ACTA MEDICA TRANSILVANICA September27(3):26-29
Online ISSN 2285-7079

DIRECT ORAL ANTICOAGULANTS IN PATIENTS WITH PERMANENT ATRIAL FIBRILLATION PRESENTING WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

MARIUS RUS[1] , GEORGIANA C. FILIMON[2]

[1]University of Oradea, [2]Doctoral School of Biological and Biomedical Sciences, University of Oradea
[1,2]Clinical County Emergency Hospital of Oradea

Keywords: *acute coronary syndromes, atrial fibrillation, oral anticoagulation, coronary heart disease, cardiogenic shock*

Abstract: *Ischemic heart disease with all of its forms is the most common cause of death worldwide. The pathophysiological substrate of coronary artery disease is atherosclerosis. Atherosclerosis was previously seen as a disease based on cholesterol storage in blood vessel, but now it is recognized as a complex process that involved inflammatory cells and a complex process that involves the arterial wall and its interaction with risk factors. Acute myocardial infarction remains the main cause of death in women. The complication of AMI with a cardiogenic shock increases the mortality risk even more. In the association between atrial fibrillation and acute coronary syndromes there is a major concern of the bleeding risk regarding the necessity of anticoagulant treatment and dual anti-platelet therapy. Although previously avoided, in the last years, direct oral anticoagulants (or non-vitamin K antagonists) began to be used in triple therapy with good results regarding bleeding and ischemic events. The case below presents a 77-year old woman with ST-elevation acute myocardial infarction, complicated with cardiogenic shock, with previously known atrial fibrillation, treated with dabigatran, clopidogrel and aspirin as triple antithrombotic therapy.*

INTRODUCTION

The acute myocardial infarction (AMI) is defined as evidence of myocardial injury (the elevation of cardiac troponin I or troponin T values with at least one value above the 99th percentile upper reference limit) associated with a clinical setting consistent with myocardial ischemia (chest pain or equivalent) and the persistent ST-segment elevation in at least two contiguous leads. Acute coronary syndrome with all of its forms occurs three to four times more often in men below the age of 60. However, after the age of 75, women are the majority of patients, AMI (acute myocardial infarction) remaining the main cause of death in women.(1) Ischemic coronary heart disease is a consequence of advanced coronary atherosclerosis, which induces a reduction in the functional diameter of the vessel. The role of inflammatory cells in the appearance and evolution of atherosclerosis has been a topic of high interest lately, the role of adiponectin, 18-interleukin and monocytes are well known. Advanced atheroma plaques are usually covered with fibrous tissue that separates them from the bloodstream and have a stabilizing role, its rupture leads to the total occlusion of the vessel, and provoking a myocardial infarction.(2) Cardiogenic shock is a severe complication of STEMI (ST-elevation myocardial infarction), has a frequency of six to ten percent of all STEMI patients, and a high rate in-hospital mortality.(3) In the case of cardiogenic shock, mechanical complications should be ruled out by echocardiology, and treatment strategies include emergency revascularization by PCI, with the reperfusion of culprit vessel, or complete revascularization in multivessel coronary disease.

Atrial fibrillation (AF) is the most common encountered arrhythmia, with a prevalence that increases with age. It is estimated that 5%–10% of patients with AF will undergo percutaneous coronary intervention.(4) In the past years, there was a significant increase in the use of direct oral anticoagulants (DOAC) for stroke prevention. In the case of a patient with chronic atrial fibrillation using DOAC and presenting with STEMI, primary percutaneous coronary intervention (PCI) is the procedure of choice, anticoagulation being a relative contraindication for fibrinolysis. Previous anticoagulation places the interventionist cardiologist into a sensitive decision-making process, regarding the choice of access site, peri-procedural antithrombotic and antiplatelet drugs, and long-term anticoagulation.(5) In the absence of randomized controlled trials, clinical practice relied on a joined consensus documents published to provide guidance on the treatment of patients which needed anti-thrombotic therapy for stroke prevention for AF and presented with acute coronary syndromes in time-frame for PCI revascularization.(6) The general consensus is to perform vessel revascularization by primary PCI regarding the time from the last dose of oral anticoagulant. Dual antiplatelet therapy is recommended in addition to antithrombotic therapy for 4 weeks, to be continued with oral anticoagulation (OAC) and one P2Y12 inhibitor, preferably Clopidogrel for a year. After 12 months OAC alone should be continued indefinitely.(7)

