

Case Report

Ventricular fibrillation and sudden cardiac death induced by upper gastrointestinal bleeding in a patient receiving PCI: a case report and literature review

Dan Han, Hua Qiang, Yingying Liu, Chaofeng Sun, Guoliang Li

Department of Cardiology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China

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Abstract: In post percutaneous coronary intervention (PCI) patients, it is a key challenge to decrease the toll of ventricular fibrillation (VF) or sudden cardiac death (SCD) induced by postoperative complications, predominantly from bleeding after the administration of dual antiplatelet therapy (DAPT). In this study, we reported a male patient who was diagnosed as unstable angina. He suffered an episode of syncope about 4 months ago, which lasted for nearly half a minute and the patient recovered on his own. He had more than 40 years of smoking history. The patient had no history of hypertension, hepatitis, diabetes mellitus, cerebrovascular disease or other health problems. There were no obvious contraindications regarding the results of preoperative examinations, except that the hemoglobin level was 110 g/L, which suggested a mild baseline anemia. The patient received PCI in our hospital. Here, we presented a case of post PCI patient developing into VF and SCD after the administration of DAPT, owing to upper gastrointestinal bleeding (UGIB) after having hard beef jerky. This study aimed to review the tragic case and facilitate the dietary management of post-PCI patients receiving DAPT.

Keywords: Ventricular fibrillation, percutaneous coronary intervention, sudden cardiac death, upper gastrointestinal bleeding, severe coronary artery lesions

Introduction

As a major complication with an increased morbidity and mortality in patients receiving percutaneous coronary intervention (PCI) for stent placement, upper gastrointestinal bleeding (UGIB) serves as an independent predictor for the prognosis [1]. The incidence of UGIB is about 0.6%~2.3% worldwide [2]. UGIB is influenced by an advanced age (>70 years old), BMI>25 kg/m², smoking, history of gastrointestinal disease, hypertension, diabetes mellitus, acute coronary syndrome, the use of anticoagulant (warfarin/heparin) and anti-platelet therapies, thrombocytopenia and baseline anemia [3-5]. On the other hand, perioperative therapies, rational drug using and appropriate nursing are also crucial for patients undergoing PCI [6]. In the present study, we presented a case of ventricular fibrillation (VF) and sudden cardiac death (SCD), which were induced by UGIB in a patient undergoing PCI treatment for severe coronary artery lesions.

Case report

Clinical data

A 72 years old man was diagnosed as unstable angina in our hospital. The patient suffered an episode of syncope about 4 months ago, which lasted for nearly half a minute and the patient recovered on his own. The patient had more than 40 years of smoking history and smoked 20 cigarettes per day on average. The patient denied any history of hypertension, hepatitis, diabetes mellitus, cerebrovascular disease or other health problems.

Routine examinations

There were no obvious contraindications regarding the results of preoperative examinations, except that the hemoglobin level was 110 g/L, which suggested a mild baseline anemia. The electrocardiogram (ECG) (**Figure 1**) taken prior to PCI did not show any obvious abnormalities.

