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„Triple Therapy" in high risk patient after primary PCI: Case report and practical application of current ESC and ACC/AHA guidelines

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A 52-year-old man with diagnosis anterolateral myocardial infarction arrived into the Coronary Care Unit, Clinical Center of Serbia. He had typical chest pain which started 36 hours before admission to hospital when he was driving the car. He knew for unregulated hypertension, hyperlipidemia, glucose intolerance and he was active smoker. ECG on admission documented like sinus rhythm with heart frequency 78 per minute and elevation ST segment in leads D2, D3, aVF and QS pattern in V1-V5 with elevation ST segment. His blood pressure was 120/80 mmHg measured on both of arms. In catheterization laboratory there were occlusion left anterior descending coronary artery (LAD) in medial segment, stenosis in ramus intermedius coronary artery (RIA) 90-99% and in medial right coronary artery (RCA) 50-70%. There were made multiple aspiration of thrombus and implantation one bare metal stent in LAD medial segment. Coronary flow after that was TIMI 3, but there were distal embolization and because that patient treated with antagonist GP IIb/IIIa and Na nitroprusid intracoronary. Conclusion after that was that PCI in RCA should perform in second intervention. On second day his breath became shortness and there were signs of heart failure. In laboratory analyses Troponin I (105.69 ng/ml) and NT pro BNP (2552 pg/ml) were elevated level. Also, markers of inflammation CRP 211.5mg/l, fibrinogen 5.1, Le 17.7x109/l were elevated level. Echocardiogram revealed systolic impairment, left ventricle (LV) and LVEF was 32% with segmental contraction abnormalities like akinesia in apical segments intraventricular septum, lateral, inferior and anterior wall (figure 1). Spontaneous echocardiographic contrast in left ventricle found therewith (figure 2). Valves were normal. Therapy with Clopidogrel has been replaced with Ticagrelor on the second day after risk assessment and platelet aggregation test and Clopidogrel and Aspirin resistance (TRAP 904 AU*min, ADP 526 AU*min, ASP 956 AU*min), and dose of Aspirin increased to 200mg. Discharge therapy was "triple therapy" with Ticagrelor (2x90mg), Aspirin 200mg and Enoxaparin 2x0.6ml. He got Furosemide, Spironolactone, Bisoprolol, Ramipril and Rosuvastatin, also. Because thrombus did not see in hospitalization, therapy with LWMH has been interrupted two weeks later.

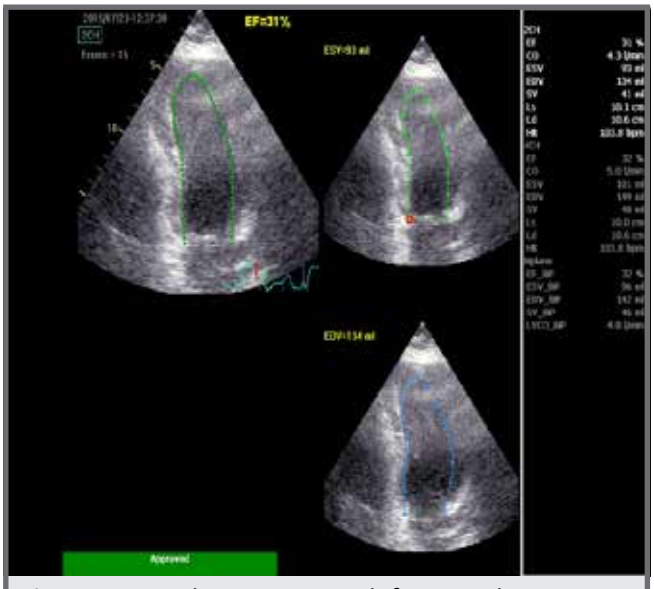

Figure 1. Systolic impairment left ventricle.

