Int J Clin Exp Med 2020;13(4):2339-2346
www.ijcem.com /ISSN:1940-5901/IJCEM0103693

Original Article

Effects of Nicorandil combined with Trimetazidine on endothelial cell microparticles, endothelial cell-specific molecule-1 and high-Sensitivity C-reactive protein in patients with acute myocardial infarction after PCI

Jian Li[1], Yaping Li[2]

[1]*Intensive Care Unit, The Central Hospital of Wuhan, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei, China;* [2]*Cardiovascular Medicine Department, Wuhan Third Hospital (Tongren Hospital of Wuhan University), Wuhan, Hubei, China*

Received October 18, 2019; Accepted November 20, 2019; Epub April 15, 2020; Published April 30, 2020

Abstract: Objective: To investigate effects of nicorandil combined with trimetazidine on endothelial cell microparticles (EMPs), endothelial cell-specific molecule-1 (ESM-1) and high-sensitivity C-reactive protein (hs-CRP) in patients with acute myocardial infarction after percutaneous coronary intervention (PCI). Methods: In total, 103 patients with acute myocardial infarction treated in our hospital were enrolled as participants of a retrospective analysis. In line with the therapeutic methods used they were divided into two groups where PCI was given. Later, patients in the control group were then managed with trimetazidine and patients in the observation group were managed with trimetazidine combined with nicorandil. In this context, the clinical efficacy, changes in EMPs, ESM-1, hs-CRP, cardiac parameters, and incidence of adverse cardiovascular events within 30 days of the treatment were recorded. Results: (1) The management used in the observation group generated superior total validity (94.23%) compared with that used in the control group (64.71%) (X^2=13.828, P<0.05). (2) Levels of EMPs, ESM-1 and hs-CRP 7 days after treatment in patients in the observation group were greater than those in the control group (P<0.05). (3) LVEDVI and LVESVI 7 days after treatment of patients in the observation group became lower, while PER and LVEF were higher, than those of the patients in the control group (P<0.05). (4) The incidence of adverse cardiovascular events, within 30 days of treatment, in the observation group was 3.85% compared with 5.88% in the control group, with non-significant differences (X^2=0.231, P>0.05). Conclusion: The application of nicorandil combined with trimetazidine is conductive to down-regulation of the expression of EMPs, ESM-1 and hs-CRP and ameliorate cardiac issues in patients with acute myocardial infarction after PCI. This treatment combination offers a good short-term prognosis which is promising.

Keywords: Acute myocardial infarction, PCI, nicorandil, trimetazidine, combined therapy, EMPs, ESM-1, hs-CRP

Introduction

Acute myocardial infarction is clinically considered a cardiovascular disease with a high incidence. This disease is often characterized by acute onset, speedy progresses and poor patient prognosis [1]. The pathogenesis of it is based on coronary atherosclerosis, plaque that ruptures and severely injures the coronary arterial endothelium, leading to platelet aggregation, fibrinous thrombus, blocking the coronary blood flow, and persistent anoxia and ischemia of cardiac muscles near the blood-supply area, which eventually cause myocardial necrosis [2, 3].

Percutaneous coronary intervention (PCI), a commonly used method in clinical treatment of acute myocardial infarction, clears blood vessels where myocardial infarction exists, in an early stage, to prompt the recovery of the ischemic myocardium after reperfusion [4, 5]. Although it has a lot of benefits, PCI affects myocardial function due to factors such as reperfusion and other treatment outcomes [6]. Studies have shown that EMPs, ESM-1 and hs-

CRP and other inflammatory markers play important roles in the occurrence and development of acute myocardial infarction. They are helpful in the guidance of prognosis and diagnosis of severity [7, 8]. Trimetazidine has effects on cardio-protection and has been widely used in clinical practice for treatment of various cardiovascular diseases [9]. Nicorandil promotes angiectasis of the coronary artery and in recent years has been used for the treatment of stenocardia as well as myocardial ischemia [10]. In this paper, for purpose of improving the prognosis of patients with acute myocardial infarction, the combination of nicorandil and trimetazidine were applied after PCI.