VF and SCD induced by USIB in patient receiving PCI

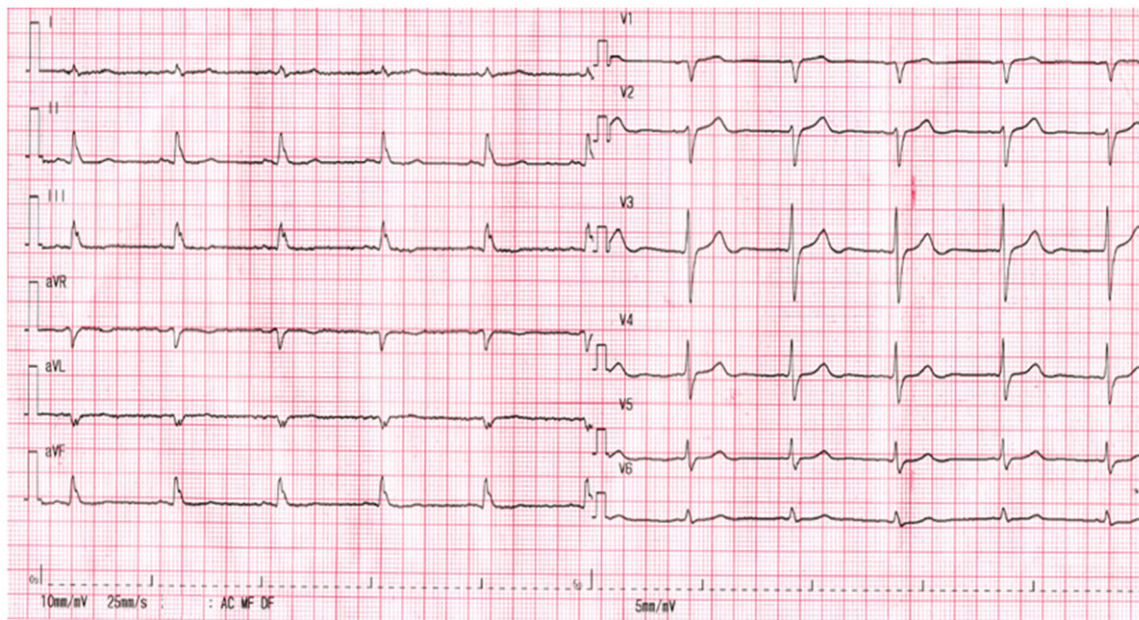


Figure 1. The electrocardiogram was taken prior to percutaneous coronary intervention.

The patient was also evaluated by echocardiography, which pointed out aortic valve calcification and stenosis. Coronary angiography showed severe coronary artery lesions, including signs of a double-vessel lesion in left main coronary artery (LM), which was associated with approximately 80% stenosis in the end. In addition, diffuse stenosis of the right coronary artery (RCA) reached 80-95%.

Treatment

Considering the high risk for revascularization complications in the LM, physicians implanted a total of 3 stents into the right coronary artery. To protect gastrointestinal mucosa, cumulative dose of 300 mg aspirin and 300 mg clopidogrel combined with lansoprazole were given to the patient prior PCI. In addition, anticoagulation and antiplatelet therapies were well managed within a reasonable range during and after the PCI. Unfractionated heparin was used during the procedure. After PCI, we adjusted the dose of aspirin at 100 mg/d, clopidogrel at 75 mg/d with others unchanged. On the third day after the patient received PCI, he felt nausea and vomited about 300-400 ml of gastric contents and fresh blood after having several hard beef cubes. ECG (**Figure 2**) showed obvious ischemic changes. The patient looked pale and was sweating, and the blood pressure was lowered down to 70/50 mmHg. We started to rescue

the patient immediately, using a fluid replacement therapy as well as appropriate equipment and drugs. Unfortunately, the patient suffered from ventricular fibrillation, which was detected by the ECG monitor (**Figure 3**) and eventually led to SCD. The hard beef jerky might be the cause of bleeding because this kind of hard food for the post-PCI patient with DAPT can injure the fragile gastric mucosa, which may exacerbate cardiac ischemia and predispose the patient to the high risk of fatal arrhythmias.

Discussion

Risk factors of UGIB

As described above, in post-PCI patient, UGIB can be caused by many factors including a history of peptic ulcer, upper gastrointestinal hemorrhage, hemorrhagic esophagitis, gastritis or other gastrointestinal diseases. In addition, the administration of thrombolytic drugs before the operation as well as inappropriate combinations of multiple anticoagulation and antiplatelet drugs during and after the procedure might injure the gastric mucosa directly. The gastric mucosa of patients suffering acute coronary syndrome and instable hemodynamics was in a hypoxic-ischemic state prone to acute myocardial infarction. PCI might induce the erosion and ischemia of gastric mucosa during a stress