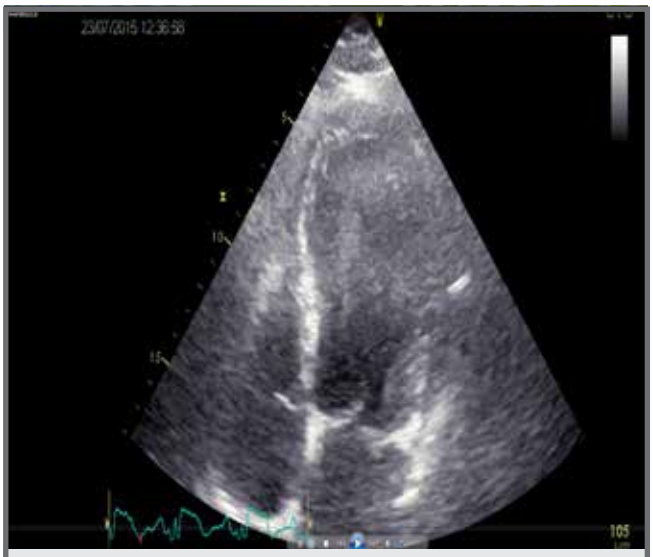

Figure 2. Spontaneous echocardiographic contrast in left ventricle

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He returned to the clinic 3 months later for control checkup and echocardiography evaluated aneurysm of apex with soft thrombus in that region and spontaneous echocardiographic contrast. We wonder for the most appropriate stroke prophylaxis therapy for this patient and anticoagulation therapy started again with Enoxaparin and after that Vitamin K antagonist. We had dilemma about interrupting dual antiplatelet therapy, but patient waited for the second percutaneous coronary intervention and dual antiplatelet therapy was continued. Fortunately, dilemma was solved after secondary coronary angiography. There were collateral circulation from left system to ramus intermedius, and no significant stenosis in RCA and any new intervention was not necessary. In the short meantime, when he took triple therapy, he came into the health center with signs epistaxis once and he checkup international normalized ratio (INR) orderly with target value 2.0. After secondary coronary angiography Aspirin interrupted. It has been more than three months since primary PCI and implantation of bare metal stent.

Discussion

In ACCF/AHA management of ST-Elevation Myocardial Infarction (STEMI) anticoagulant therapy with a vitamin K antagonist should be provided to patients with STEMI and AF with CHADS2 score ≥2, mechanical heart valves, venous thromboembolism, or hypercoagulable disorder (Class I, Level of Evidence: C). The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y12 receptor inhibitor should be minimized to the extent possible to limit the risk of bleeding. (Class I, Level of Evidence: C). Anticoagulant therapy with a vitamin K antagonist is reasonable for patients with STEMI and asymptomatic LV mural thrombi (Class IIa, Level of Evidence: C). Opinion that anticoagulant therapy may be considered for patients with STEMI and anterior apical akinesis or dyskinesis is in class IIb as well as targeting vitamin K antagonist therapy to a lower INR (e.g., 2.0 to 2.5) in patients with STEMI who are receiving dual antiplatelet therapy (DAPT)[1]. Triple therapy with a vitamin K antagonist, aspirin, and a P2Y12 receptor inhibitor should be restricted to specific clinical situations after STEMI in which the risk of systemic or venous thromboembolism or stent thrombosis is considered to exceed that of bleeding. The novel oral anticoagulants have not been recommendation. The duration of vitamin K antagonist therapy can be limited to 3 months in patients with or at risk for LV thrombus (e.g., those with anteroapical akinesis or dyskinesis), whereas the duration of DAPT could be predicated on stent type. Also, for patients undergoing primary PCI who require anticoagulation, avoidance of a DES is strongly preferred. When triple therapy is used, an international normalized ratio targeted to a range of 2.0 to 2.5 might be reasonable.

In the last years, the frequency of mural LV thrombus has decreased, largely because of the progress made in reperfusion therapy, the widespread use of multiple antithrombotic agents in STEMI, and the limitation of myocardial infarct size produced by effective, early myocardial reperfusion[2]. Although some studies suggest that up to a quarter of anterior MIs have detectable LV thrombi[3]. LV thrombi are associated with poor prognosis because of their association with extensive infarcts, particularly anterior infarcts with apical involvement, and a risk of systemic embolism[4]. Consensus is that mural thrombi, once diagnosed, require oral anticoagulant therapy with vitamin K antagonists for up to 6 months, but this has not been revisited in the era of stenting and DAPT[2]. Combining oral anticoagulation and DAPT into a triple therapy increases bleeding risks[5]. The optimal duration of such triple antithrombotic therapy is unknown and should take into account the relative risks of bleeding and stent thrombosis. Repeated imaging of the left ventricle after 3 months of therapy may allow discontinuation of anticoagulation earlier than 6 months, if evidence of thrombus is no longer present, particularly if there is recovery of apical wall motion. In the last ESC guidelines for the management of STEMI and patients with LV thrombus anticoagulation should be instituted for a minimum 3 months (Class IIa, Level B)[2].

It was established that spontaneous echo contrast (SEC) had a strong association and predisposition to thromboembolism and stroke in patients with dilated cardiomyophatia[6]. In study of patients with severe LV dysfunction, the stroke rate was 14.9% in patients with and 9.5% in those without thrombus in LV[7]. The pathogenesis of SEC is not clearly established. However, it appears that multiple factors [e.g., aging, low blood flow velocity, high erythrocyte sedimentation (ESR), increased serum fibrinogen level, elevated hematocrit, structural abnormalities of cardiovascular system] potentially contribute to red blood cell and plasma protein interactions that lead to the development of SEC[6]. Even though additional factors such as mitral regurgitation,

Table 1. Risk factors for bleeding in patients with acute coronary syndrome (ACS)