The study was to investigate the effects of nicorandil combined with trimetazidine on EMPs, ESM-1, and hs-CRP in acute myocardial infarction patients after PCI in the hope of finding evidence that this combination effectively improves prognosis of patients with acute myocardial infarction. The cases enrolled were divided into two groups where trimetazidine or trimetazidine + nicorandil were given.

Material and methods

Materials

In total, 103 patients with acute myocardial infarction who were treated in our hospital were enrolled as participants of a retrospective analysis. In line with the therapeutic methods used, they were divided into two groups. In the control group, there were 51 patients (29 males and 22 females, aged 52-72 years) who were given trimetazidine after PCI. In the observation group, there were 52 patients (30 males and 22 females, aged 53-71 years) who were given trimetazidine + nicorandil after PCI. (1) Inclusion criteria: a patient who: was evaluated as Grade 1-3 based on the Killip scale; was diagnosed with acute myocardial infarction; had their first heart attack; did not spend more than 12 hours since hospital admission; showed indications of emergency PCI; and signed the informed consent, could be enrolled. (2) Exclusion criteria: a patient who: is allergic to the drugs used in the study; has severe hypertension; has combined malignant tumor; has peptic ulcer; has blood disease (s); has acute and chronic infections; or has combined endocrine disease (s), shall be excluded. The study has been approved by the ethics committee of Wuhan Third Hospital.

Methods

Patients in both groups underwent PCI. Before the surgery, patients in the two groups were orally administered 600 mg clopidogrel (Approval No.: SFDA H20123116 Manufacturer: LEPU Pharmaceutical Co., Ltd. Specification: 75 mg*7 tablets) and 300 mg aspirin (Approval No.: SFDA H14021593 Manufacturer: Shanxi Tongda Pharmaceutical Co., Ltd. Specification: 50 mg*18 tablets*4 plates), whilst after the surgery they were routinely given antiplatelet drugs (ticagrelor, clopidogrel and aspirin, etc) and β-blockers, in addition to anticoagulant therapy by low molecular weight heparin, anti-atherosclerosis by statins, and other patient-specific symptomatic treatments including blood pressure control, cardiac failure resistance or improvement of heart failure, etc.

Furthermore, after the surgery patients in the control group were also managed with oral trimetazidine (Approval No.: SFDA H20073969 Manufacturer: Nanjing Hencer Pharmaceutical Co., Ltd. Specification: 20 mg*30 tablets/box), 200 mg three times a day; and patients in the observation group were managed with oral trimetazidine combined with nicorandil (Approval No.: SFDA H41024517 Manufacturer: Tianfang Pharmaceutical Co., Ltd. Specification: 5 mg), 5 mg three times a day for 7 days.

Observed indicators

Evaluation of therapeutic efficacy: with reference to *Internal Medicine*, clinical efficacy was evaluated 7 days after PCI. When compared with results before operation and the patient's ECG did not show any change, a score of invalid was recorded. If the ST segment went up 0.5 mV but was still not up to normal, both intraventricular block and atrioventricular block were improved, and T-Wave direction in lead of the infarction site was upright, or upside down with the amplitude being decreased 25%, but was still not up to normal, a score of effective was recorded. If after treatment the patient's ECG is basically in its normal state, a score of excellence was recorded. Total validity = effective + excellence.

Serum factors: before and 7 days after PCI, respectively, 5 ml of fasting venous blood from patients in both groups were collected and stored in a freezer for 1-hour for coagulation before centrifugation at 3000 r/min for 15 min.

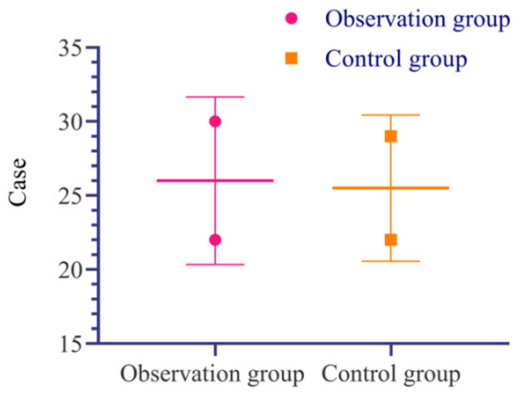

Figure 1. Gender distribution in both groups. The proportion of male patients in the observation group was 57.69% compared with 56.86% in the control group, $P>0.05$. Similarly, the proportion of females in the observation group was 42.31% compared with 43.14% in the control group, $P>0.05$.