CASE REPORT

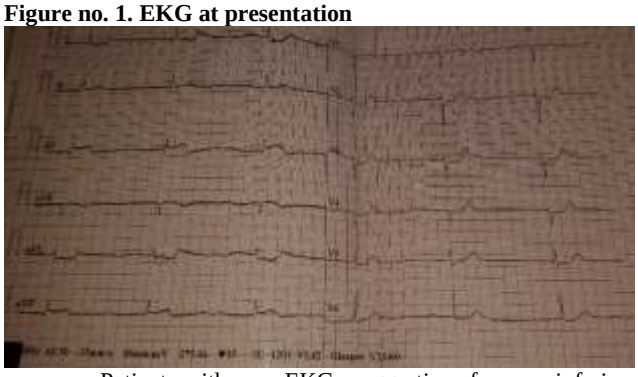
A 77-year old female, with history of atrial fibrillation with medium heart rate (HR), arterial hypertension and diabetes mellitus on insulin, presenting in the Emergency Room for retrosternal chest pain, resting shortness of breath and diaphoresis. Previous to this acute event, the patient followed continuous treatment with DOAC (Dabigatran 150mg twice a day), angiotensin converting enzyme inhibitors (ACEi),

[1]Corresponding author: Marius Rus, Str. Gh. Doja Nr. 99 G, Oradea, România, E-mail: rusmariusr@yahoo.com, Phone: +40744 526723
Article received on 09.08.2022 and accepted for publication on 02.09.2022

betablockers, basal insulin.

Clinical examination revealed a fully conscious but anxious patient, with grade I obesity (IMC=32,3kg/m2), with pale, wet tegument. Respiratory system: pulmonary vesicular murmur present bilateral, crackle rales present bilateral, respiratory rate of 20/minute, oxygen blood saturation= 90% peripheral. Cardiovascular system: bradycardic arrhythmic heart beats, no added sound or murmur, blood pressure (BP) of 80/55mmHg, heart rate (HR) of 45beats/min. Electrocardiogram (EKG) was performed, that revealed AF, HR=40beats/min, ST-segment elevation in DIII, AvF, ST-segment depression in DI, AvL, V2-V4 (figure no. 1).

Figure no. 1. EKG at presentation



Patient with an EKG suggestive for an inferior STEMI, complicated with cardiogenic shock, in need to rule out mechanical complications of acute myocardial infarction or cardiac tamponade. That was done by performing an echocardiography: aortic annulus=25mm, ascending aorta=30mm, left atrium =50mm, right ventricle=24mm, interventricular septum in diastole=16mm, left ventricle posterior wall in diastole=16mm, left ventricle inferior and lateral wall with hypokinesia, with concentric hypertrophy, ejection fraction of left ventricle= 40%, diastolic dysfunction type I (figure no. 2).

Figure no. 2. Echocardiography, a parasternal long axis view

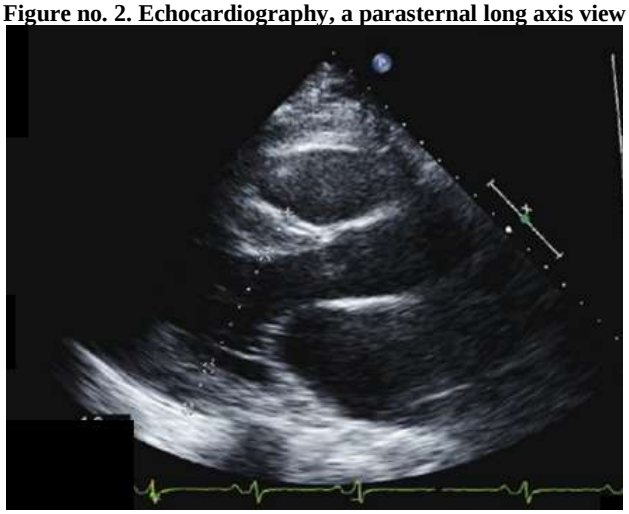


Table no. 1. Laboratory blood test with modified values

Test	Patient value	Normal rage
WBC	14.980/ 10^3 /uL	4.0-10.0/ 10^3 /uL
ALAT (GPT)	175 U/L	0-55 U/L
ASAT (GOT)	136 U/L	0-34 U/L
GLU	499 mg/dl	65-110 mg/dl
TROPONIN I	1347 ng/dl	0.0-27 ng/dl