Advanced age (>75 y)
Female sex
Heart failure or shock cardiacus
Diabetes mellitus
Body size
History of gastrointestinal bleeding
Presentation with STEMI or NSTEMI (vs UA)
Severe renal dysfunction (CrCl<30 mL/min)
Elevated white blood cell count
Anemia
Fibrinolytic therapy
Invasive strategy
Inappropriate dosing of antithrombotic medications
Chronic oral anticoagulant therapy

Legend: ACS-acute coronary syndrome; CrCl-creatinine clearance; NSTEMI- non–ST-elevation myocardial infarction; STEMI-ST-elevation myocardial infarction; and UA- unstable angina

(Adapted from O'Gara PT, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: a Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013)

Table 2. Definitions of BARC, TIMI and GUSTO and ISTH bleeding criteria

Definition	**Criteria**
BARC	
Type 0	No bleeding
Type 1	• Not actionable bleeding which not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional. • It may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
Type 2	• Any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional (2) leading to hospitalization or increased level of care or (3) prompting evaluation.
Type 3	
Type 3a	• Overt bleeding plus hemoglobin drop of 3 to <5 g/dl • Any transfusion with overt bleeding
Type 3b	• Overt bleeding plus hemoglobin drop =5 g/dL • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) • Bleeding requiring intravenous vasoactive agents
Type 3c	• Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) • Subcategories confirmed by autopsy or imaging or lumbar puncture • Intraocular bleed compromising vision
Type 4: CABG-related bleeding	• Perioperative intracranial bleeding within 48 h • Reoperation after closure of sternotomy for the purpose of controlling bleeding • Transfusion of =5 U whole blood or packed red blood cells within a 48-h period • Chest tube output =2L within a 24-h period.
Type 5: Fatal bleeding	
Type 5a	• Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation.
Type 5b	• Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious.
TIMI	
Major	• Intracranial or clinically significant overt signs of hemorrhage associated with a hemoglobin decrease greater than 5 g/L • The diagnosis of intracranial bleeding required confirmation by computed tomography or magnetic resonance imaging of the head.
Minor	Observed blood loss and a decrease in hemoglobin level of 3 to 5 g/dL
GUSTO	
Severe	Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention
Moderate	Bleeding that requires blood transfusion but does not result in hemodynamic compromise
ISTH	
Major	1. Fatal bleeding, and/or 2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or 3. Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

(Adapted from Kikkert WJ. et al. The Prognostic Value of Bleeding Academic Research Consortium (BARC)-Defined Bleeding Complications in ST-Segment Elevation Myocardial Infarction: A Comparison With the TIMI (Thrombolysis In Myocardial Infarction), GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), and ISTH (International Society on Thrombosis and Haemostasis) Bleeding Classification. J Am Coll Cardiol 2014)

hypercoagulability and elevated hematocrit may lead to development of SEC, LV systolic dysfunction may also predispose SEC with low flow rates and low shear rates[6].

The CHA_2DS_2-VASc score, among other risk stratification schema, can be used to provide an idea of a patient's risk for TE event[8]. Our patent had high risk for thromboembolic event (TE), CHA_2DS_2-VASc score was 4. Triple therapy (Aspirin, Clopidogrel, and (N)OAK) after PCI in ESC/EACTS guidelines on myocardial revascularization should be used if there are strong indications: paroxysmal, persistent or permanent atrial fibrillation, heart failure, hypertension, age ≥75 years (2x), diabetes, CVI (2x) - vascular disease, age 65-74 years old and the female sex, CHA2DS2-Vasco skor≥2; mechanical valve replacement, recent or recurrent deep vein thrombosis or pulmonary embolism[9].

Such as the previously mentioned, application of "triple therapy" over a longer period of time is associated with an increased risk of bleeding. Of all the bleeding 1 in 10 is fatal and the half of that is intracranial, and the other half is gastrointestinal[10]. Risk factors for bleeding in patients with acute coronary sindrom have been identified from several clinical trials[11-14] (table 1).

We was considering and comparing the risk for major bleeding as calculated by the HAS-BLED score to the risk for thromboembolic events by the CHA2DS2-VASc to determine if the benefit of anti-coagulation outweighs the risk for bleeding. HAS-BLED score in our patient was 1 and other bleeding defined criteria by BARC, TIMI and GUSTO and ISTH were on low level also (table 2)[15].

We guided with recent studies were rates of thrombotic and bleeding events were similar in patients with triple therapy (Clopidogrel, Aspirin, Warfarin) and patients with Ticagrelor and Warfarin[16].

Conclusion

Patient preferences should be always taken into consideration because individuals may weigh these outcomes differently. What is therapy option in patient with spontaneous echo contrast in left ventricle who had a high risk for thromboembolism and low risk for bleeding after primary PCI, who treated with Ticagrelor because high risk and Clopidogrel resistance and who had multiple PCI interventions? Guidelines should be strictly respected, but sometimes the situation is complicated and unexpected. Risk scores for thrombosis and bleeding are certainly of great help in therapy of complicated patients with acute coronary syndrome.

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