups after treatment, and the serum BNP, CRP, and IL-6 levels were lower in the combined group than in the conventional group ($p < 0.05$; Table 4).

Incidence of adverse reactions

In the conventional group, documented adverse reactions included 2 cases of creatinine elevation, 2 cases of muscle pain, and 3 cases of gastrointestinal reactions, resulting in an incidence of adverse reaction of 16 %. In the combined group, documented adverse reactions included 1 case of muscle pain, resulting in an incidence of adverse reaction of 2 %. The PCI plus atorvastatin was associated with a significantly lower incidence of adverse reaction in patients compared with PCI ($p < 0.05$; Table 5).

DISCUSSION

Acute myocardial necrosis and rupture of the fibrous cap of the unstable plaque lead to lumen occlusion, local thrombosis, myocardial cell ischemia and hypoxia, and interruption of myocardial blood flow, resulting in myocardial infarction [10-12]. Current treatment of myocardial infarction includes symptomatic therapy such as heart rate control, anticoagulation, antiplatelet, thrombolysis, and percutaneous coronary intervention, which can effectively alleviate the symptoms, recanalize the obstructed coronary artery, and prevent local thrombosis. However, studies have found potentiated treatment efficiency with a combination of statin therapy, which inhibits platelet function and restores cardiomyocyte perfusion.

Table 5: Comparison of adverse reactions (mean ± SD, n = 44, n[%])

Variable	Conventional group (n=44)	Combined group (n=44)	χ^2	*P*-value
Creatinine elevation	2	0	-	-
Muscle pain	2	1	-	-
Gastrointestinal reactions	3	0	-	-
Incidence of adverse reactions	7(16%)	1(2%)	4.95	0.026

Atorvastatin has immunomodulatory, antiplatelet, antioxidant, and anti-inflammatory effects. It improves vascular endothelial diastolic function, promotes the decomposition and uptake of serum low-density lipoprotein, lowers lipoprotein and cholesterol, suppresses hepatic cholesterol biosynthesis, regulates cardiac autonomic function, improves platelet activation, and reduces thrombus formation [13-15].

The results of the present study showed that PCI plus atorvastatin resulted in better LDL-C, TC, HDL-C, TG, BNP, CRP, and IL-6 levels versus PCI alone. The reason for this is that atorvastatin inhibits Na+ -Ca2+ exchange by decreasing intracellular calcium ion concentration, promotes endothelial nitric oxide (NO) catabolism, reduces lipid nucleation within plaques, and inhibits inflammatory responses by decreasing fibrous cap tension, thereby preventing thrombosis.

Deteriorating cardiac function may result in insufficient intrinsic circulation in organs and tissues and thus deficient cardiac function. In the current study, the better LVEDD, LVESD, and LVEF levels in the combined group compared with the conventional group indicated that atorvastatin exerted anti-inflammatory and lipid-regulating effects and inhibited the progression of myocardial hypertrophy and cardiomyocyte fibrosis, reduced cardiac load, improved cardiac function, and reversed ventricular remodeling. Post-thrombolytic ischemia-reperfusion injury is an important cause of myocardial injury, which exacerbates myocardial damage and causes symptoms such as enlarged infarct size or persistent ventricular systolic hypoperfusion.

Despite the poorly understood pathogenic mechanism of post-thrombolytic ischemia-reperfusion injury, reduction of the incidence of post-thrombolytic myocardial injury and improvement of ischemia-reperfusion injury status through medications constitute the focus of clinical improvement of patient prognosis [16-19]. Atorvastatin can repair vascular damage, increase cardiac perfusion and reperfusion damage to the myocardium, promotes myocardial repair, and avoids immune damage, thus reducing myocardial damage. In the present study, The cTnI and CK-MB levels of patients in the combined group were significantly better than those of patients in the conventional group, which indicates that atorvastatin facilitates the activity of the nitric oxide system within the vascular endothelium by inhibiting the biosynthesis of mevalonate, reduces the release of inactive nitric oxide from endothelial cells, induces apoptosis in vascular smooth muscle cells, and improves endothelial function to adapt to the ischemia-reperfusion state. Furthermore, the results also showed a significantly lower incidence of adverse events in the combined group than in the conventional group, suggesting a high safety profile of atorvastatin [20-22].

CONCLUSION

The findings of this study show that atorvastatin plus PCI is effective in the treatment of acute myocardial infarction, as it mitigates myocardial injury, improves cardiac function and lipid levels. It also decreases serum BNP, CRP, and IL-6 levels, and lowers the incidence of adverse events during treatment. Therefore, the combined therapy has potentials for use in the treatment of acute myocardial infarction.

DECLARATIONS

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Ethical approval

The study was approved by the ethics committee of Zhangqiu District People's Hospital (approval no. 20100020).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