The centrifuged serum was stored in a frozen box. ESM-1 was determined by enzyme-linked immunosorbent assay following the kit instructions provided by SHANGHAI MLBIO CO., LTD. hs-CRP was determined with automatic protein analyzer BNII (SIEMENS, Germany) and the supporting kits. EMPs were determined using flow cytometry for which the collected venous blood was placed into a citrate anticoagulation vacuum tube for 10-minutes of centrifugation, and after extraction of platelet-rich plasma, another 6-minutes of centrifugation, followed by extraction of 50 μg of the platelet-poor plasma, and then 0.5 μg CD31-PE antibody and CD42-FITC antibody were added at room temperature. After 20 minutes of incubation 1 ml of phosphate buffer was added for detection [11].

Cardiac parameters: before and 7 days after PCI, left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (FID), peak ejection rate (PER) and left ventricular ejection fraction (LVEF) were detected using Philip IE33 Diasonograph [12, 13].

Incidence of adverse cardiovascular events: the patients in both groups were compared for the incidence of adverse cardiovascular events within 30 days of treatment including death, stroke, recurrent myocardial infarction, and emergency coronary revascularization, etc.

Statistics

In the statistical analysis using SPSS 22.0, measurement data were expressed as mean ± standard deviation where those following the normal distribution were tested with an independent-sample T test and those not following normal distribution were tested with Mann-Whitney U test. Paired t-test was used for intra-group comparison. Enumeration data were expressed by [n (%)] in addition to X^2 test for comparison between groups. $P<0.05$ indicates statistically significant.

Results

Comparison of general information of both groups

The observation group includes 30 males (57.69%) and 22 females (42.31%), with an age range of 53-71 years (averaged 62.18±1.28). The period of time since the onset to the commencement of PCI was 221-362 min, averaged (289.63±12.59). The number of cases having combined hyperlipemia, diabetes mellitus, and hypertension were 20 (38.46%), 22 (42.31%), and 18 (34.62%), respectively; and the number of patients graded 1, 2, and 3 in the Killip scale were 19 (36.54%), 26 (50.00%), and 7 (13.46%), respectively. The control group includes 29 males (56.86%) and 22 females (43.14%), with an age range of 52-72 years (averaged 62.22±1.19). The period of time since the onset to the commencement of PCI was 229-373 min, averaged (292.06±12.16). The number of cases having combined hyperlipemia, diabetes mellitus, and hypertension were 21 (41.18%), 20 (39.22%), and 17 (39.22%), respectively; and the number of patients graded 1, 2, and 3 in the Killip scale were 18 (35.29%), 26 (50.98%), and 7 (13.73%), respectively. There were no statistically significant differences in terms of gender (**Figure 1**), age, period since the onset to PCI, complications (**Figure 2**), and Killip grading (**Figure 3**) (P>0.05) between the groups (**Table 1**).

Comparison of clinical efficacy of both groups

The observation group generated a total validity of 94.23% including excellence from 30 cases (57.69%) and effective from 19 cases (36.54%). Three cases reported invalid (2.11%) management. The control group generated a total validity of 64.71% including excellence from 21 cases (41.18%) and effective from 12 cases (23.53%). Eighteen cases reported invalid (35.29%) management. Clearly, the total validity of the observation group (94.23%) was