An emergency coronarography was performed, with a right coronary artery (RCA) occlusion and a 75-90% stenosis of left anterior descending artery (LAD). Primary PCI was needed, as the patient presented cardiogenic shock, complete multivessel revascularization was preferred to revascularization of culprit vessel. A direct stent implantation was performed with a drug eluting stent 3.5 / 28mm at ACD level and another drug eluting stent 3.0 / 8mm at ADA level, with optimal angiographical result. After the revascularization, the evolution of the case was favourable, with the remission of symptoms, improvement of haemodinamical parameters (BP = 140 / 75mmHg, AV = 60bpm) and of biological parameters (WBC = 9 870 * 10^3 uL, ALAT = 55 U/L , ASAT = 33 U/L, Blood glucose = 135mg/dl).

Diagnosis: ST – segment elevation acute myocardial infarction in inferior territory and of the right ventricle. Cardiogenic shock. Bivasculary coronarian disease (ACD, LAD). Permanent atrial fibrilation. Diabetes mellitus type II with insulin treatment.

Patient has a history of permanent atrial fibrilation, with DOAC chronic treatment before presenting with STEMI, is now in need for double antiplatelet therapy (DAPT). First step, calculating risk scores: CHA2DS2-VASC= 5 points (stroke/transitory ischaemic accident/peripheral emboli risk = 10%), HAS-BLED = 2 points (moderate bleeding risk), PRECISE-DAPT > 25 points. Taking the patient's high ischaemic risk into consideration and the moderate bleeding risk, the decision of triple antithrombotic therapy was made (DOAC and DAPT). Although parenteral anticoagulation is of choice for patients with STEMI, in this particular case the decision of continuing with patients chronic dabigatran treatement was made. Patient received triple association with dabigatran 150mg bid, clopidogrel 600mg loading dose, continued with 75mg/ day, acetylsalicylic acid (ASA) 300mg loading dose, continued with 75mg/day, high dose of statin (atorvastatin 80mg/day), ACEi (ramipril 5mg/day) after the normalization of blood pressure, proton pump inhibitors. The triple association was continued for 4 weeks, after that ASA was stopped, and dabigatran in association with clopidogrel was continued to 12 months from the myocardial infarction.

The patient did not develop any possible or probable complications (rhythm disorders, post-AMI pericarditis, acute stent thrombosis, hemorrhagic events due to the administration of DAPT + DOAC). The patient did not present any major hemorrhagic event within the first year post the acute myocardial infarction. In a one year follow-up, patient did not present with recurrent AMI, there was no need for new target vessel revascularization, no major ischemic event.

DISCUSSIONS

Atrial fibrillation is the most common rhythm disorder appearing in patients with acute myocardial infarction, with a prevalence of 10-15%. It is estimated that 10% of the patients with permanent atrial fibrillation will require a coronary angiography.(8) Even with the continuous evolution of antithrombotic agents, patients who associate AF with acute coronary syndrome (ACS) have an increased mortality risk. Atrial fibrillation is considered an independent marker for increased long-term mortality postinfarct.(9) One of the most feared complication in patients with AF and ACS is major or life-threatening bleeding, due to the association between oral anticoagulation and anti-platelet therapy. One of the first trials made to observe the benefit of dual versus triple therapy was the WOEST trial, that compared clopidogrel and warfarin association, with ASA, clopidogrel and warfarin. After a one year follow-up, it has been noticed a lower combined secondary endpoint of death, stroke, target vessel revascularization, acute stent thrombosis, recurrent myocardial infarction in the dual therapy group.(10)