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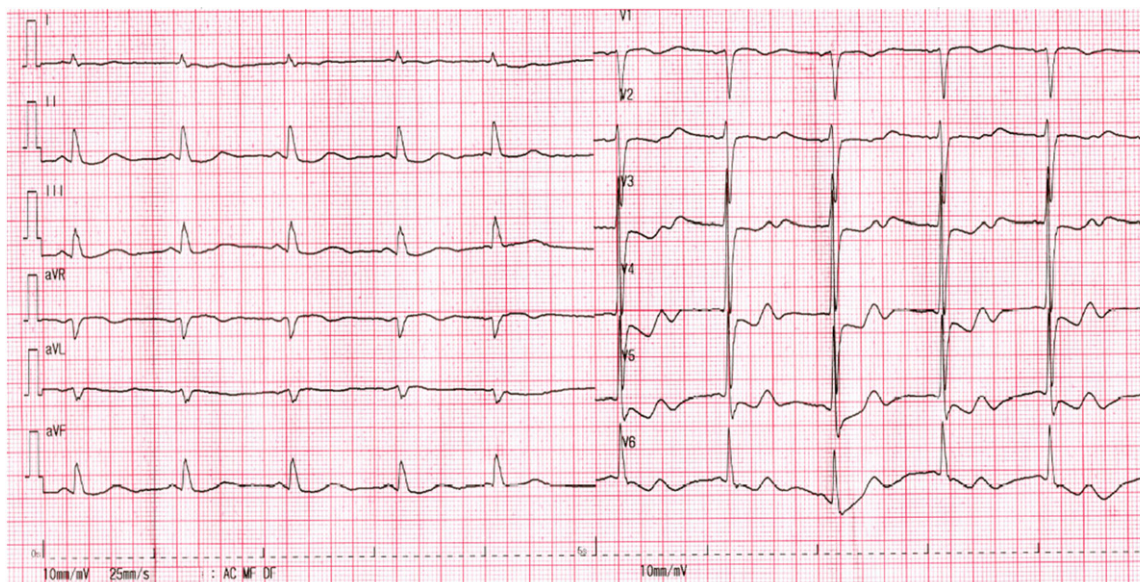


Figure 2. The electrocardiogram was taken after percutaneous coronary intervention.



Figure 3. The electrocardiogram monitor recorded upper gastrointestinal bleeding induced a sudden ischemia of coronary artery and the patient suffered ventricular fibrillation.

response. Furthermore, elder patients usually suffered from microcirculation disturbance, which might lead to gastrointestinal hemorrhage. The patient in this study displayed 5 potential risk factors for UGIB: an advanced age, baseline anemia, smoking history, PCI induced stress, aortic valve calcification and stenosis that resulted in the hypoperfusion of systemic organs. The CRUSADE bleeding score of the patient was 35, suggesting a moderate risk of bleeding. In addition, the patient's risk for a major bleeding episode was 7.9%. Therefore, it was concluded that the potential risk predictors for UGIB were present, and the risk for spontaneous bleeding of the upper gastrointestinal tract was not high, unless any other predispositions gave rise to a sudden hemorrhage. The patient's diet after the PCI procedure was

investigated, and we found that the patient did not eat any special food except beef jerky. It was realized that the hard texture of beef jerky might injure the fragile gastric mucosa of the patient and led to gastrointestinal hemorrhage. These findings suggest that the acute LM stenosis induced by UGIB contribute to ventricular fibrillation and SCD.

Antithrombotic therapies for acute coronary syndrome

Relevant guidelines recommended the administration of aspirin in a loading dose (162-325 mg) immediately after the attack of myocardial infarction. In addition, aspirin in a low dose (75-100 mg) is suggested for secondary prevention, as aspirin can prevent ischemic events

effectively and lower the risk of bleeding [7-9]. Compared with clopidogrel alone, the CURE trial demonstrated that aspirin in combination with clopidogrel (loading dose of 300 mg followed by a daily dose of 75 mg) reduced the risks of cardiovascular death, non-fatal myocardial infarction, and stroke by 20% (9.3% vs. 11.4%; relative risk [RR] 0.80, 95% CI: 0.72-0.90; $p < 0.001$), accompanied with an increased risk of massive hemorrhage [10].

