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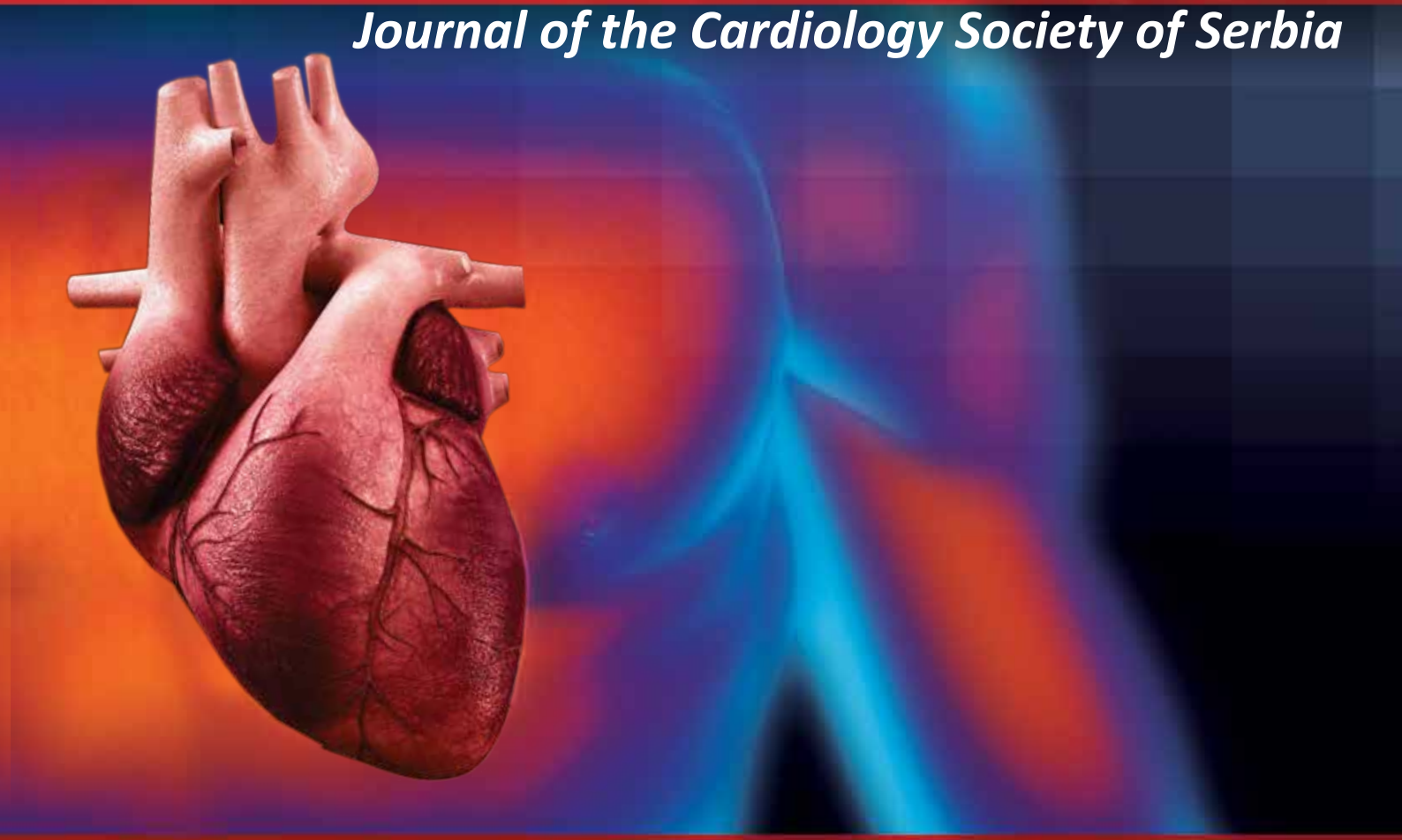
Heart and Blood Vessels

Journal of the Cardiology Society of Serbia



Pozdravna reč Prvog kongresa 34-og ogranka Američkog koledža kardiologije za Srbiju i Republiku Srpsku

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

Stable coronary artery disease: clinical case analysis according to esc and ACC/AHA guidelines (ESC 2013, ACC/AHA 2012 and focused update 2014)

Asymptomatic severe aortic stenosis: case report and practical application of current ESC and ACC/AHA guidelines

Stroke prevention in atrial fibrillation patients with a single stroke risk factor: clinical decision-making and guideline recommendations

Catheter ablation for atrial fibrillation- therapeutic dilemmas

Prikaz slučaja u svetlu preporuka za kardiološku evaluaciju bolesnika koji su upućeni na nekardijalnu hirurgiju

Differential Diagnosis and Management of Chronic Pericarditis in the Context of 2015 ESC Guidelines on Pericardial Diseases

Volumen 35 Broj 1
2016. godina

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Volumen 35 Broj 1 2016. godina

Sadržaj

Prvi kongres 34-og Ogranka Američkog koledža kardiologije za Srbiju i Republiku Srpsku

Poštovane koleginice i kolege,
Veliko mi je zadovoljstvo da Vas pozdravim na početku Prvog kongresa 34. Ogranka Američkog koledža kardiologa za Srbiju i Republiku Srpsku, koji će se održati 9-10. maja 2016. godine, u hotelu M "Best Western" u Beogradu.
34. Ogranak Američkog koledža kardiologa za Srbiju i Republiku Srpsku (*ACC Consortium Chapter for Serbia and Republic of Srpska*) je osnovan početkom 2015. godine, a promovisan 15. marta 2015. godine u San Dijegu na 64. kongresu Američkog koledža kardiologa. Ovaj Ogranak je formiran sa ciljem unapređenja saradnje i povezivanja Američkog koledža kardiologa sa Udruženjem kardiologa Srbije i Udruženjem kardiologa Republike Srpske. Prvi vidovi ove saradnje su bili realizovani kroz organizaciju zajedničkih sesija na XX Kongresu Udruženja kardiologa Srbije održanom na Zlatiboru oktobra 2015. godine, i 65. Kongresu Američkog koledža kardiologa održanom u Čikagu u martu 2016. godine.
Tema Prvog kongresa biće prikaz i analiza najvažnijih preporuka Američkog koledža kardiologa i Evropskog udruženja kardiologa. Predavači i moderatori će biti najistaknutiji kardiolozi Udruženja kardiologa Srbije i Udruženja kardiologa Republike Srpske.

S poštovanjem,
Milan Nedeljković
Prof. dr Milan A. Nedeljković
Prvi predsednik 34. Ogranka Američkog koledža kardiologa
za Srbiju i Republiku Srpsku

Dear Colleagues,
It is my great pleasure to greet you at the beginning of the First Congress of the 34th American College of Cardiology Consortium Chapter of Serbia and Republic of Srpska, which will be held on May 9-10, 2016, at Hotel M "Best Western" in Belgrade.
34th Chapter of the American College of Cardiology of Serbia and the Republic of Srpska was founded in early 2015 and was promoted on March 15, 2015 in San Diego at the 64th Congress of the American College of Cardiology. This Chapter was founded with the aim of improving cooperation and connection with the American College of Cardiology, Cardiology Society of Serbia, and Cardiology Society of the Republic of Srpska. The first steps of this cooperation were realized through the organization of joint sessions at the 20th Congress of the Cardiology Society of Serbia that was held on Zlatibor in October 2015, and the 65th Congress of the American College of Cardiology held in Chicago in March 2016.
The main topic of this Congress will be the analysis of the most important clinical guidelines of the American College of Cardiology and the European Society of Cardiology. Speakers and moderators will be the most prominent cardiologists of the Cardiology Society of Serbia and the Cardiology Society of Republic of Srpska.

I wish you successful meeting.
Milan Nedeljkovic
Professor Milan A. Nedeljkovic
First president of the 34the ACC Consortium Chapter
of Serbia and Republic of Srpska

Srce i krvni sudovi 2016; 35(1): 6-9

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

Gordana Krljanac[1,2], Siniša Stojković[1,2], Milika Ašanin[1,2], Igor Mrdović[1,2], Danka Matović[1], Milan Nedeljković[1,2]

[1]Cardiology Clinic, Clinical Center of Serbia, [2]Belgrade Medical School, Serbia

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.

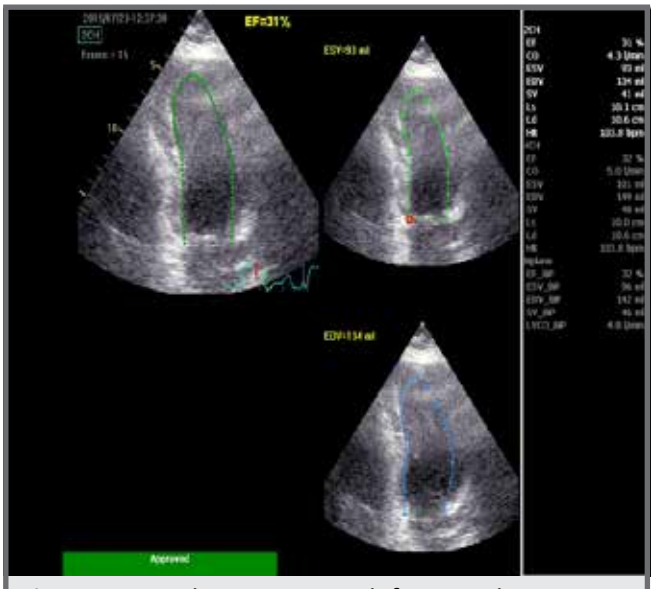

Figure 1. Systolic impairment left ventricle.