The RE-DUAL PCI trial was a multicenter study that

compared dabigatran in 110 mg and 150 mg twice per day with warfarin, as the oral anticoagulant to be used in triple therapy (in association with clopidogrel and ASA). In both dabigatran arms there was a significant reduction of major bleeding events, with comparable ischemic complications. However, there was an increased rate of stent thrombosis and myocardial infarction in the 110 mg dabigatran with clopidogrel and without aspirin group.(11)

The AUGUSTUS trial studied the composite endpoint of death, myocardial infarction, target vessel revascularization, major bleeding between apixaban and vitamin k antagonist (VKA). There was a reduction in major bleeding with apixaban compared to VKA. Also, the rate of death or hospitalization was lower in the apixaban group.(12) This trial also demonstrated the benefit of aspirin regarding major ischemic events and stent thrombosis. The PIONEER-AF PCI trial tested the efficacy of rivaroxaban 15mg daily in association with clopidogrel, but the trial was underpowered to exclude an increased risk for stroke.(13)

In patients with ongoing oral anticoagulation that need emergency PCI for STEMI, it is important to reduce the bleeding risk by choosing the radial access site for the coronarography. Radial access was associated with lower vascular complications, lower transfusion need, and a significant mortality benefit.(14) If the patient is using warfarin and at the time of PCI the International normalized ratio (INR) is between therapeutic rages, there is no need for additional peri-procedural anticoagulation.(15) There are not enough evidence to support the safety to perform PCI on DOAC therapy, therefore additional parenteral anticoagulation is needed during the stenting procedure for patients using DOAC.(16)

Patients with permanent atrial fibrillation presenting with acute coronary syndromes, that undergo PCI with stent implantation should receive triple antithrombotic therapy for as short as possible (usually 30 days). Dual antithrombotic therapy with an oral anticoagulant and a P2Y12 inhibitor is recommended, preferably clopidogrel can be used for the first 6-12 months after the primary PCI. It is recommended to use non-vitamin K antagonist (DOAC) in the absence of contraindication, to the detriment of AVK. After 12 months, oral anticoagulation alone is recommended.(7)

In unstable STEMI patients, as described in the case above, timing is very important. The FITT-STEMI analysis showed that for every 10 minutes delay between 60-180 minutes from the first medical contact, the mortality increases by 3.3%.(17)

Patients presenting with STEMI and multivessel coronary disease have a higher mortality risk. A complete coronary revascularization is defined as a residual GRACE score lower than 8. Patients with complete revascularization have lower rate of recurrent AMI, death, rehospitalisation for ACS, and repeat coronary revascularization.(18) There is no common ground in favour of immediate versus staged complete revascularization, although many studies were made. In general, a staged complete revascularization is recommended in stable patients. The most frequent ischemic complications were reported during direct complete revascularization, staged revascularization being an independent predictor of survival in patients with no hemodynamic instability.(19)

The CULPRIT-SHOCK trial compared one-stage versus staged complete revascularization in patients presenting with AMI and cardiogenic shock. Results showed that a strategy with PCI of the culprit lesion, with possible staged revascularization determined a lower 30 day risk of the of all-cause mortality or severe renal failure compared with immediate multivessel stenting.(20)

Despite the attempt to standardize the time and method of multivessel coronary artery disease, all guidelines leave a small place for the interventionist cardiologist to decide the proper stenting strategy for the patient. Each case has its singularity, and needs to be treated in the most suited method for that case.

CONCLUSIONS

Antithrombotic and anti-platelet treatment in patients with permanent atrial fibrillation and acute myocardial infarction with persistent ST-segment elevation should be chosen depending on the ischemic and the bleeding risk of the patient. In the presented case, dabigatran was chosen for initial triple antithrombotic therapy, and continued in dual therapy in association with clopidogrel for 12 months. The patient did not experience any major bleeding during this treatment, had no major cardiovascular event, no need for new revascularization, no recurrent MI. Complete one-staged revascularization was chosen for this particular case because ten non-culprit lesion was a proximal LAD stenosis, artery which provides 75% of myocardial vascularization.