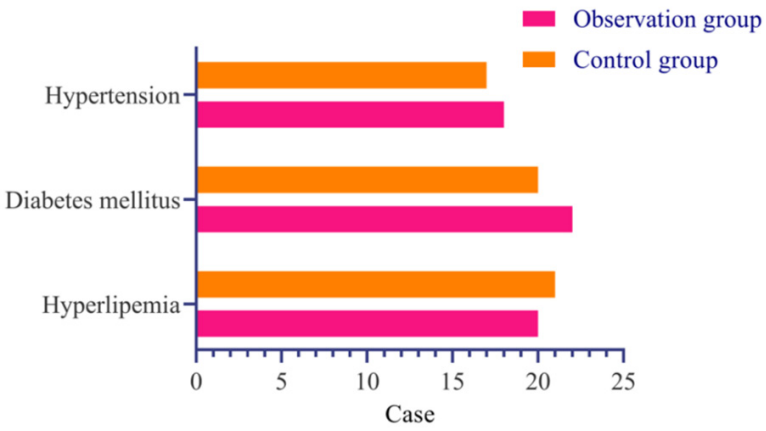

Figure 2. Complications in both groups. The percentages of patients with combined hyperlipemia, diabetes mellitus and hypertension in the observation group were 38.46%, 42.31%, and 34.62%, respectively; and as compared with the same of 41.18%, 39.22%, and 33.33%, respectively, in the control group, no significant difference were found, *P*>0.05.

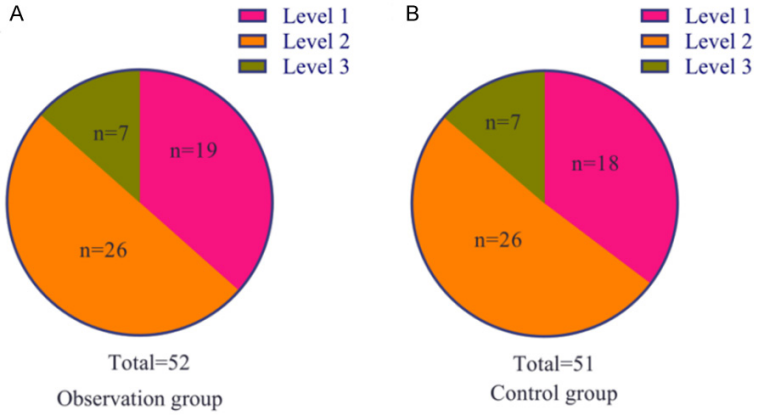

Figure 3. Killip grading in both groups. Patients who were evaluated as Grade 1, 2, and 3 in the observation group held a scale of 36.54%, 50.00%, and 13.46%, respectively; and there was no significant difference between that of 35.29%, 50.98%, and 13.73% respectively, in the control group, *P*>0.05.

significantly higher than that of control group (64.71%) (**Figure 4**).

Comparison of serum factors of both groups

Comparison between the two groups in serum factors before PCI proved not significantly different (P>0.05). However, compared with those before PCI: PCI, EMPs, ESM-1, and hs-CRP 7 days after treatment were decreased in both groups (*P*<0.05), and the levels of the same measures in the observation group were all lower than those in the control group (*P*<0.05) (**Table 2**).

Comparison of cardiac parameters of both groups

Comparison between the two groups of cardiac parameters before PCI proved not to be significantly different (P> 0.05). Compared with those before PCI; LVEDVI and LVESVI decreased, while PER and LVEF increased, in both groups 7 days after treatment (*P*<0.05), and the records of LVEDVI and LVESVI in the observation group were lower, whilst PER and LVEF were higher, than those in the control group (*P*<0.05) (**Table 3**).

Comparison of incidence of adverse cardiac events in both groups

The observation group reported an incidence of adverse cardiac events, within 30 days, at 3.85%, including death, stroke, recurrent myocardial infarction, and emergency coronary revascularization from 1, 1, 0, and 0 patients, respectively. The control group generated an incidence of adverse cardiac events, within 30 days, at 5.88%, including death, stroke, recurrent myocardial infarction, and emergency coronary revascularization from 1, 0, 1, and 1 patient, respectively. The differences between the two groups were not statistically significant (X^2=0.231, *P*>0.05) (**Table 4**).