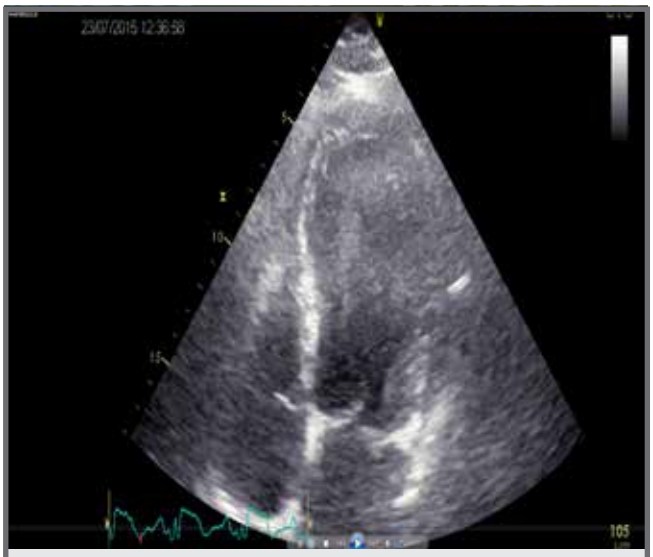

Figure 2. Spontaneous echocardiographic contrast in left ventricle

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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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Case report

Stable coronary artery disease: clinical case analysis according to esc and ACC/AHA guidelines (ESC 2013, ACC/AHA 2012 and focused update 2014)

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A 47 years old patient, with no previous history of heart disease, presented to the cardiologist with effort chest pain. He is ex-smoker, with hypertension grade I and has combined hyperlipoproteinemia (total cholesterol 6.7 mmol /l, LDL-Hol 4.1 mmol /l, HDL 0.8 mmol / l and TG 2.8 mmol /l). The patient was without therapy, but after initial medical examination, the doctor prescribed the following treatment: Acetyl-salicilic acid 1 x 100 mg, Nebivolol 1 x 2.5mg, Ramipril 1 x 1.25 mg, Isosorbide mono-nitrate 20 mg + 20 mg +0, Pravastatin 1 x 20 mg and Fenofibrate 1 x 160 mg. The patient was referred to the echocardiography and stress test. Echocardiography (30.06.2011.) revealed normal left ventricle diameters (5.4 / 3.2 cm), preserved global systolic function (EF 70%), without segmental wall motion abnormalities and with preserved diastolic function. The treadmill exercise test according to Bruce protocol (30.11.2011.) was stopped in the first minute of the fourth stage, due to the patient's fatigue and mild chest pain. One millimeter ST-segment depression in leads D2, D3, aVF and V4-V6 occurred during the test and recovery period. Based on these results the patient was referred to coronary angiography. Coronary angiography (30.08.2011.) showed mid LAD stenosis up to 50%, distal LAD stenosis of 70-90%, 70-90% ostial stenosis of the first diagonal branch, distal Cx narrowing of 70% and 90-99% stenosis of the proximal RCA. Syntax score was 19. PCI with stent implantation in proximal RCA was attempted during the procedure, but without success. Based on these findings it was decided to refer patient to stress echocardiography test (SEHO) in order to determine the extent and time of onset of myocardial ischemia. SEHO test was done under the full medical therapy (26.09.2011.) and stopped in the first minute of the IV stage, without chest pain, clinical, electrocardiographic and echocardiographic signs of reduced coronary reserve. The patient had Duke score of 10, functional capacity of 11 MET and reached submaximal frequency (SMF). His heart rate recovery (HRR) was appropriate (42 /min). Based on these results and high degree of workload achieved without clear signs of myocardial ischemia, it was decided to leave the patient on optimal medical therapy (OMT) and schedule him for the control SEHO tests. The control SEHO tests were done annually and the last (16.03.2016.) was still negative for ischemia at the same workload. Prognostic parameters were similar compared to the SEHO results from 26.09.2011: Duke score 10, functional capacity 11 MET, sub maximal frequency (SMF) was reached and the recovery of cardiac frequency (HRR) was appropriate. During the follow-up period the patient was asymptomatic.

The therapeutic challenges and management dilemmas

The patient from our case is a typical patient with stable coronary artery disease (SCAD). The basic dilemma regarding the management of these patients is whether optimal medical therapy (OMT) alone is sufficient or the patient should be referred to the invasive coronary angiography (ICA) and, if necessary, to myocardial revascularization. The essential question is which of these two therapeutic approaches, OMT or revascularization, has better effect on the quality of life and survival?

What do the guidelines say?

Ischemic heart disease (IHD) is the most common cause of mortality and morbidity in developed and developing countries[1]. Today, there are numerous scores and tables helping us to determine, with great certainty, the probability of having IHD, and further on to perform risk stratification based on clinical data and results of non-invasive diagnostic methods[2-5]. Standard treatments for IHD is OMT, risk factors control with life style modification and, when needed, invasive treatment (percutaneous coronary interventions - PCI or coronary artery bypass grafting-CABG). In the recent years invasive management with PCI and/or CABG is frequently preferred over OMT alone. However, although progression and development

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of invasive technique for IHD are impressive in the last decade, up to now, we do not have clear, strong and convincing evidence based data from clinical trials in favors of invasive IHD treatment over the OMT alone[3-8].

Guidelines for SCAD were issued by European Society of cardiology (ESC) in 2013[4], and by American College of Cardiology/American Heart Association (ACC/AHA) in 2012 and updated version in 2014[3,5].

Approach to the patient with suspected stable coronary artery disease

Guidelines for the management of SCAD issued by European Society of Cardiology (ESC) in 2013 proposed three-step approach for the management of patient with chest pain and suspect SCAD [(4)]**.** The first step is to determine *pre-test probability* (PTP), clinical judgment that the patient has SCAD. In the second step, patients with intermediate PTP for SCAD should be referred to non-invasive testing in order to confirm or rule out the SCAD diagnosis. In the third step, a patient with a confirmed diagnosis of SCAD is given OMT and risk of adverse coronary events (so call *event risk*) is assessed based on the results of available non-invasive tests. The aim is to identify those patients who may benefit from invasive diagnostics (coronary angiography) and revascularization. According to the same guidelines, depending on the severity of symptoms, the patient can undergo early coronary angiography with, if necessary, invasive confirmation of the significant stenosis (using FFR), followed by revascularization, thus skipping steps 2 and 3.

Determination of pretest probability in patients with chest pain

In clinical practice, the most used is is Diamond Forrester table (modified by Tessa Genders et al. 2011.) to determine the pre-test probability of the SCAD based on the nature of chest pain, sex and age. [(9)] **Typical anginal pain** has the following characteristics: (1) retrosternal localization with characteristic quality and duration; (2) it is provoked by physical exertion or emotional stress; (3) it is stopped with the rest or nitroglycerin application. **Atypical chest pain** has two of the given characteristics, and **non cardial pain** has one or none of the following characteristics. This table is Table 13 is the 2013 ESC recommendations for the diagnosis and treatment of SCAD and is identical to the table from the 2012 ACC/AHA guidelines for SCAD. Using this table we can divide the patients with the chest pain into three categories: patients with low pretest probability (PTP) <15%, patients with intermediate PTP (16-85%) and patients with high PTP (>85%) [(4)]**.**

According to the 2013 ESC recommendations for SCAD, patients with low pre-test probability (<15%) do not require testing; patients with intermediate pre-test probability (15-65%) and LVEF ≥50%, should be referred to the stress ECG as the initial test, but if stress imaging test available, it is more desirable (SEHO, MRI, SPECT, PET); patients with high PTP (66-85%) and LVEF <50% even without typical angina symptoms, should go directly to stress imaging test (SEHO, CMR, SPECT, PET); for patients with very high PTP (over 85%)it can be considered that SCAD already exists. For them it is not necessary to do diagnostic tests, and coronary angiography without noninvasive testing is indicated. Tests can be done for risk stratification. In these recommendations coronary CTA may be considered as a first noninvasive test in patients with intermediate PTP (15-50%) if the patient is suitable for the test and if adequate technology and local expertise are available. Also, coronary CTA (computed tomography angiography) is recommended if the results of the ECG stress test or stres imaging tests are unclear. This is represented as Figure 2 in the ESC guidelines [(4)]**.**

According to ACC/AHA recommendations for SCAD from 2012 and updated version from 2014, patients with intermediate PTP (15-65%) should be addressed to the stress ECG test, if the ECG at rest is interpretable, independently of LVEF. If the ECG at rest is not interpretable (LBBB, pacemakers, WPW syndrome, ST segment depression), patients should be referred to stress imaging test (SPECT, SEHO test, pharmacological CMR). Also, patients with high-intermediate pre-test probability (66-85%) should be refered to the imaging stress test (SPECT, SEHO test, pharmacological CMR), just like in the ESC guidelines. Patients whose ECG is not interpretable in rest or who have had previous myocardial revascularization sould be refered to the pharmalogical myocardial perfusion stress test or stress ECHO test. Patients who are not able to exercise should be referred to the pharmalogical myocardial perfusion stress test, stress ECHO test or coronary CTA. Also patients who have contraindications to stress testing should be referred to coronary CTA. This is represented as Figure 2 in the ACC/AHA guidelines [(3)]**.**

ESC and ACC/AHA guidelines: how to manage our patient?

According to Diamond-Forrester table, our patient had 69% PTP for SCAD. Since he did not have previous CVD, and his ECG in rest was interpretable and EF >50%, the decision to refer him to stress test was in accordance with the current guidelines. Based on the positive stress test, the patient was referred to coronary angiography, as also suggested by the guidelines.

Risk stratification for the adverse cardiovascular events

Non-invasive tests are used not only for diagnosing SCAD, but also to assess risk for adverse cardiovascular events (cardiovascular death or myocardial infarction). The risk is usually expressed as an annual probability of myocardial infarction or death and is defined as *low* (annual probability of less than 1%), *medium* (annual probability of 1-3%) and *high risk* (annual probability of > 3%). Risk stratification of patients with SCAD can be done using various non-invasive tests (**Table 17 in the ESC guidelines and Table 14 in theACC/ AHA guidelines**) **(3,4).** In the ESC guidelines if the patient referred to the ECG stress testing and had a ST depression ≥2mm he/she has a high risk, if

the ST depression was 1-2mm it is intermediate risk and if there were no ST changes and no chest pain then it is low risk. For the patient referred to **stress imaging tests** the risk is defined as *high* in case of area of ischaemia >10% (>10% for SPECT; limited quantitative data for CMR – probably ≥2/16 segments with new perfusion defects or ≥3 dobutamine-induced dysfunctional segments; ≥ 3 segments of LV by stress echo); *intermediate* risk is defined if area of ischaemia is between 1 to 10% or any ischaemia less than high risk by CMR or stress echo; *low* risk is considered in case of no ischemia on the test. If the patient referred to the coronary CTA, the risk is high in case of significant high risk lesion (three-vessels disease with proximal stenoses, LM, and proximal anterior descending CAD), the risk is intermediate in case of significant lesion(s) in large and proximal coronary artery(ies) and the risk is low in caseof normal coronary arteries or presence of plaques only.

ACC/AHA guidelines are very similar regarding this issue and AHA recommendations also includes Agatston calcium score. In these guidelines patients with CAC score is >400 Agatston units are in the high risk, patients with CAC score between 100 and 399 Agatston units have intermediate risk and patients with CAC score <100 Agatston units have low risk.