Conflict of interest

The authors declare no conflict of interest

REFERENCES

1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2018;39(2):123-124, doi.org/10.1093/eurheartj/ehx393.
2. Ross R. Atherosclerosis-an inflammatory disease. N Engl J Med. 1999 Jan 14;340(2):115-126.
3. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction a population-based perspective. Circulation 2009;119(9):1211–1219.
4. Ntaios G, Papavasileiou V, Milionis H, Makaritsis K, Manios E, Spengos K, et al. Embolic strokes of undetermined source in the Athens stroke registry: A descriptive analysis. Stroke. 2015;46:176–81.
5. Potpara TS, Lip GY, Dagres N, et al. Management of acute coronary syndrome in patients with non-valvular atrial fibrillation: results of the European Heart Rhythm Association Survey. Europace. 2014;16:293-8.
6. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Antithrombotic management of ACS in AF patients. Eur Heart J. 2014;35:3155–79.
7. Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients With Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021 Feb;77(5):629–658.
8. Ntaios G, Papavasileiou V, Milionis H, Makaritsis K,

Manios E, Spengos K, et al. Embolic strokes of undetermined source in the Athens stroke registry: A descriptive analysis. Stroke. 2015;46:176–81.
9. Alkindi FA, Rafie MI. Anticoagulation in Patients with Atrial Fibrillation and Coronary Artery Disease. Heart Views. 2020 Jan-Mar;21(1):32–36.
10. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al. 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;381:1107–15.
11. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med. 2017;377:1513–24.
12. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med. 2019;380:1509–24.
13. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: A joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS) Eur Heart J. 2014;35:3155–79.
14. Valgimigli M, Gagnor A, Calabro P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Ando G, Repetto A, Limbruno U, Cortese B, Sganzerla P, Lupi A, Galli M, Colangelo S, Ierna S, Ausiello A, Presbitero P, Sardella G, Varbella F, Esposito G, Santarelli A, Tresoldi S, Nazzaro M, Zingarelli A, de Cesare N, Rigattieri S, Tosi P, Palmieri C, Brugaletta S, Rao SV, Heg D, Rothenbuhler M, Vranckx P, Juni P, MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomisedmulticentre trial. Lancet. 2015;385(9986):2465–2476.
15. Karjalainen PP, Vikman S, Niemelä M, et al. Safety of percutaneous coronary intervention during uninterrupted oral anticoagulant treatment. Eur Heart J. 2008;29:1001-10.
16. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015 Aug 31.
17. Scholz KH, Maier SKG, Maier LS, Lengenfelder B, Jacobshagen C, Jung J, Fleischmann C, Werner GS, Olbrich HG, Ott R, Mudra H, Seidl K, Schulze PC, Weiss C, Haimerl J, Friede T, Meyer T. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: Results from the German prospective, multicentre FITT-STEMI trial. Eur Heart J. 2018;39:1065–1074.
18. Valgimigli M, Gagnor A, Calabro P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Ando G, Repetto A, Limbruno U, Cortese B, Sganzerla P, Lupi A, Galli M, Colangelo S, Ierna S, Ausiello A, Presbitero P, Sardella G, Varbella F, Esposito G, Santarelli A, Tresoldi S, Nazzaro M, Zingarelli A, de Cesare N, Rigattieri S, Tosi P, Palmieri C, Brugaletta S, Rao SV, Heg D, Rothenbuhler M, Vranckx P, Juni P, MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomisedmulticentre trial. Lancet. 2015;385(9986):2465–2476.
19. Kornowski R, Mehran R, Dangas G, Nikolsky E, Assali A, Claessen BE, Gersh BJ, Wong SC, Witzenbichler B, Guagliumi G, Dudek D, Fahy M, Lansky AJ, Stone GW, HORIZONS-AMI Trial Investigators. Prognostic impact of staged versus "one-time" multivessel percutaneous intervention in acute myocardial infarction: Analysis from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. J Am Coll Cardiol. 2011;58:704–711.
20. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, Nordbeck P, Geisler T, Landmesser U, Skurk C, Fach A, Lapp H, Piek JJ, Noc M, Goslar T, Felix SB, Maier LS, Stepinska J, Oldroyd K, Serpytis P, Montalescot G, Barthelemy O, Huber K, Windecker S, Savonitto S, Torremante P, Vrints C, Schneider S, Desch S, Zeymer U; CULPRIT-SHOCK Investigators. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med. 2017;377:2419–2432.