Discussion

The onset of acute myocardial infarction severely injures myocardial cells. At infarction and non-infarction zones the effected myocardium may behave non-synchronously or contradictory with mechanical dilation and contraction, including inverse motions, loss or attenuation of movements. Furthermore, edges of myocardial infarction zones are in a state of stretching and loading, which causes ventricu-

Table 1. Comparison of general information of both groups [n (%)]/($\bar{x} \pm s$)

Items		Observation group (n=52)	Control group (n=51)	t/X^2	P
Gender (cases)	Male	30 (57.69)	29 (56.86)	0.007	0.932
	Female	22 (42.31)	22 (43.14)		
Age (years)		62.18±1.28	62.22±1.19	0.164	0.870
Onset-to-PCI Period (min)		289.63±12.59	292.06±12.16	80.985	0.000
Complications					
Hyperlipemia		20 (38.46)	21 (41.18)	0.012	0.996
Diabetes mellitus		22 (42.31)	20 (39.22)		
Hypertension		18 (34.62)	17 (33.33)		
Killip Grade					
Grade 1		19 (36.54)	18 (35.29)	0.052	0.635
Grade 2		26 (52.00)	26 (50.98)		
Grade 3		7 (13.46)	7 (13.73)		

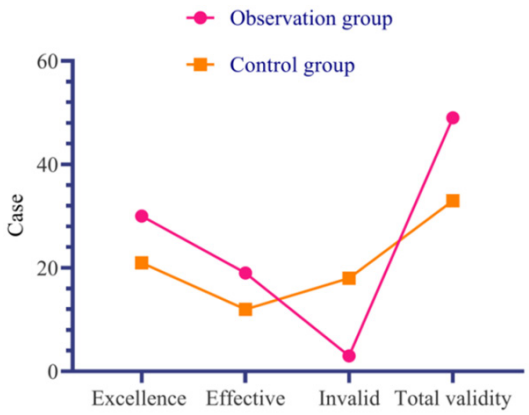

Figure 4. Comparison of clinical efficacy of both groups. Patients who reported excellence and effective in the observation group account for 57.69%, and 36.54%, respectively; both higher than those of 41.18%, and 23.53%, respectively, in the control group (P<0.05). The reported invalid cases in the observation group was 2.11%, lower than 35.29% in the control group (P<0.05). The total validity of the observation group was 94.23% superior to 64.71% from the control group (P<0.05).

lar remodeling [14, 15]. In elderly patients, acute myocardial infarction often develops as diffuse lesions of multiple coronary arteries that if not treated in a timely manner lead to cardiac failure, malignant arrhythmia, and in serious cases, sudden death [16].

PCI is a commonly used method for the treatment of acute myocardial infarction. It promotes the recovery of the myocardium after reperfusion and rescues the dying myocardium [17]. Generally, however, patients with diffuse lesions of multiple coronary arteries share a higher incidence of ischemia reperfusion injury compared with those with single-coronary artery lesions, due to the inadequacy in coronary revascularization [18]. Trimetazidine, with a number of piperazine derivatives in its family, acts primarily at the cellular level, is not be affected by oxygen supply and demand, and does not affect the haemodynamics [19, 20]. That is, in state of motion or rest, trimetazidine will not affect hemodynamic indicators such as heart rate, blood pressure and coronary blood flow [21]. Moreover, it maintains function of mitochondrial membrane, relieves cardiomyocyte acidosis, down-regulates the production of oxygen radicals, and inhibits neutrophil infiltration in myocardial tissues, protecting cells by anti-apoptosis and oxidation resistance, etc [22]. Nicorandil, one of nitric acid esters, causes depolarization of the mitochondrial membrane by increasing the outflow of intracellular K^+ by stimulating the opening of mitochondrial K^+-ATP channels in cardiomyocytes, and inhibits the opening of mitochondrial permeability transition pores leading to Ca^{2+} overloading and decreased inflow [23]. In addition, it suppresses the Ca^{2+} inflow to smooth muscle cells to control excitation-contraction coupling while leaving vascular smooth muscles in a relaxed state, resulting in effective prevention of coronary spasms [24]. In this paper, the total validity in the observation group (94.23%) was superior to that in the control group (64.71%) (P<0.05), suggesting the combination of trimetazidine + nicorandil offers better therapeutic effects compared with trimetazidine alone. This could be explained by nicorandil