According to ESC guidelines, prognostic markers useful for risk stratification during ECG stress test (ergometry) are: functional capacity (MET - Metabolic Equivalent of Task), i.e. exercise capacity, blood pressure changes during the test and exercise induced myocardial ischaemia based on clinical and ECG parameters. From all of these prognostic markers, functional capacity has the strongest relation with adverse CV events and mortality, independent of age, gender and the presence and severity of coronary artery disease.[10,11] Functional capacity can be expressed as the maximum duration of exercise, maximal achieved metabolic equivalent (1 MET = 3.5 ml O2 / kg / min), maximal workload (expressed in watts), maximal heart rate and the so-called "double product" (blood pressure x heart rate). Duke treadmill score is well-validated risks score that combines treadmill exercise time (in minutes), maximum net ST segment deviation during the test (in mm) and exercise induced angina: Duke treadmill score = exercise time – 5xST deviation-4x angina index. According to Duke risk score the risk can be low (scor≥5), medium (-10≤skor <5) and high (score <-10).[12,13] Heart Rate recovery (HRR) is a predictor of mortality, independent of the angiographic severity of coronary artery disease (HRR = maximal HR during exercise -HR 1 min after exercise; abnormal (inadequate) heart rate recovery is ≤18 beats per minute).[14,15]

Management of the stable coronary artery disease

According to the ESC guidelines, treatment options for patients with SCAD are based on risk stratification (**Figure 3 in the ESC guidelines**) and can help in deciding whether a patient should be referred to, in addition to OMT and invasive coronary angiography (ICA), followed by angiographic findings and myocardial revascularization. If the patients have a low event risk they should be on optimal medicament treatment (OMT). If the symptoms are improved continue OMT, if not the medical treatment should be intensified. If the patients have symptoms even after intensifying the medical treatment, refer the patient to the ICA. In patients with intermediate event risk start administering OMT in the same way as in the patients with low risk but ICA may be considered based on the co-morbidities and patient's preference. Patients with high event risk should be referred to ICA.[4]

Risk factors control and pharmacological management of the stable coronary artery disease

It has been shown that optimal medical therapy (which includes the optimal way of life with the achievement of target lipid levels, blood pressure, and glucose in the blood) have the same prognostic, and symptomatic character as revascularization, if reversible ischemia induced by the ischemia provocation tests does not involve more than 10% of the left ventricular myocardium (which corresponds to echocardiographic deterioration of kinetics in at least two segments).

Regardless of the chosen management, pharmacological treatment or invasive methods, the first-line therapy in all patients should be risk factors control (smoking cessation, dietary intake, control of the blood lipids level, hypertension and diabetes) as well as the lifestyle modification (moderate physical activity, regulation of body weight, etc.). ESC and ACC/AHA guidelines in this regard are very similar, but the ACC/AHA guidelines provide much more information about the education of doctors on the approach to patients, as well as different methods of education patients themselves and methods of counseling (education via the Internet, group counseling, etc). Also ACC/AHA guidelines, as opposed to the ESC guidelines, suggest different ways of patient's monitoring.[8]

Depending on the symptoms, the functional and anatomical complexities, stable angina pectoris can be treated with optimal medical therapy and/or revascularization.

The goals of optimal medical therapy are to eliminate or reduce angina and to prevent adverse cardiovascular events.

Myocardial ischaemia occurs due to the mismatch between myocardial oxygen supply and myocardial needs, as defined by the "double product" (heart rate x systolic blood pressure). For this reason, any antianginal drugs are aimed to reduce the consumption of oxygen by the myocardium (by reducing heart rate and/or blood pressure: beta blockers, non-dihydropyridine calcium channel blockers, all antihypertensives, vasodilators). In therapy of vasospastic angina (Prinzmetal) vasodilators are essential (long and short-acting nitrates and calcium channel blockers).

Pharmacological treatment should be administered to all patients, regardless of whether they were treated invasively or not, and the ESC and ACC/AHA guidelines are identical. The first-line treatment of symptoms in patients with suspected or proven SCAD includes: **short-acting**

nitrates in combination with β-blockers or **calcium channel blockers** in case of intolerance /contraindication for the use of β-blockers or in combination if CCS > 2. Several classes of drugs have been proved to have essential impact on the progression of coronary atherosclerosis and atherothrombosis, consequently influence symptoms of IHD, but more importantly, prevent adverse cardiovascular event and modify prognosis. These drugs are: **antiplatelet drugs (primarily aspirin), statins, ACE inhibitors and angiotensin receptor blockers.** If symptom control in patients with SCAD is not satisfactory, introduction of the one of the second line drugs is needed: long-acting nitrates, trimetazidine, ranolazine, nicorandil or ivabradine.

Pharmacological treatment of SCAD according to the ESC guidelines is shown as Figure 4. and there is no difference in the therapeutic algorithm compared to the ACC/AHA guidelines.[3,4]

CASS (*Coronary artery surgery study*) study included 780 patients with stable angina pectoris class I or II of the Canadian Association of Cardiovascular Diseases (CCS), who had angiographically verified ≥70% stenosis of the LAD, RCA or Cx or ≥ 50% stenosis of the proximal LAD or LM, and who had a previous CABG or unstable angina. This study compared the results of CABG + OMT vs OMT only. Patients were followed for an average of 46 months. The results showed that there was no significant difference in mortality between the two groups, regardless of the number of diseased vessels. The annual mortality rate in patients with one, two and three-vessels disease who were treated with the combined therapy (CABG + OMT) was 0.7%, 1% and 1.5% and in patients only on OMT was 1.4%, 2.1% and 2.5%.[6]

The *Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation* (COURAGE) trial (n = 2287) compared PCI + OMT with OMT only, in patients with SCAD or ischaemia and coronary lesions suitable for PCI. The target study population for the COURAGE trial included patients with chronic angina pectoris Canadian Cardiovascular Society (CCS) Class I–III, stable post-MI patients and asymptomatic patients with objective evidence of myocardial ischaemia. All patients had angiographically defined CAD, with at least one vessel meeting AHA/American College of Cardiology (ACC) Class I or II indications for PCI. Patients with a prior CABG were accepted. Patients with stenosis >80% in one or more vessels, supplying the large area of the myocardium, could be enrolled even in the absence of objective ischaemia. The primary endpoint, all-cause death or non-fatal MI, did not differ between the two groups during a mean follow-up of 4.6 years. However, in patients who were invasively treated, freedom from angina was significantly better up to 3 years of follow-up. In a sub-study, patients with >10% ischaemia on stress myocardial perfusion scintigraphy had a higher rate of death or MI. More PCI + OMT patients exhibited significant ischaemia reduction (33 vs. 19%; P= 0.0004). Patients with ischaemia reduction had lower unadjusted risk for death or MI, particularly if baseline ischaemia was moderate to severe[7].

COURAGE II study, a 15-year follow-up of 1,211 patients patients included in the original study, also showed no difference in mortality and incidence of non-fatal MI between patients with PCI +OMT vs OMT (HR 0.95: 95% CI 0,79 to 1.13, p = 0.53).[8]

The ISCHEMIA study is currently in progress (*International Study of Comparative Health Effectiveness with Medical and Invasive Approaches.* It is aimed to define the role of an invasive approach in patients with stable ischemic heart disease (SIHD) and substantial ischemia. The trial hypothesis is that cardiac catheterization followed by complete revascularization plus optimal medical therapy (OMT) is superior to OMT alone, for patients with moderate-severe ischemia on stress imaging. The primary endpoint will be time to cardiovascular death, myocardial infarction (MI), or hospitalization for unstable angina, resuscitated cardiac arrest, or heart failure. The hypothesis that the invasive strategy will improve quality of life will also be tested. Cost-effectiveness will be assessed. Observational data suggest that revascularization of patients with moderate-severe ischemia is associated with a lower likelihood of death and MI; this was not observed in patients with lesser degrees of ischemia. Only about half of patients with moderate-severe ischemia are referred for catheterization. It is unknown whether used rates for catheterization and revascularization are appropriate for optimal patient management in the era of modern medical therapy (particularly with high dose statins and antiplatelet therapy). This issue cannot be resolved using available data, because prior clinical trials regarding SIHD have enrolled patients after catheterization, at which point there is substantial selection bias for the enrollment based on coronary anatomy. Given the potential for improved survival and fewer cardiac events, as a result of revascularization and the significant expense and risks associated with invasive management, the role of an invasive strategy is critically important to define. The proposed ISCHEMIA trial will be a prospective, multicenter, international, randomized, controlled trial that will directly address the need for an invasive strategy-cath and revascularization-in patients with SIHD. A total of 8,000 patients with moderate-severe ischemia and left ventricular ejection fraction >35% will be enrolled after stress imaging from more than 400 sites. Based on the need to exclude significant left main coronary artery disease, patients who meet eligibility criteria will undergo blinded coronary CT angiography. Patients will be randomized to an invasive group that will undergo routine cath with optimal revascularization, if feasible, plus OMT or to a group that receives OMT alone (http://grantome.com/grant/NIH/U01-HL105907-03)[16].

However, none of these studies took into account the prognostic markers of exercise testing such as functional capacity, heart rate recovery, blood pressure response, Duke treadmill score, which proved to be good predictors of morbidity and mortality of cardiovascular disease[15]. The study of the Myers et al. compared the effect of physical activity (expressed as a MET-tested load) on the mortality of any cause among patients who did not and those who had a previous history of cardiovascular disease. This study included 6213 men who were followed for 6.2 ± 3.7 years. It turned out that the greater achieved MET reduces the risk of dying in both populations[10]. Patients were

divided into two groups: 3679 with a positive test or previous coronary artery disease and 2534 patients with a normal test and without coronary artery disease. After the test all patients were divided in the five groups (quintiles of exercise capacity) according to the achieved MET: les than 5 MET, 6-7.9 MET, 8-9.9 MET, 10-12.9 MET and those who achieved 13 MET or higher. The group of patients who achieved 13 MET or higher was used as a reference group. It has been showed that the relative risk of death was the highest among the groups who achieved less than 5 MET (2.95-6.83 among healthy subjects and 3.29-5.16 among the patients with previous history of CAD, p= ns) and gradually decreased among the groups with the smallest value among the patients who achieved 10-12.9 MET (0.68-2.22 2.95-6.83 among healthy subjects and 1.35-2.19 among the patients with previous history of CAD, p= ns). In both groups, in healthy and in patients with coronary artery disease, achieved maximum functional capacity was a stronger independent predictor of increased risk of mortality compared to the known risk factors such as hypertension, smoking, diabetes as well as other prognostic test parameters, including ST segment depression, and the maximum achieved heart rate during the test or the occurrence of the arrhythmias during the test.