REFERENCES

1. *Bai S, Liao J, Zhang B, Zhao M, You B, Li P, Ran H, Wang Z, Shi R, Zhang G. Multimodal and multifunctional nanoparticles with platelet targeting ability and phase transition efficiency for the molecular imaging and thrombolysis of coronary microthrombi. Biomater Sci 2020; 8(18): 5047-5060.*
2. *Choo EH, Chang K, Lee KY, Lee D, Kim JG, Ahn Y, Kim YJ, Chae SC, Cho MC, Kim CJ, et al; KAMIR-NIH Investigators. Prognosis and Predictors of Mortality in Patients Suffering Myocardial Infarction With Non-Obstructive Coronary Arteries. J Am Heart Assoc 2019; 8(14): e011990.*
3. *DeFilippis AP, Chapman AR, Mills NL, de Lemos JA, Arbab-Zadeh A, Newby LK, Morrow DA. Assessment and Treatment of Patients With Type 2 Myocardial Infarction and Acute Nonischemic Myocardial Injury. Circulation 2019; 140(20): 1661-1678.*
4. *Dimitrov K, Maier J, Sandner S, Riebandt J, Wiedemann D, Moayedifar R, Schlöglhofer T, Angleitner P, Niederdöckl J, Schima H, et al. Thrombolysis as first-line therapy for Medtronic/HeartWare HVAD left ventricular assist device thrombosis. Eur J Cardiothorac Surg 2020; 58(6): 1182-1191.*
5. *Harrington DH, Stueben F, Lenahan CM. ST-Elevation Myocardial Infarction and Non-ST-Elevation Myocardial Infarction: Medical and Surgical Interventions. Crit Care Nurs Clin North Am 2019; 31(1): 49-64.*
6. *Ichihara Y, Hamasaki A, Saito S, Niinami H. Complete coronary thrombolysis on continuous-flow left ventricular assist device. Eur J Cardiothorac Surg 2021; 60(3): 721.*
7. *Jenča D, Melenovský V, Stehlik J, Staněk V, Kettner J, Kautzner J, Adámková V, Wohlfahrt P. Heart failure after myocardial infarction: incidence and predictors. ESC Heart Fail 2021; 8(1): 222-237.*
8. *Ghati N, Roy A, Bhatnagar S, Bhati S, Bhushan S, Mahendran M, Thakur A, Tiwari P, Dwivedi T, Mani K, et al. Atorvastatin and Aspirin as Adjuvant Therapy in Patients with SARS-CoV-2 Infection: A structured summary of a study protocol for a randomised controlled trial. Trials 2020; 21(1): 902.*
9. *World Medical Association General Assembly. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Int Bioethique 2004; 15(1): 124-9. PMID: 15835069.*
10. *Kassimis G, Faliagkas P, Pshochias P, Karagiannidis E, Peteinidou E, Chatzinikolaou E, Ziakas A, Sianos G. Intracoronary thrombolysis and stentless primary percutaneous coronary intervention in an ectatic right coronary artery with large thrombus burden. Future Cardiol 2021; 17(6): 999-1006.*
11. *Kumar A, Shariff M, Doshi R. Index of microvascular resistance and outcomes following intra-coronary thrombolysis with percutaneous intervention in STEMI: a meta-analysis of randomized control trials. J Thromb Thrombolysis 2020; 49(3): 487-491.*
12. *Majeed H, Khan MN, Naseeb K, Soomro NA, Alam S, Ahmed S, Bhatti U, Saghir T. Multivessel Coronary Artery Disease and Subsequent Thrombolysis in Myocardial Infarction Flow Grade After Primary Percutaneous Coronary Intervention. Cureus 2020; 12(6): e8752.*
13. *Szarek M, Amarenco P, Callahan A, DeMicco D, Fayyad R, Goldstein LB, Laskey R, Sillesen H, Welch KM; SPARCL Committees and Investigators. Atorvastatin Reduces First and Subsequent Vascular Events Across Vascular Territories: The SPARCL Trial. J Am Coll Cardiol 2020; 75(17): 2110-2118.*
14. *Yu H, Jin F, Liu D, Shu G, Wang X, Qi J, Sun M, Yang P, Jiang S, Ying X, Du Y. ROS-responsive nano-drug delivery system combining mitochondria-targeting ceria nanoparticles with atorvastatin for acute kidney injury. Theranostics 2020; 10(5): 2342-2357.*
15. *Yu M, Liu W, Li J, Lu J, Lu H, Jia W, Liu F. Exosomes derived from atorvastatin-pretreated MSC accelerate diabetic wound repair by enhancing angiogenesis via AKT/eNOS pathway. Stem Cell Res Ther 2020; 11(1): 350.*
16. *Pelliccia F, Greco C, Tanzilli G, Viceconte N, Schiariti M, Gaudio C. Long-term outcome of patients with ST-segment elevation myocardial infarction treated with low-dose intracoronary thrombolysis during primary percutaneous coronary intervention: the 5-year results of the DISSOLUTION Trial. J Thromb Thrombolysis 2021; 51(1): 212-216.*
17. *Shah AH, Puri R, Kalra A. Management of cardiogenic shock complicating acute myocardial infarction: A review. Clin Cardiol 2019; 42(4): 484-493.*
18. *Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, Lerman A, Cushman M, Kumbhani DJ, Arslanian-Engoren C, et al; American Heart Association Interventional Cardiovascular Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; and Council on Quality of Care and Outcomes Research. Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. Circulation 2019; 139(18): e891-e908.*
19. *Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial*

Infarction. Fourth Universal Definition of Myocardial Infarction. J Am Coll Cardiol 2018; 72(18): 2231-2264.

20. *Zhang L, Zhang S, Yu Y, Jiang H, Ge J. Efficacy and safety of rosuvastatin vs. atorvastatin in lowering LDL cholesterol: A meta-analysis of trials with East Asian populations. Herz 2020; 45(6): 594-602. English.*
21. *Zhang P, Zhang X, Huang Y, Chen J, Shang W, Shi G, Zhang L, Zhang C, Chen R. Atorvastatin alleviates microglia-mediated neuroinflammation via modulating the microbial composition and the intestinal barrier function in ischemic stroke mice. Free Radic Biol Med 2021; 162: 104-117.*
22. *Maqsood M, Sadeeqa S, Ahmad M, Afzal H. Efficacy and safety of atorvastatin and rosuvastatin in ischemic heart disease patients: A prospective study. Trop J Pharm Res 2019; 18(7):1533-1538.*