Table 2. Comparison of serum factors in both groups ($\bar{x} \pm s$)

Group	EMPs (particles/μL)		ESM-1 (μg/L)		hs-CRP (mg/L)	
	Pre-operation	7 d after	Pre-operation	7 d after	Pre-operation	7 d after
Control (n=51)	1415.25±12.58	1089.96±10.33	1.36±0.12	1.18±0.08	14.85±1.25	8.15±1.16
Observation (n=52)	1418.16±12.43	818.82±8.88	1.39±0.09	0.81±0.06	14.89±1.23	6.12±1.08
t	1.181	142.940	1.437	26.588	0.164	9.194
P	0.240	0.000	0.154	0.000	0.870	0.000

Table 3. Comparison of cardiac parameters in both groups ($\bar{x} \pm s$)

Group	LVEDVI (mL/m^2)		LVESVI (mL/m^2)		PER (EDV/s)		LVEF (%)	
	Pre-operation	7 d after	Pre-operation	7 d after	Pre-operation	7 d after	Pre-operation	7 d after
Control (n=51)	113.63±8.52	98.56±5.12	60.52±2.58	43.69±1.26	1.59±0.15	1.75±0.18	51.12±0.18	53.26±0.25
Observation (n=52)	113.69±8.46	80.12±2.28	60.69±2.46	38.12±0.28	1.63±0.13	1.86±0.23	51.13±0.22	59.12±0.88
t	0.036	23.688	0.342	31.107	1.447	2.670	0.252	45.774
P	0.972	0.000	0.733	0.000	0.151	0.001	0.801	0.000

Table 4. Comparison of incidence of adverse cardiovascular events in both groups [n (%)]

Group	N=	Cardiac death	Stroke	Recurrent myocardial infarction	Emergency coronary revascularization	Total incidence
Control	51	1 (1.96)	0 (0.00)	1 (1.96)	1 (1.96)	3 (5.88)
Observation	52	1 (1.92)	1 (1.92)	0 (0.00)	0 (0.00)	2 (3.85)
X^2						0.231
P						0.631

playing dual roles in expansion of the coronary artery and also promoting the opening of KATP channels, further accelerating the recovery of myocardial microcirculation, whilst trimetazidine effectively maintains myocardial function, and the combination of them showed synergistic outcomes.

EMPs, ESM-1, and hs-CRP are familiar serological markers. EMPs are produced after endothelial cell apoptosis or activation and are highly expressed in cardiovascular diseases with endothelial dysfunction [25]. ESM-1 is released mainly by endothelial cells and the increase of its release promotes the migration and proliferation of vascular smooth muscle cells. It plays important roles in the progress of atherosclerosis [26]. hs-CRP reflects the inflammatory state and shows high specificity and sensitivity. It is considered to be an important independent risk factor for acute coronary syndrome as well as providing good prediction of cardiovascular events and plaque stability [11]. In this study, levels of EMPs, ESM-1, and hs-CRP 7 days after treatment in the observation group were lower than those in the control group ($P<0.05$) because, nicorandil maintains the dilation of micro-vessels by inhibiting calcium influx and increasing potassium ion outflow, and exerts anti-inflammatory effects by suppressing the opening of mitochondrial permeability transition pores. Chen et al [27] also found that nicorandil not only maintains coronary dilation but also improves local oxygen radical metabolism and vascular endothelial function. Upon the occurrence of acute myocardial infarction, ultrasound cardiograms showed significantly reduced PER and LVEF. The ventricular wall at non-infarcted zones may appear dilatated and have compensatory hypertrophy that points to ventricular remodeling. Interspace enlargement and thinning of the ventricular wall at infarcted zones are major manifestations of earlier ventricular remodeling. Increasing end-diastolic and end-systolic volumes are manifestations of late ventricular remodeling. The results showed LVEDVI and LVESVI 7 days after treatment in the observation group were lower, and PER and LVEF were higher, than those in the control group ($P<0.05$), indicating the com-

bined therapy improved cardiac functions of patients with acute myocardial infarction after PCI in a more efficient way, as compared with the trimetazidine alone. The incidence of adverse cardiovascular events in the observation group was 3.85% superior to 5.88% in the control group, with the difference not being statistically significant (P>0.05). This was further proof of the safety of such combination that offers good short-term prognosis, although its roles in long-term prognosis are to be determined.