According to non-invasive risk stratification our patient had low probability for the occurrence of myocardial infarction or death. In concordance with current guidelines OMT was initiated, relieving the symptoms, therefore further follow up is recommended.

Conclusion

Early diagnosis and appropriate treatment of coronary artery disease is one of the greatest challenges in modern cardiology. Despite major breakthrough in non-invasive and invasive diagnostic procedure and modern treatment options, CAD still has high morbidity and mortality. Since there is no solid evidence to show the advantages of the invasive treatment compared to OMT, it is necessary to have an *individual approach* for each patient. Studies such as COURAGE I and II, CASS and the study of Myers et al., as well as our patient from the case report showed that besides the test results prognostic parameters of the test, especally functional capacity (expressed through MET), Duke treadmill score, achieved target heart rate and heart rate recovery have great importance. These studies also suggest that regardless of the therapeutic mode (medical or invasive therapy), risk factors control and lifestyle modifications are the first and necessary steps when treating these patients and highlight the importance of primary and secondary prevention of coronary artery disease.

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Case presentation

Asymptomatic severe aortic stenosis: case report and practical application of current ESC and ACC/AHA guidelines

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A 65-year old male with a history of degenerative aortic stenosis (AS) presented to our department for regular echocardiographic evaluation. He denied any symptoms, but he also emphasized that he is not physically active. The clinical exam revealed no specific abnormalities beside the existence of systolic mormour and blunted second aortic sound, his blood pressure was normal (with antyhipertensive therapy) and his ECG was without ST-T segment abnormalities. Analyzed laboratory parameters (complete blood count and biochemistry analysis) were within referent values, but he was also taking atorvastatin for lipid control. His Brain natriuretic peptide level was 28pg/ml. Echocardiogram confirmed the existence of isolated severe AS (figure 1) with echocardiogaphically observed heavily calcified aortic valve (figure 2) and normal left ventricular ejection fraction (LVEF). To evaluate his symptomatic and functional status we have performed cardio-pulmonary and stress-echocardiography testing (as a single test) on semisupine ergobicycle, Ramp 15 protocol. Adequate load was achieved (> 80% of predicted heart rate and 12 minutes of pedalling, and RER has been achieved at cardiopulmonary testing). The stress-echocardiography test revealed significant rise in his mean pressure gradient (Pmean = 19.6mmHg); figure 3, and normal LV wall motion, while

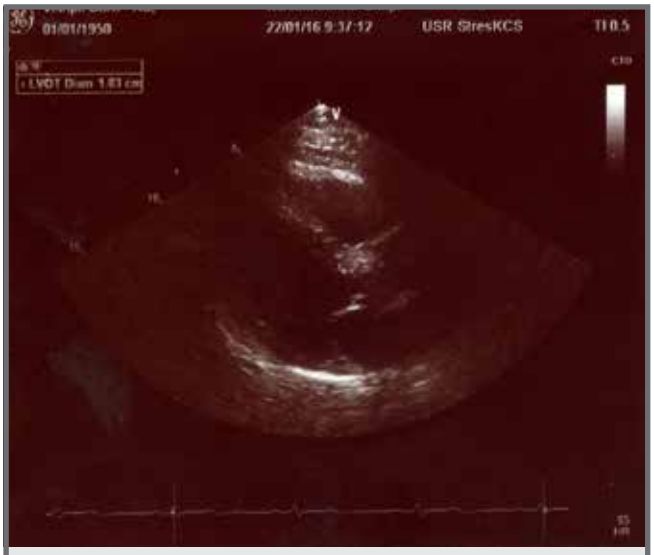

Figure 2. 2-D echocardiographic view of the aortic valve and LVOT

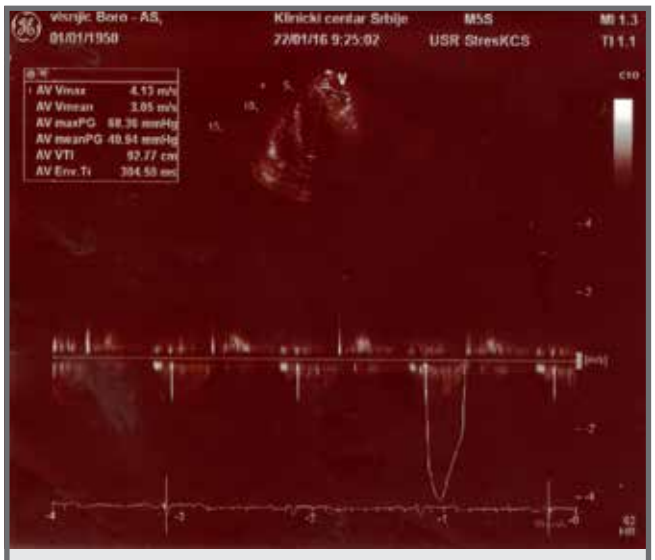

Figure 1. Continues Doppler recording across the aortic valve at rest

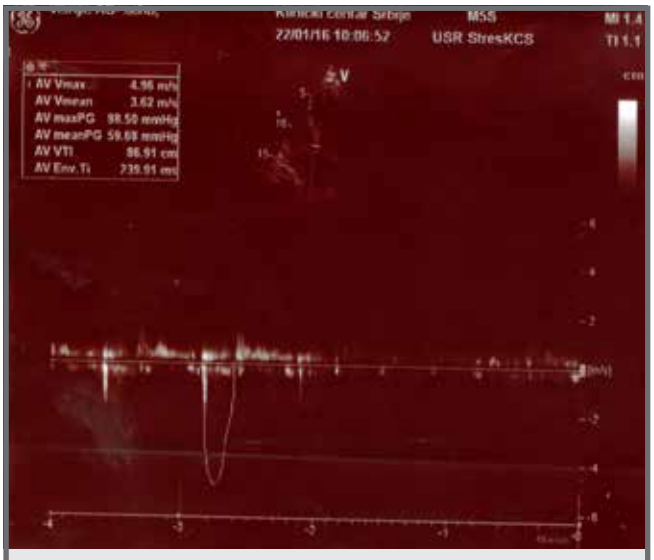

Figure 3. Increase in maximal aortic gradient after exercise testing

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his cardio-pulmonary test revealed preserved cardiac and pulmonary function. The subsequent coronary angiogram revelead no significant coronary artery stenosis. After all the testing and anaysis performed, the remained question was should we reffer this patient to the aortic valve replacement (AVR), or should we opt for „watchful waiting" strategy.

Discussion

Asymptomatic patients with isolated severe AS and normal LVEF represent one of the most challenging and probably the least explored group of patients in contemporary cardiovascular medicine (stage C1 in current ACC/AHA valvular guidelines). This additionaly gains importance if one is aware that AS is one of the most common valvular diseases encountered in clinical practice, and affects ~5% of adults above the age of 65 years[1]. Moreover, its prevalence is projected to increase over the next decade with the aging population[2-3]. Untreated, symptomatic severe AS is associated with a dismal prognosis, with estimated mortality around 2-2.5% per month[4-5]. In this context the treatment of symptomatic AS patients is clear and includes either surgical AVR or TAVR (transcutaneous aortic valve replacement). Conversely, the treatment of asymptomatic patients with severe AS is unclear and a matter of ongoing debate. The main argument for this ongoing debate is that the risk of sudden death in these patients with severe AS and without symptoms is not 0%, but ~1% to 1.5% per year[6]. Importantly, ~70% of sudden deaths in patients with asymptomatic severe AS are not preceded by any of the classical AS symptoms, thus representing the first clinical manifestation of AS[5-7].

Given the current low periprocedural mortality rate for isolated AVR, earlier intervention has been increasingly advocated. Although current ACC/AHA and European guidelines recommend AVR for selected patients with asymptomatic severe AS, in practice, a "watchful waiting" strategy applies for the vast majority of asymptomatic patients, with intervention scheduled once symptoms emerge or left LV systolic dysfunction develops[8-9]. In that sense, of particular importance are two facts:

a) no randomized trial in the setting of asymptomatic severe AS has ever been conducted (one has recently started;[10-11]

b) current ESC and ACC/AHA guidelines are not fully concordant regarding referral to AVR in certain subgroups of asymptomatic severe AS patients.

It is important to emphasize that the level of evidence substantiating each of these recommendations is either B or C, meaning that they are made on the basis of small, retrospective, observational studies or expert consensus opinions, with no randomized clinical trial available. The consequence of the lack of the randomized trials and discordance in ESC – ACC/AHA guidelines is that decisions are made on individual basis. For this reason, a patient with identical echocardiographic/clinical characteristics may have surgery in one institution, but not in the neighboring one.

The current ESC guidelines (ESC) state that AVR can be considered in subgroup of asymptomatic patients with isolated severe AS in whom P_{mean} rises >18mmHg during exercise testing (the case of our patient), or in patients with elevated BNP and/or in case of severe LV hypertrophy (Class IIB, level of evidence C). This ESC recommendation is based on two prospective, single-center studies in which increase in P_{mea}n > 18mmHg and > 20mmHg, respectively, was independently associated with mid - and long term adverse events[12-13]. Conversely, current ACC/AHA guidelines are not even considering these subgroups of patients for AVR. Our patient belongs exactly to this subgroup of patients, who are differently recognized and stratified (or unrecognized) in ESC and ACC/AHA guidelines.

After analyzing all data described above, and talking to patient, we opted to recommend to patient AVR. The surgery was successfully performed and mechanical St Jude valve was implanted. Now, 3.5 months after the surgery patient is feeling well and no complication has been observed. In the absence of clear guidelines how to manage this patient we opted for surgery for several reasons:

1) detecting symptom onset in this patient might be notoriously difficult, particularly considering his sedentary way of life

2) AS progression could be highly variable and unpredictable, and rapid deterioration may occur

3) operative risk would only increase with patient age. For example, if no comorbidities develop during 2 years of follow-up, the Society of Thoracic Surgeons risk calculator for cardiac surgery projects that as age increases from 73 to 75 years, absolute operative mortality risk increases by 0.1% and combined mortality and serious morbidity increases by 0.5%[14]. Obviously, new significant disease would only make the operative risk even higher.