For treatment of acute myocardial infarction, administration of prasugrel and ticagrelor, more potent P2Y₁₂ receptor inhibitors, was recommended in recent ESC and ACC/AHA guidelines [11, 12]. Studies demonstrated that prasugrel or ticagrelor in powder, instead of tablet, might be conducive to gastrointestinal absorption and platelet inhibition [13, 14]. On the other hand, the ACCOAST trial demonstrated that ischemic outcomes were not affected by such factors, but prasugrel pretreatment increased the risk of massive hemorrhage (HR: 1.90, 95% CI: 1.19-3.02; $p = 0.006$) [15, 16]. The efficacy of cangrelor and clopidogrel in a dose of 300 or 600 mg before PCI was compared in a recent study, and the results showed that for the composite deaths and ischemic events (e.g. stent thrombosis) in 48 h after PCI, cangrelor exhibited a more promising efficacy than clopidogrel (4.7% vs. 5.9%; OR 0.78; 95% CI: 0.66-0.93; $p = 0.005$) without any increasing risk of bleeding, suggesting that P2Y₁₂ inhibitor was insufficient for patients and cangrelor might be the better choice [17]. Guidelines recommended that dual antiplatelet therapy (DAPT) should be initiated at least one year after the last episode of acute coronary syndrome [8, 18]. The optimal duration of DAPT remains unclear because of the association between the increased risk of bleeding and the prolonged DAPT. The DAPT score serves as a useful index in estimating the individual duration of antiplatelet therapies [12]. During follow-up, aspirin should be immediately withdrawn, and, if possible, replaced with P2Y₁₂ inhibitor once DAPT was interrupted due to a high risk of bleeding period, because patients might suffer high risk of ischemia due to the withdrawal of P2Y₁₂ inhibitor therapy [19].

Another study suggested that, after PCI, patients received individual administration of three drugs (clopidogrel, warfarin and aspirin) and combined administration of clopidogrel and

warfarin for one month. The results showed that in individual administration group and combined administration group, the incidences of major or minor bleeding (19.4% vs. 44.4%; HR: 0.36, 95% CI: 0.26-0.50; $p < 0.0001$), ischemic events (11.1% vs. 17.6%; 0.60, 0.38-0.94; $p = 0.025$), and mortality (2.5% vs. 6.3%; 0.39, 0.16-0.93; $p = 0.027$) were significantly lowered [20, 21]. For patients with high risk of bleeding, proton-pump inhibitor (PPI) therapy should be considered for protection of gastrointestinal tract. Pantoprazole is superior to other PPIs when combined with a P2Y₁₂ inhibitor. In addition, ranitidine or other H2 receptor antagonist is also alternative [22].

Unfractionated heparin was recommended for a conservative therapy or for a PCI procedure. In comparison of the effect with medication of unfractionated heparin or enoxaparin-based regimens, bivalirudin monotherapy reduced the risk of major bleeding, but litter evidence supported the efficacy of bivalirudin in NSTEMI [19]. Based on the guidelines and the economic conditions of the patients, lansoprazole in conjunction with 300 mg aspirin and 300 mg clopidogrel were given to protect the gastrointestinal mucosa, which was still in an adequate state before the PCI. Unfractionated heparin was used during the procedure. After PCI, the doses of aspirin and clopidogrel were adjusted to 150 mg/d, while the dosage of other medications was unchanged. Considering the fact that elderly patients usually suffered from microcirculation disturbance, alprostadil was also given to the patient to improve the microcirculation.