In conclusion, nicorandil combined with trimetazidine for patients with acute myocardial infarction after PCI is beneficial to down-regulate the expression of EMPs, Esm-1 and hs-CRP, ameliorate cardiac issues and offer good short-term prognosis.

The small size of sample in this study limited the scope of the results obtained, by which enlarged size and in-depth studies are warranted.

Disclosure of conflict of interest

None.

Address correspondence to: Yaping Li, Cardiovascular Medicine Department, Wuhan Third Hospital, No. 216, Guanshan Road, Hongshan District, Wuhan 430070, Hubei, China. Tel: +86-027-65399981; E-mail: gw9t8rzv@163.com

References

[1] Poku N and Noble S. Myocardial infarction with non obstructive coronary arteries (MINOCA): a whole new ball game. Expert Rev Cardiovasc Ther 2017; 15: 7-14.

[2] Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE and Wenger NK. Acute myocardial infarction in women: a scientific statement from the american heart association. Circulation 2016; 133: 916-947.

[3] Bajaj A, Sethi A, Rathor P, Suppogu N and Sethi A. Acute complications of myocardial infarction in the current era: diagnosis and management. J Investig Med 2015; 63: 844-855.

[4] de Waha S, Jobs A, Eitel I, Poss J, Stiermaier T, Meyer-Saraei R, Fuernau G, Zeymer U, Desch S and Thiele H. Multivessel versus culprit lesion only percutaneous coronary intervention in cardiogenic shock complicating acute myocardial infarction: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care 2018; 7: 28-37.

[5] Johansson S, Rosengren A, Young K and Jennings E. Mortality and morbidity trends after the first year in survivors of acute myocardial infarction: a systematic review. BMC Cardiovasc Disord 2017; 17: 53.

[6] Lassen JF, Burzotta F, Banning AP, Lefevre T, Darremont O, Hildick-Smith D, Chieffo A, Pan M, Holm NR, Louvard Y and Stankovic G. Percutaneous coronary intervention for the left main stem and other bifurcation lesions: 12th consensus document from the European Bifurcation Club. EuroIntervention 2018; 13: 1540-1553.

[7] Nalluri N, Patel N, Saouma S, Anugu VR, Anugula D, Asti D, Mehta V, Kumar V, Atti V, Edla S, Grewal RK, Khan HM, Kanotra R, Maniatis G, Kandov R, Lafferty JC, Dyal M, Alfonso CE and Cohen MG. Utilization of the Impella for hemodynamic support during percutaneous intervention and cardiogenic shock: an insight. Expert Rev Med Devices 2017; 14: 789-804.

[8] Flaherty MP, Khan AR and O'Neill WW. Early Initiation of impella in acute myocardial infarction complicated by cardiogenic shock improves survival: a meta-analysis. JACC Cardiovasc Interv 2017; 10: 1805-1806.

[9] Liu MY and Zhang LJ. Impact of trimetazidine pre-treatment on 5-hydroxytryptamine and serotonin transporter in rats with experimental myocardial infarction and depressionZhonghua Xin Xue Guan Bing Za Zhi 2017; 45: 137-141.

[10] Kwon O and Park DW. Nicorandil for maximal hyperemia: a theoretical advantage awaiting clinical significance. Coron Artery Dis 2017; 28: 95-97.

[11] Asemi Z and Esmaillzadeh A. DASH diet, insulin resistance, and serum hs-CRP in polycystic ovary syndrome: a randomized controlled clinical trial. Horm Metab Res 2015; 47: 232-238.

[12] Petersen SE, Sanghvi MM, Aung N, Cooper JA, Paiva JM, Zemrak F, Fung K, Lukaschuk E, Lee AM, Carapella V, Kim YJ, Piechnik SK and Neubauer S. The impact of cardiovascular risk factors on cardiac structure and function: insights from the UK Biobank imaging enhancement study. PLoS One 2017; 12: e0185114.