An important addition to our analysis and decision making was emerging evidence of elective AVR usefulness. Four observational studies, which in total included 2.486 patients, compared outcomes of patients with asymptomatic severe AS undergoing early AVR to those treated with medical therapy only (5-7, 15). Five hundred twenty-two (21%) patients underwent early AVR, and 1,964 (79%) patients underwent a conservative approach. The very recent polled analysis of these studies by Genereux et al indicated that patients with severe asymptomatic AS have 3.5-fold higher rate of all-cause death with a watchful-waiting strategy compared with AVR. Although these studies have limitations and were probably biased in several ways (i.e no stress test were performed to confirm asymptomatic status; also is possible that some of the patients were not offered AVR in the first place because of their increased operative risk) they are indicative for beneficial effect of early/elective AVR. This might be especially true in the era of low periprocedural mortality rates for isolated AVR, reported in high-volume centers[16]. However, despite of the presented case who was successfully electively operated, most of the asymptomatic patients with isolated severe AS and normal LVEF, on the basis of the current evidence, should be managed conservatively, with close monitoring to detect new onset of symptoms, increasing AS se-

verity, deterioration in LV function, or other risk factors that might prompt consideration of early AVR.

Conclusion

The optimal approach to the individual asymptomatic patient with severe isolated AS and with normal LVEF is best made by an expert heart team consisting of cardiologists, interventional cardiologists, cardiac surgeons, imaging specialists, and nurses. Given the uncertainty regarding the value of AVR in asymptomatic severe AS and the large and increasing number of affected patients, a randomized clinical trial comparing AVR to conservative treatment is warranted.

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Case report

Stroke prevention in atrial fibrillation patients with a single stroke risk factor: clinical decision-making and guideline recommendations

A case report and comparative analysis of the European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) Guidelines on the Management of Atrial Fibrillation

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A 58-year old female patient was referred to our hospital because of recurrent paroxysmal atrial fibrillation (AF) and labile International Normalised Ration (INR) values.

Sixteen months ago, she presented to the local Emergency Room with palpitations and mild shortness of breath. Her electrocardiogram (ECG) revealed AF with rapid ventricular rate of 120 bpm (Figure 1), and her blood pressure was 150/90mmHg. Otherwise, physical examination yielded normal findings, as well as the chest radiography and routine blood testing. The patient reported cigarette smoking, but her medical record was otherwise unremarkable. There was no record of previous AF, history of hypertension, or antihypertensive treatment, but the patient reported intermittent slight elevations in her blood pressure on several recent occasions. The patient was administered metoprolol 5mg i.v. and spontaneous cardioversion to sinus rhythm occurred 4 hours after the onset of symptoms. On echocardiographic examination (performed in sinus rhythm, after spontaneous cardioversion), the left atrial (LA) anteroposterior diameter was 40mm, and left ventricular ejection fraction (LVEF) was 68%, with a normal pattern of transmitral flow. At discharge, the patient was diagnosed with first-onset lone AF and prescribed metoprolol 2x50mg. She has also been advised a closer blood pressure monitoring.

On regular follow-up visits she was in sinus rhythm, but her blood pressure ranged from 110/70mmHg to 160/95mmHg. The patient had been doing apparently well for the next eight months, when she woke up one morning with palpitations and severe neurologic deficit (right-sided hemiparesis and speech disorder). On admission to hospital her ECG showed AF with ventricular rate of 110 bpm, and a clinical diagnosis of acute ischemic stroke was subsequently confirmed by the brain computed tomography scan showing left-sided massive frontoparietal ischemia. Spontaneous cardioversion to sinus rhythm occurred 3 hours after the admission. Since thrombolytic therapy was not available in the local hospital, acute ischemic stroke was treated conservatively. Four weeks later, oral anticoagulant therapy with adjusted-dose warfarin (with target INR of 2.0-3.0) was initiated, and the patient was also prescribed propafenone 450mg daily and an angiotensin-converting enzyme inhibitor (ACEi).

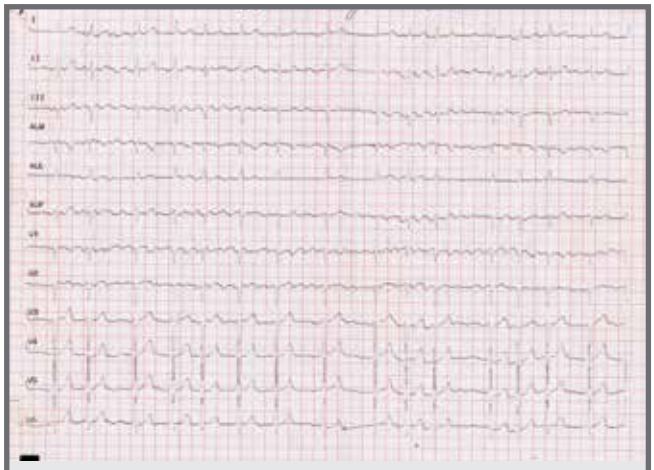

Figure 1. Atrial fibrillation at presentation (1 hour after intravenous administration of Metoprolol 5mg).

Six months later the patient was referred to our hospital. On admission, she was in sinus rhythm, with normal blood tests (excluding the INR of 1.8), normal chest radiogram and echocardiographic finding. Physical examination revealed a permanent neurologic deficit (disturbed walk and right-sided hemiplegia). The patient was switched to dabigatran (Pradaxa) 150mg twice daily, and propafenone dose was increased to 750mg daily, with AF catheter ablation planned in case of recurrent AF. Her hypertension was well-controlled with an ACEi and thiazide diuretic (blood pressure was below

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140/90mmHg during the course of hospitalization). On the regular follow-up visit 2 months after discharge, the patient reported no AF-related symptoms (sinus rhythm was confirmed by ECG and 24-hour holter monitoring). However, she complained of pronounced gastrointestinal (GI) symptoms (dyspepsia, nausea, GI upset) despite the administration of a proton pump inhibitor (PPI), which she had been regularly taking for 6 weeks. Due to a poor tolerance to dabigatran, she was switched to rivaroxaban (Xarelto) 20mg once daily. On the next follow-up visit, the patient was in apparently stable sinus rhythm, without AF-related or GI symptoms, but with permanent, disabling neurologic deficit.

In summary, our apparently healthy 58-year old female patient presented with first-onset paroxysmal AF approximately one and a half year ago. She was considered as a low-risk patient (a CHA2DS2-VASc score of 0) at that point and hence she was not given OAC, but later in her clinical course she experienced recurrent AF and a massive ischemic stroke with residual permanent neurologic deficit. Thereafter, she was treated with warfarin but, due to suboptimal quality of anticoagulation with warfarin, she was switched to dabigatran, and subsequently (due to intolerable side effects she experienced with dabigatran) she was switched from dabigatran to rivaroxaban.

Key points for discussion

- Stroke and bleeding risk assessment,
- The use of oral anticoagulant therapy (OAC) for stroke prevention in AF patients with a single stroke risk factor.

Comment

On average, patients with AF have a 5-fold greater risk of stroke than their counterparts in normal sinus rhythm[1,2]. Compared with other strokes, AF-related strokes are more often fatal or associated with more severe permanent disability[3], and can be most effectively prevented using OAC therapy with either VKAs or NOACs (that is, dabigatran, rivaroxaban, apixaban or edoxaban)[4-8].

However, the individual risk of stroke widely varies among AF patients, depending on the presence (or absence) of various stroke risk factors, and many stroke risk factors also increase the risk of bleeding associated with the use of OAC therapy[9]. Indeed, individual stroke and bleeding risks often track each other, thus posing a challenge to the physician considering the use of OAC for stroke prevention in a given patient with AF. Balancing the benefit of stroke prevention against the risk of bleeding with OAC therapy is a mandatory step in the management of stroke risk in patients with AF, since the ultimate goal is to achieve a positive net clinical benefit of treatment in all our patients.

Stroke and bleeding risk assessment in AF patients

The annual stroke rate estimate for individual untreated AF patient can be appreciated using several stroke risk assessment scores (e.g., the CHA_2DS_2-VASc, $CHADS_2$, or ATRIA score), which have been derived from various AF cohorts[10]. Due to its relative simplicity (the score can be easily calculated at bedside using readily identifiable clinical variables) and greater accuracy in identifying AF patients at truly low risk of stroke in comparison to other stroke risk assessment tools, the CHA_2DS_2-VASc score (Table 1) has been recommended by the European Society of Cardiology (ESC) AF Guidelines[1], the American Heart Association/American College of Cardiology/Heart Rhythm Society AF Guidelines[11] and several other major guidelines (e.g., the National Institute for Health and Clinical Excellence [NICE] AF Guidelines, Canadian Cardiology Society AF Guidelines, etc.)[12].

Bleeding events are a downside of OAC therapy. By virtue of the principal mechanism of their action (i.e., interference with one or more components of the coagulation cascade), all anticoagulant drugs increase the risk of bleeding to some extent. Due to its high fatality[13,14], intracranial bleeding (ICH) is the most feared OAC-related bleeding complication. Of note, with increasing use of VKAs for stroke prevention in AF during 1990s, the rate of ICH also increased from 0.8 to 4.4 per 100 000 patients taking warfarin[15], and a meta-analysis

Table 1. The CHA2DS2-VASc score.

CHA_2DS_2VASc score Point score Adjusted stroke rate (%/year)[40]			**Annual stroke rates with increasing score**	
	Risk factor		**0**	0.0 %
C	Congestive heart failure/LV dysfunction	**1**	**1**	1.3 %
H	Hypertension	**1**	**2**	2.2 %
A_2	Age >75	**2**	**3**	3.2 %
D	Diabetes mellitus	**1**	**4**	4.0 %
S_2	Stroke/TIA/thromboembolism	**2**	**5**	6.7 %
V	Vascular disease*	**1**	**6**	9.8 %
A	Age 65–74	**1**	**7**	9.6 %
Sc	Sex category (i.e. female sex)	**1**	**8**	6.7 %
	Maximum score	**9**	**9**	5.2 %

*Prior myocardial infarction, peripheral artery disease, complex aortic plaque.
LV: left ventricular; TIA: transient ischemic attack.

of 16 randomised trials and 31 observational studies reported a 2% annual rate of major bleeding in patients taking OAC[16].