Recommendations for lifestyle and physical activities after acute coronary syndrome

Reports and guidelines suggested that for all patients, mortality might be improved by cardiac rehabilitation, smoking cessation, a good mindset, a heart-healthy diet with low saturated fat and cholesterol, and improved medication adherence, especially for those undergoing DAPT after PCI. As for physical activity, exertion is to be avoided but physical activity can be gradually increased over a period of 1-2 weeks. Physical and sexual activities should be stopped in the first 2 weeks. Concomitant administration of nitrate and sildenafil or tadalafil should be avoided and the patients can be back to work within 2-4 weeks [19]. However, few studies mentioned the dietary manage-

ment for this type of patients, and only recommendations were diets with low saturated fat and cholesterol. Therefore, in this report, hard food (e.g. beef jerky, apple and other air-dried food) was not recommended for patients with high risk of UGIB.

Patient management: For patients with acute coronary syndrome and at high risk of gastrointestinal bleeding, special attention should be paid in perioperative and follow-up management of stent replacement operations. Before PCI, the history of previous diseases should be confirmed and relevant tests should be completed, especially the occult blood test and the test for coagulation functions. If possible, electron gastroscopy and thrombelastogram (TEG) should be performed. Risk stratification has to be considered by calculating CRUSADE, and GRACE scores should be used to evaluate the patients. The most important issue is to use medications according to guideline recommendations. For patients with the left ventricular ejection fraction (LVEF) <35% (NYHA class II or III), or patients with a left ventricular ejection fraction less than 30% (NYHA class I), an implantable cardioverter-defibrillator, if necessary, should be considered in case of the sudden cardiac death [20, 22-28]. The dietary management for these patients should also be emphasized. The tragic ending of the patient in this study was caused by eating hard food. In terms of therapies for patients suffering from acute coronary syndrome, there is still a long way to go.

Disclosure of conflict of interest

None.

Address correspondence to: Guoliang Li, Department of Cardiology, The First Affiliated Hospital of Xi'an Jiaotong University, West of Yanta Road #277, Xi'an, Shaanxi, 710061, China. Fax: +86-029-82657140; E-mail: liguoliangday@163.com

References

[1] Lee JM, Park SY, Choi JH, Kim UJ, Rew SJ, Cho JY, Ahn Y, Lim SW, Jun CH, Park CH, Kim HS, Choi SK and Rew JS. Clinical risk factors for upper gastrointestinal bleeding after percutaneous coronary intervention: a single-center study. *Gut Liver* 2016; 10: 58-62.

[2] Tielleman T, Bujanda D and Cryer B. Epidemiology and risk factors for upper gastrointesti-

nal bleeding. *Gastrointest Endosc Clin N Am* 2015; 25: 415-428.

[3] Ahmed M. Blood thinners and gastrointestinal endoscopy. *World J Gastrointest Endosc* 2016; 8: 584-590.

[4] Bingener J and Gostout CJ. Management of nonvariceal upper gastrointestinal bleeding. *Gastrointest Endosc Clin N Am* 2011; 21: 721-730.

[5] Tantau M, Crisan D, Popa D, Vesa S and Tantau A. Band ligation vs. N-Butyl-2-cyanoacrylate injection in acute gastric variceal bleeding: a prospective follow-up study. *Ann Hepatol* 2013; 13: 75-83.

[6] Tsurumaki Y, Haraguchi Y and Nakamura T. Safety of radial access for primary percutaneous intervention in patients with ST-elevation acute myocardial infarction: results from a low-volume center. *Angiology* 2017; 331971-7722282.

[7] Correction to: 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American college of cardiology/American Heart Association Task Force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-Elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation* 2016; 134: e192-194.

[8] Hochholzer W and Neumann FJ. [The new 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation]. *Dtsch Med Wochenschr* 2016; 141: 782-785.