[13] Sengupta PP, Kramer CM, Narula J and Dilsizian V. The potential of clinical phenotyping of heart failure with imaging biomarkers for guiding therapies: a focused update. JACC Cardiovasc Imaging 2017; 10: 1056-1071.

[14] Zang X and Qi X. Association between PM2.5 exposure and the prognosis of patients with acute myocardial infraction. Arch Med Res 2017; 48: 292-296.

[15] Khan HA, Ekhzaimy A, Khan I and Sakharkar MK. Potential of lipoproteins as biomarkers in acute myocardial infarction. Anatol J Cardiol 2017; 18: 68-74.
[16] Hundahl LA, Tfelt-Hansen J and Jespersen T. Rat models of ventricular fibrillation following acute myocardial infarction. J Cardiovasc Pharmacol Ther 2017; 22: 514-528.
[17] Milasinovic D, Wijns W, Ntsekhe M, Hellig F, Mohamed A and Stankovic G. Step-by-step manual for planning and performing bifurcation PCI: a resource-tailored approach. EuroIntervention 2018; 13: e1804-e1811.
[18] Habib RH, Dimitrova KR, Badour SA, Yammine MB, El-Hage-Sleiman AK, Hoffman DM, Geller CM, Schwann TA and Tranbaugh RF. CABG versus PCI: greater benefit in long-term outcomes with multiple arterial bypass grafting. J Am Coll Cardiol 2015; 66: 1417-1427.
[19] Kim YH, Her AY, Rha SW, Choi BG, Choi SY, Byun JK, Mashaly A, Park Y, Jang WY, Kim W, Choi JY, Park EJ, Na JO, Choi CU, Lim HE, Kim EJ, Park CG, Seo HS and Oh DJ. Impact of trimetazidine treatment on 5-year clinical outcomes in patients with significant coronary artery spasm: a propensity score matching study. Am J Cardiovasc Drugs 2018; 18: 117-127.
[20] Kolik LG, Nadorova AV, Stolyaruk VN, Miroshkina IA, Tsorin IB and Kryzhanovskii SA. Anxiolytic properties of trimetazidine in experimental models of increased anxiety. Bull Exp Biol Med 2017; 162: 643-646.
[21] Ibrahim TA, El-Mawardy RH, El-Serafy AS and El-Fekky EM. Trimetazidine in the prevention of contrast-induced nephropathy in chronic kidney disease. Cardiovasc Revasc Med 2017; 18: 315-319.
[22] Zhao Y, Peng L, Luo Y, Li S, Zheng Z, Dong R, Zhu J and Liu J. Trimetazidine improves exercise tolerance in patients with ischemic heart disease: a meta-analysis. Herz 2016; 41: 514-522.
[23] Zhan B, Huang X, Jiang L, Bao H and Cheng X. Effect of nicorandil administration on preventing contrast-induced nephropathy: a meta-analysis. Angiology 2018; 69: 568-573.
[24] Babic V, Petitpain N, Guy C, Trechot P, Bursztejn AC, Faillie JL, Vial T, Schmutz JL and Gillet P. Nicorandil-induced ulcerations: a 10-year observational study of all cases spontaneously reported to the French pharmacovigilance network. Int Wound J 2018; 15: 508-518.
[25] Bammert TD, Hijmans JG, Kavlich PJ, Lincenberg GM, Reiakvam WR, Fay RT, Greiner JJ, Stauffer BL and DeSouza CA. Influence of sex on the number of circulating endothelial microparticles and microRNA expression in middle-aged adults. Exp Physiol 2017; 102: 894-900.
[26] Tariket S, Sut C, Arthaud CA, Eyraud MA, Meneveaux A, Laradi S, Hamzeh-Cognasse H, Garraud O and Cognasse F. Modeling the effect of platelet concentrate supernatants on endothelial cells: focus on endocan/ESM-1. Transfusion 2018; 58: 439-445.
[27] Chen HT, Wu YT, Yang WC, Tarng DC and Lin CC. Nicorandil-induced hyperkalemia in a hemodialysis patient. Am J Med Sci 2017; 353: 411-412.