Individual risk of bleeding in AF patients taking OAC therapy depends on the presence and combination of the bleeding risk factors[17]. Importantly, the risk of haemorrhage complications can be decreased by optimal risk factor management addressing several bleeding risk factors which are modifiable (Table 2). Both ESC and U.S. AF Guidelines (as well as most other major guidelines) recommend the HAS-BLED score (Figure 2) as bleeding risk assessment tool in patients with AF considered for OAC therapy (or taking OAC)[1,11]. There are several other bleeding risk assessment tools (e.g., the HEMORR2HAGES score or ATRIA score) but those scores have been less validated in AF patients, or performed less well in comparison to the HAS-BLED score[9,10,18]. A HAS-BLED score of 3 or more indicates increased risk of OAC-related bleeding. However, no specific value of the HAS-BLED score should itself be considered prohibitive for OAC use, but should serve to flag up patients at increased risk of bleeding in whom modifiable bleeding risk factors should be addressed, and closer clinical follow-up planned[17].

At her initial presentation, our patient was apparently healthy and younger than 65 years. Thus, her CHA_2DS_2-VASc score was 1 (female gender), and her HAS-BLED score was 0. However, she should have been diagnosed with arterial hypertension early in the course of her clinical follow-up, with an increase in her CHA_2DS_2-VASc score for 1 point. Should our patient have been given OAC therapy at that point?

The use of OAC in AF patients with a single stroke risk factor

Recent reports on various real-world AF cohorts consistently show increasing use of OAC therapy for stroke prevention in patients with non-valvular AF[19-21], but OAC use seems to be in relation with the patients' stroke (and bleeding) risk in only a few of those reports. A recent combined national survey of randomly selected physicians and AF patients in Canada, for example, revealed that physicians often misestimate stroke and bleeding risk in their AF patients, over- or underestimating the risks in considerable proportions of patients[22]. In addition, physicians ranked the fear of bleeding the highest in the list of their concerns with respect to the use of OAC, whilst patients were far less concerned about OAC-related risk of bleeding[23]. Of note, another study showed that most AF patients are willing to sustain 4 major bleeding events in exchange for preventing one AF-related stroke[24]. However, efforts are needed to improve patients' knowledge and understanding of AF and its complications[25,26], as well as the decision-making on OAC use in routine clinical practice.

Whilst various AF Guidelines consistently recommend no therapy in patients with AF and no additional stroke risk factors (that is, a CHA_2DS_2-VASc of 0 in males and 1 in females), and OAC therapy for all AF patients with 2 or more additional stroke risk factors (in the absence of contraindications to OAC therapy, of course), there is some inconsistency among Guidelines regarding AF patients with a single additional stroke risk factor (that is, a CHA_2DS_2-VASc of 1 in males and 2 in females)[27]. In brief, the ESC Guidelines favour a simplified approach to stroke prevention in patients with non-valvular AF, whereby the first step would be to identify AF patients with no additional stroke risk factors using the CHA_2DS_2-VASc score, which outperforms other stroke risk assessment tools in identification of AF patients at truly low risk of stroke[28]. Such patients would not need any antithrombotic therapy, whilst all other AF patients should be considered for OAC therapy in the absence of contra-

Table 2. The HAS-BLED score. Modifiable bleeding risk factors are highlighted in grey.

HAS-BLED score Point score Bleeds per 100 Patient-Years[41]			**Annual stroke rates with increasing score**	
	Clinical characteristic		**0**	1.13
H	Hypertension (uncontrolled)	**1**	**1**	1.02
A	Abnormal renal and liver function (1 point each)	**1 or 2**	**2**	1.88
S	Stroke	**1**	**3**	3.74
B	Bleeding	**1**	**4**	8.70
L	Labile INR	**1**	**5**	12.50
E	Elderly (e.g. age >65 years)	**1**	**6**	0.0
D	Drugs or alcohol (1 point each)	**1 or 2**	**7**	…
Maximum score		**9 9 Any score**	**8**	…
			…	
			1.56	

Hypertension is defined as systolic blood pressure of >160 mmHg. Abnormal kidney function is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 mmol/L. Abnormal liver function is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin>2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.). Bleeding refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. Labile INRs refers to unstable/high INRs or poor time in therapeutic range (e.g., <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc.

INR: international normalized ratio.

indications to OAC use (again, a HAS-BLED of ≥3 itself is not a contraindication for OAC)[1]. Many other AF guidelines (e.g., the Canadian Cardiovascular Society guidelines[12], Asia Pacific Heart Rhythm Society guidelines[29], etc.)[27] also recommended OAC in AF patients with a single stroke risk factor. The AHA/ACC/HRS Guidelines, however, recommended no therapy, or OAC or aspirin in such patients[11].

What would be the rationale for OAC use (or non-use) in AF patients with a single additional stroke risk factor? As recently reported, the threshold for OAC use at ≥1.7% annual stroke risk (which justified the use of VKAs considering the net clinical benefit of those drugs) should be decreased to the cut-off at ≥0.9% annual stroke risk with increasing availability of the safer oral anticoagulant drugs (that is, NOACs)[30]. Indeed, several reports on the nationwide cohorts of AF patients have clearly shown a positive net clinical benefit of OAC in almost all AF patients (excluding those with no additional stroke risk factors)[31,32]. The two recent observational analyses focusing on the large cohorts of patients with AF and one additional stroke risk factors reported the annual stroke rates ranging from 1.55%[33] to 2.75%[34], which is well above the threshold for NOACs use. The net clinical benefit of OAC in comparison to aspirin or no therapy was clearly shown in these and other studies[33-35]. Another real-world observational study of untreated AF patients with a single additional stroke risk factor reported considerably lower annual rates of stroke (<0.9%) and the authors concluded that the use of OAC in such patients might not be justified[36]. However, the study has several major limitations, including a strong selection bias. Namely, all AF patients with a single additional stroke risk factor who were subsequently prescribed OAC at any time point during the follow-up were excluded from the final analysis, which may have resulted in the selection of the very low-risk patients. Thus, the results of the aforementioned study cannot be translated to all patients presenting with AF and a single additional stroke risk factor[37,38].

Another key message from the observational real-world studies on AF patients with a single additional stroke risk factor would be that various conventional stroke risk factors (Table 1) may not have the same 'weight' with respect to the risk of stroke. A history of prior stroke has been repeatedly shown to be the single most powerful predictor of recurrent stroke, even in patients taking OAC[39]. In the aforementioned cohorts with first-diagnosed AF and no prior history of stroke, age was the strongest stroke risk factor in both male and female AF patients, followed by diabetes mellitus, hypertension, heart failure and other components of the CHA_2DS_2-VASc score[33,34]. Clearly, individual patient risk profile may significantly differ depending on the presence or absence of a 'stronger' or 'weaker' risk factor but, again, the overall net clinical benefit has been shown to be positive in the AF cohorts with a single additional stroke risk factor. Therefore, instead of attempting to weight a single stroke risk factor (that is, to quantify its impact on the patient's overall risk of stroke), physicians should focus on identification of the presence of any of the stroke risk factors and should always consider the use of OAC as the most effective means of stroke prevention in patients with AF and one or more additional stroke risk factors.

Importantly, various AF guidelines (including the ESC and AHA/ACC/HRS Guidelines on AF management), increasingly emphasize the need for individualized approach to stroke prevention in patients with AF, taking into account individual patient's values and preferences and reaching the final decision on OAC use through an informed, shared decision-making process. Finally, we should also remember how deleterious consequences AF-related strokes may be associated with and how strong is the AF patients' fear from thromboembolic complications of their arrhythmia.

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Case report

Catheter ablation for atrial fibrillation- therapeutic dilemmas

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Atrial fibrillation (AF) is a cardiac rhythm abnormality most commonly encountered in clinical practice. The presence of AF is linked to a higher mortality and morbidity rate. Treatment for patients with AF primarily focuses on reducing the symptoms (rhythm and frequency control) and preventing thromboembolism. Numerous studies have not indicated a reduction in patient mortality in case of rhythm control strategy application, while a large number of patients in whom the frequency control strategy had been applied, displayed severe symptoms, despite adequate control of ventricular response. For patients suffering from AF three modalities of treatment are available: antiarrhythmic treatment, catheter ablation and a surgical procedure. Bearing in mind that rhythm control drugs have shown limited efficiency, a case of a patient with paroxysmal atrial fibrillation, treated with catheter ablation, has been described in this paper[1-3].

At the Cardiology Clinic of the Clinical Center of Serbia, a sixty-six-year-old man was treated for AF paroxysms occurring every two months, which were accompanied by chest discomfort, feeling of accelerated heart rhythm, labored breathing, and, on several occasions, vertigo. Prevention of arrhythmia was attempted with the application of propafenone, which proved ineffective. In fact, during treatment with this drug, an episode of typical atrial flutter (AFL) occurred, with a rapid ventricular response complicated by the development of transient tachycardiomyopathy. Consequently, prevention of AF paroxysms was continued with amiodarone. Later, amiodarone treatment was discontinued due to the fact that the patient was experiencing nightmares. Three years previously, due to an AFL episode, ablation of the cavotricuspid isthmus (CTI) had been performed.

The patient was admitted to the Cardiology Clinic with almost daily AF paroxysms, lasting from 20 minutes to 24 hours. The echocardiogram discovered an enlarged left atrium (LA), measuring 45x76x46 mm, and a preserved left ventricular systolic function. 24 hours ECG Holter Monitoring, prior to the procedure, had registered persistent atrial fibrillation, of 92/min. average frequency. Before the procedure, a CT angiography of the LA and pulmonary veins (PV) had been performed, revealing normal anatomical characteristics of these structures. For a period of at least six weeks prior to the procedure INR had been within the therapeutic range[2-3]. Upon hospital admission the patient was switched to low-molecular-weight heparin (LMWH), which was not administered on the day of the procedure. The procedure was performed under general intravenous analgosedation.