[9] Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK and Smith SC Jr. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Sur-

- gery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* 2016; 134: e123-155.
- [10] Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345: 494-502.
- [11] Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association for Clinical Chemistry. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American college of cardiology/American heart association task force on practice guidelines. *J Am Coll Cardiol* 2014; 64: e139-228.
- [12] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF and Windecker S. [2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)]. *G Ital Cardiol (Rome)* 2016; 17: 831-872.
- [13] Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, ten Berg JM, Miller DL, Costigan TM, Goedicke J, Silvain J, Angioli P, Legutko J, Niethammer M, Motovska Z, Jakubowski JA, Cayla G, Visconti LO, Vicaut E, Widimsky P; ACCOAST Investigators. Pre-treatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med* 2013; 369: 999-1010.
- [14] Montalescot G, Collet JP, Ecollan P, Bolognese L, Ten Berg J, Dudek D, Hamm C, Widimsky P, Tanguay JF, Goldstein P, Brown E, Miller DL, LeNarz L, Vicaut E; ACCOAST Investigators. Effect of prasugrel pre-treatment strategy in patients undergoing percutaneous coronary intervention for NSTEMI: the ACCOAST-PCI study. *J Am Coll Cardiol* 2014; 64: 2563-2571.
- [15] Parodi G, Xanthopoulou I, Bellandi B, Gkizas V, Valenti R, Karanikas S, Migliorini A, Angelidis C, Abbate R, Patsilinakos S, Baldereschi GJ, Marcucci R, Gensini GF, Antonucci D, Alexopoulos D. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. *J Am Coll Cardiol* 2015; 65: 511-512.
- [16] Rollini F, Franchi F, Hu J, Kureti M, Aggarwal N, Durairaj A, Park Y, Seawell M, Cox-Alomar P, Zenni MM, Guzman LA, Suryadevara S, Antoun P, Bass TA, Angiolillo DJ. Crushed prasugrel tablets in patients with STEMI undergoing primary Percutaneous Coronary Intervention: the CRUSH study. *J Am Coll Cardiol* 2016; 67: 1994-2004.
- [17] Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, Price MJ, Leonardi S, Gallup D, Bramucci E, Radke PW, Widimsky P, Tousek F, Tauth J, Spriggs D, McLaurin BT, Angiolillo DJ, Genereux P, Liu T, Prats J, Todd M, Skerjanec S, White HD, Harrington RA; CHAMPION PHOENIX. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* 2013; 368: 1303-1313.
- [18] Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016; 68: 1082-1115.
- [19] Bazemore TC, Nanna MG, Rao SV. Benefits and risks of P2Y₁₂ inhibitor preloading in patients with acute coronary syndrome and stable angina. *J Thromb Thrombolysis* 2017.
- [20] Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijssen JG, van 't Hof AW, ten Berg JM; WOEST Study Investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013; 381: 1107-1115.
- [21] Erlinge D, Koul S, Eriksson P, Schersten F, Omerovic E, Linder R, Ostlund OP, Wallentin L, Frobert O and James S. Bivalirudin versus heparin in non-ST and ST-segment elevation myocardial infarction-a registry-based randomized

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- clinical trial in the SWEDEHEART registry (the VALIDATE-SWEDEHEART trial). *Am Heart J* 2016; 175: 36-46.
- [22] Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, Shook TL, Lapuerta P, Goldsmith MA, Laine L, Scirica BM, Murphy SA, Cannon CP; COGENT Investigators. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010; 363: 1909-1917.
- [23] Fox KM; EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; 362: 782-788.
- [24] McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371: 993-1004.
- [25] Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992; 327: 669-677.
- [26] Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurlley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348: 1309-1321.
- [27] Roberts R, Rogers WJ, Mueller HS, Lambrew CT, Diver DJ, Smith HC, Willerson JT, Knatterud GL, Forman S, Passamani E, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) II-B study. *Circulation* 1991; 83: 422-437.
- [28] Matsuda Y, Kawate H, Matsuzaki C, Sakamoto R, Shibue K, Ohnaka K, Anzai K, Nomura M and Takayanagi R. Eplerenone improves carotid intima-media thickness (IMT) in patients with primary aldosteronism. *Endocr J* 2016; 63: 249-255.