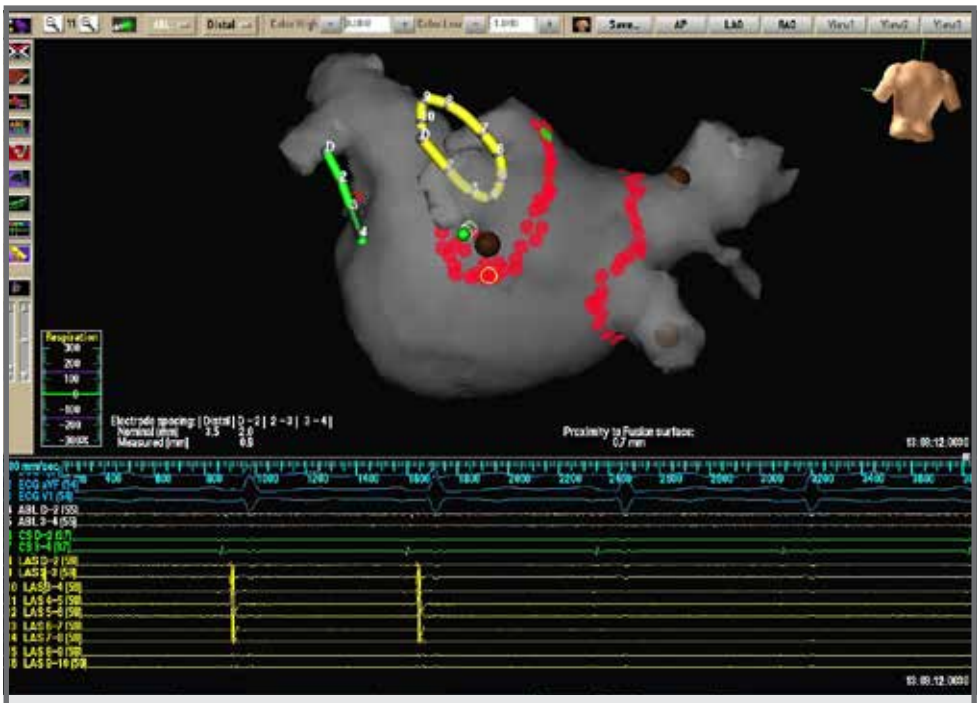

Image 1. The image shows LP reconstruction and, in red dots, places of RF ablation around the PV. The brown spot shows the site of electrical isolation of the left PVs, as visible on the intracardial electrocardiogram in the lower half of the image (disappearance of yellow signals on the circular mapping catheter).

With access via the right femoral vein, transseptal puncture was performed under control of fluoroscopy, while the ablation itself was navigated with the use of a 3D electroanatomical mapping system (Ensite NaVX, St Jude) whereby the cavities of the LA and the PV were reconstructed. The signals were registered, recorded and analyzed on the standard EP system (Work Mate, St Jude). During the entire procedure unfractionated heparin was administered, maintaining the ACT within the 300-350 seconds range. A circular catheter for mapping electrical signals within the pulmonary veins (PV) was positioned, during ablation, on the ostio-antral segment of each PV. With the application of radiofrequency (RF) energy circumferential antral ablation around paired ipsilateral veins was performed, while PV isolation was proven by absence of electrical activity in the veins, which was registered on the circular mapping catheter as well as by appropriate pacing maneuvers (Image 1). In the our EP lab at the Cardiology Clinic the endpoint of the ablation of AF lasting less than 48h is the isolation of all PVs. After an observation period lasting 30 minutes upon isolation of the last PV, it was established that electrical PV isolation was being maintained, while revision of conduction through the CTI confirmed that the bidirectional CTI block was being maintained (previous procedure). The procedure was carried out without complications, therapy with LMWH was continued the same evening, while the following day warfarin was reintroduced, overlapping with LMWH until the achievement of therapeutic INR. Propafenone was continued after the procedure in a blanking period of three months, upon which treatment with this drug was discontinued. Anticoagulant therapy (CHADS2VASc=1) was also, withdrawn three months after the procedure. During follow up period of 20 months there were no symptomatic recurrences of tachyarrhythmia, which was also confirmed with 24-hour Holter ECG Monitoring after one, three, six, twelve and eighteen months after the procedure.

Discussion and reference literature overview

Ablation of paroxysmal AF is a schematic procedure. For each patient, the basis of the procedure is to create a permanent block on the ablation line around the PVs, with the purpose of electrical isolation of the PVs, thus preventing the propagation of electrical potentials from the PV to the LA and AF initiation, since, as it has been established earlier, in these patients, arrhythmia triggers are located in the PVs[4].

The Clinical Practice Guidelines of the European Society of Cardiology and the European Heart Rhythm Association (EHRA) clearly outline the recommended AF ablation strategy, in case of either paroxysmal or persistent form of arrhythmia, this being only PV isolation. On the other hand, the guidelines of the American Heart Association (AHA), American College of Cardiology (ACC) and the American Heart Rhythm Society (HRS) have not clearly defined the strategy of RF ablation. Today, additional strategies are available, and are aimed at increasing the overall success of the procedure, both for paroxysmal AF (left atrial roof linear ablation, additional left atrial ganglionated plexi ablation, ablation of extravenous foci), as well as for persistent AF (linear left atrial ablation, additional ablation of complex fractionated atrial electrocardiograms- CFAE in the left or right atrium, posterior box lesion set, stepwise ablation approach)[1,3,5].

Catheter ablation is efficient both in short and long-term AF control. However, the differences in ablation techniques and technologies, the different definitions of success and recurrence of arrhythmia, as well as the differences and limitations of clinical follow-up upon the procedure, make it difficult to establish the real result, which is why the significant differences in reported outcomes come as no surprise[3,4,6-11].

The success of catheter ablation of paroxysmal AF is within the 60% - 80% range. Early recurrences of atrial tachyarrhythmia in the first three months (so called blanking period) are frequent (30 – 50%) and can be the result of transient inflammation of the atrial tissue and the immaturity of the ablative lesion, and can therefore be prevented with antiarrhythmic and anti-inflammatory drugs and can gradually spontaneously disappear in 40% – 60% of patients, which is why the final outcome of the procedure is assessed only after this early postoperative period has elapsed. Late recurrences occur in 10% of patients, between the first and the second year of follow-up. Data on long-term outcome after AF ablation are still scarce and limited to the follow-up period of between three and five years[3,4,6-13].

Randomized controlled studies have not succeeded in demonstrating the benefit of a sinus rhythm maintained with antiarrhythmic medication. Namely, both pharmacological strategies, rhythm control and frequency control, have demonstrated a comparable mortality rate and stroke in patients with AF. Subsequent subanalysis has, however, shown that the maintenance of the sinus rhythm is connected with an increase in survival by 47% in comparison with AF, and that the application of antiarrhythmic drugs increases mortality by 49%, whereby the advantage of sinus rhythm maintenance over AF is annulled by the adverse effects of antiarrhythmic drugs. Catheter ablation of AF provides the possibility of maintaining sinus rhythm without the application of medication therapy in a significant proportion of the selected patients with AF[14-17].

Randomized studies have shown that catheter ablation for AF is more efficient in maintaining sinus rhythm in comparison with antiarrhythmic therapy (Table 1). Seven studies analyzed the efficiency of ablation and antiarrhythmic therapy in patients with AF, refractory to at least one class Ic or class III antiarrhythmic drug[18-24]. Prevention of atrial tachyarrhythmia episodes was registered more frequently in groups of patients subjected to catheter ablation than in the groups of patients undergoing medication therapy (74% vs. 25%). These studies mostly included patients with paroxysmal AF. The success of ablation was 63% - 85%, after the first procedure, and 85% - 89%, after repeated procedures. On the other hand, in patients with paroxysmal AF, already refractory to pharmacological therapy, success in

Table 1. Randomized studies comparing antiarrhythmic drugs and catheter ablation in treatment of atrial fibrillation.

Year	№ pts	Age (years)	Study design	AF type	SHD	LA (mm)	Ablation strategy	AAD strategy	Follow-up (months)	Ablation results			AAD results		
										Freedom of AF	Cross-over to AADs	Adverse events	Freedom of AF	Cross-over to ablation	Adverse events
2006 [18]	137	62	AF refractory to ≥1 AAD: ablation+AAD vs. „new" AAD	67% PAF	63%	≈45	RF, 8 mm or irrigated-tip, EAM-CPVA (± lines)	62% amiodarone 26% flecainide 10% propafenone 6% sotalol 1% disopyramide	12	56%	-	4% (1 CVI, 1 tamponade, 1 phrenic nerve palsy)	9%	57%	3% (1 SCD, 1 TIA)
2006 [19]	146	57	PeAF>6 m: amiodarone vs. ablation	100% PeAF	8%	45	RF, 8 mm, EAM-CPVA (± lines)	100% amiodarone (first 3 months)	12	74%	1%	-	4%	77%	-
2008 [20]	112	51	PAF refractory to ≥1 AAD: ablation vs. „new" AAD	100% PAF	26%	40	RF, irrigated-tip, PVI (± non PV triggers)	83% Class I 76% Class III (59% amiodarone)	12	89% (1.8 procedures/ pt.)	9%	3% (155 procedures: 2 tamponades, 2 hematomas, 1 PV stenosis)	23%	63%	2% (1 hypothyreosis) + 2 unrelated deaths
2009 [21]	70	≈64	AF refractory to ≥AAD: ablation vs. „new" AAD	41% PAF	50%	45	RF, irrigated-tip, EAM-PVAI (± lines)	77% Class IC 63% amiodarone 9% sotalol	12	80%	-	3% (1 hematoma)	43%	-	17% (5 bradycardias, 1 AFL)
2010 [22]	167	56	PAF refractory to ≥1 AAD: ablation+AAD vs. „new" AAD	100% PAF	11%	40	RF, irrigated-tip EAM-PVAI (± lines or CFAE)	41% propafenone 36% flecainide 20% sotalol 4% dofetilide	9	63%	7%	5% (2 CHF, 1 pericardial effusion, 1 vascular complications, 1 pneumonia)	17%	76%	9% (2 proarrhythmia, 3 intolerance)
2006 [23]	198	56	PAF refractory to ≥1 AAD: ablation vs. „new" AAD	100% PAF	≈6%	≈39	RF, 8 mm or irrigated-tip, EAM-CPVA (± lines)	33% flecainide 33% sotalol 33% amiodarone	48	72%	-	5% (3 AT, 1 pericardial effusion, 1 TIA)	12%	88%	68% (19 hyperthyreosis, 15 bradycardia, 11 sexual dysfunction, 10 wide QRS, 2 visual and dermatological events, 1 hepatitis)
2013 [24]	146	55	PeAF (<1 year) refractory to ≥1 AAD: ablation vs. AAD	100% PeAF	≈3%	≈42	RF, irrigated-tip, EAM-PVAI (± lines or CFAE)	44% Class IC (flecainide) 56% Class III (amiodarone)	12	60% (8% redo)	36%	6% (2 pericarditis, 1 pericardial effusion, 3 vascular complications)	29%	0% (48%)	2% (1 intoxication with flecainide)

Abbreviations:
AAD – antiarrhythmic drug, PAF – paroxysmal atrial fibrillation, PeAF – persistent atrial fibrillation, EAM – electroanatomical mapping, CPVA=circumferential pulmonary vein ablation; SCD=sudden cardiac death; TIA=transitory ischemic attack; CHF=congestive heart failure; AT=atrial tachycardia; AFL=atrial flutter.

maintaining sinus rhythm by change in antiarrhythmic therapy was only 9% – 21%[18,20,22,23]. Therefore, the superiority of catheter ablation of AF in comparison with pharmacological treatment is most evident in patients with paroxysmal AF and previous failure of antiarrhythmic therapy.

AF is linked to a higher mortality and risk of stroke. It is, therefore, expected that the superiority of a non-pharmacological method offering a possibility of AF cure, in comparison with potentially dangerous medication therapy, may reflect a reduction in the mortality rate and systemic thromboembolism. However, meta-analysis of 8 randomized studies has not yielded significant differences either in the mortality rate or the rate of adverse cerebrovascular events between patients treated with catheter ablation (486 patients) and those treated with antiarrhythmic medication (444 patients). The average age of the patients was 51 to 64 years, with a low prevalence of structural heart diseases (4% - 24%). A low mortality rate and a low rate of adverse cerebrovascular events in both observed subgroups of patients in these studies was the result of the selection of a low risk AF population with a high prevalence of lone AF and a short follow-up period after the procedure[25]. On the other hand, several non-randomized studies analyzing mostly a „sicker", more at risk and/or older AF population, have demonstrated a beneficial effect of ablation on the survival of AF patients. In one study, where the prevalence of cardiovascular and pulmonary disease was 58%, and the average age of patients 65 years, over the monitoring period of 2.5 years, the mortality rate was significantly lower (6% vs. 14%) as was the rate of adverse cerebrovascular events (2% vs. 8%) amongst patients treated with ablation as opposed to patients treated with antiarrhythmic medication [26]. Therefore, a positive effect of ablation on survival and systemic thromboembolism (in comparison to medication therapy) could be expected in a basically high-risk population of older AF patients with structural heart disease and increased risk of thromboembolism.

Conclusion

Triggers and rotors in the PV and on the posterior wall of the LA have a crucial role in the initiation and persistence of AF, which is why the concept of catheter ablation of AF entails electrical isolation of the pulmonary veins in case of paroxysmal AF, while patients with persistent AF most probably require an additional modification of the substrate in the LA. The superiority of catheter ablation over pharmacological treatment can mostly be detected in patients with the paroxysmal form of the disease and after unsuccessful prevention via minimum one class Ic or class III antiarrhythmic drug. At this point there is no conclusive evidence that catheter ablation of AF can reduce mortality or the risk of thromboembolism. However, successful rhythm control by means of catheter ablation can in some patients contribute to the restoration of systolic function in the LVs, especially in patients with tachycardiomyopathy. In addition, catheter ablation improves the quality of life in these patients. Due to a limited success of the procedure (60% – 80%) and potential complications occurring in 1% - 4% of interventions (cardiac tamponade, PV stenosis, atrio-esophageal fistula, stroke) the procedure is still reserved for carefully selected patients (**Fig 1.**). Younger patients with symptomatic paroxysmal AF are amongst the best candidates for RF ablation.

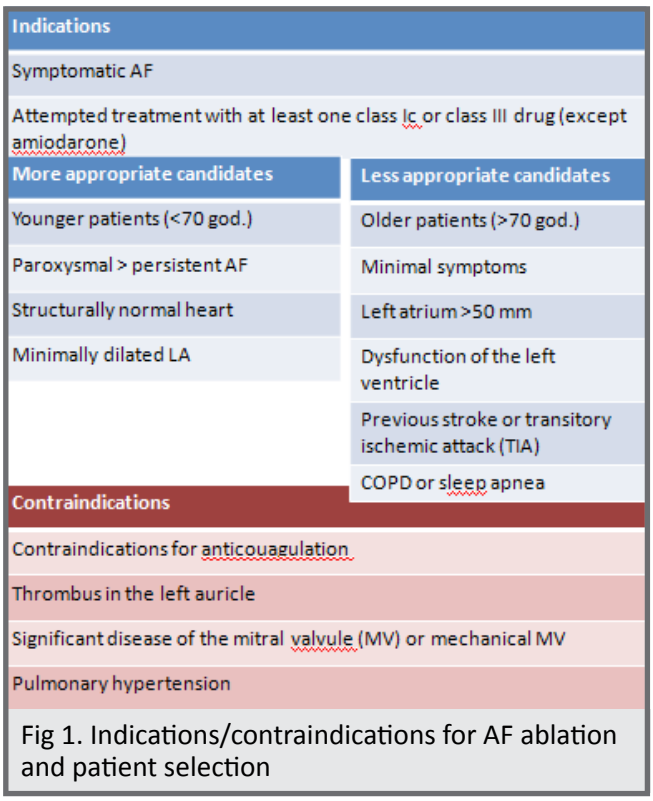

Fig 1. Indications/contraindications for AF ablation and patient selection

For now, ablation is indicated in symptomatic patients in whom AAD therapy has proven unsuccessful. However, catheter ablation can be the first therapeutic option for selected patients with lone AF, in whom ablation results are better; the rate of redo procedures is lower as is the rate of recurrence. One should bear in mind that it may be advisable to perform the procedure at an earlier stage of the disease when the result is better.

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Prikaz slučaja u svetlu preporuka za kardiološku evaluaciju bolesnika koji su upućeni na nekardijalnu hirurgiju

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Pacijent star 65 godina primljen je na Kliniku za Vaskularnu i Endovaskularnu hirurgiju radi operativnog lečenja nerupturirajuće trombozirane aneurizme infrarenalnog segmenta abdominalne aorte. Radi se o dugogodišnjem kardiološkom bolesniku kome je 1997 godine, nakon prebolelog infarkta miokarda, urađena hirurška revaskularizacija miokarda, dvostruki aortokoronarni bypass graft (CABG) sa implantacijom jednog arterijskog grafta LIMA LAD i jednog venskog grafta SVG-RCA. Pri prijemu, pacijent negira značajnije tegobe kardiovaskularnog sistema. Dobro toleriše fizički napor, po ravnom može da hoda 2-3km, penje se 2-3 sprata. Od pre 1 godine zna za paroksizme apsolutne aritmije .Od fakora rizika se navodi samo hipertenzija.

Objektivno kod bolesnika se registruje ritmična srčana radnja, tonovi tmuli, bez šuma, fr 72/min, TA 110/70mmHg. Od terapije koristi Amiodaron 1x1/2 na II dan, Bisoprolol 2,5mg 1x1, Lodoz 1x1/4, Norvasc 1x1/4, Diunorm 1x1, Preductal MR 2x1, Hipolip 20mg 1x1. Elektrokardiografski se registruje sinusni ritam fr 68/min, levogram, QS sa neg T u D3 aVF, AV blok I stepena.

Ehokardiografski nalaz je pokazao dilatiranu levu komoru 6.0/4.4cm sa hipoknezjom bazalnog segmenta inferoseptuma i bazomedijalnog segmenta donjeg zida, EF 50%, LP 4.6cm,DK 3.0cm, MR2+,TR2+, SPDK 36mmHg. Aorta dilatirana u korenu i ascedentnom segmentu, dimenzija 4.2-4.6 cm. U sklopu preoperativne kardiološke evaluacije bolesnik je, odlukom nadležnog lekara, upućen na koronarografiju koja je pokazala trosudovnu koronarnu bolest, glavno stablo bez stenoze, LAD okludirana u svom medijalnom delu, D1 grana ostijalno i na račvi sužena 70-90%, proksimalna Cx okludirana, ali se preko epikardijalne kolaterale puni završna Cx i OM grana velike distribucije. RCA je okludirana u proksimalnom segmentu a njene završne grane se pune preko homokolaterala kao i iz LAD, a daje epikardijalnu kolateralu za Cx i OM. Nalaz je pokazao i da je arterijski graft celom dužinom bez značajnih stenoza dok je venski graft okludiran na mestu proksimalne anastomoze. Radi procene značajnosti ovih stenotičnih lezija, pacijentu je urađen farmakološki stres ehokardiografski test (SEHO) sa dobutaminom koji je bio bez sigurnih znakova za smanjenu koronarnu rezervu pri dostignutoj frekvenci od 131/min. Test je prekinut pri punoj dozi dobutamina od 40mcgkg/tt, nakon dostignute SMF od 131/min. Bolesnik je bio subjektivno bez anginoznih tegoba tokom testa. Elektrokardiografski u naporu i oporavku bez denivelacije ST segmenta, registrovane su retke pojedinačne VES i SVES. Ehokardiografski se u miru registruje aneurizmatski proširen i akinetičan bazalni segment donjeg zida i inferoseptuma. Tokom testa bez jasnih poremećaja u segmentnoj kinetci. Pacijentu je potom urađena operacija aneurizme abdominalne aorte i u daljem toku se osećao dobro.

Šta kažu preporuke ?

Kardiološke komplikacije su glavni uzrok perioperativnog morbiditeta i mortaliteta kod pacijenata koji su upućeni na veliku vaskularnu operaciju.[1] Vaskularna hirurgija spada u nekardijalne operacije sa visokim rizikom za pojavu kardioloških komplikacija, a koji se javljaju u preko 5% slučajeva.[2] Ova činjenica se objašnjava vrlo čestim udruženim javljanjem koronarne bolesti i periferne vaskularne bolesti.

Preporuke za kardiovaskularnu evaluaciju bolesnika upućenih na nekardijalnu hirursku intervenciju, Evropsko udruženje kardiologa (*eng European Society of cardiology; ESC*) izdalo je 2014 godine[3] a iste godine je Američko udruženje za srce (*eng*. American Heart Association; AHA) iznelo svoju verziju vodiča za perioperativnu procenu kardiovaskularnog statusa ovih bolesnika.[4]

U odnosu na pojavu kardioloških komplikacija (pojava kardiovaskularne smrti ili infarkat miokada u vremenskom intervalu do 30 dana od intervencije), hirurske procedure se mogu svrstati u intervencije niskog (<1%), intermedijernog (1-5%) i visokog rizika (>5%).[3] Operacija aneurizme abdominalne aorte (AAA) spada u visoko rizične inervencije.

Da bi se umanjio rizik od srčanih incidenata u perioperativnom periodu, prvenstveno akutnog infarkta miokarda, neophodna je adekvatna preoperativna evaluacija kardiološkog statusa bolesnika. Sa druge strane, a naročito u našim uslovima potreban je racionalni pri-

stup ovom problemu kako bi se dijagnostički resursi koristili na najbolji način.[5-7]

Prema najnovijim Evropskim preporukama za nesrčane operacije, u odsustvu aktivnog srčanog oboljenja (nestabilna angina pektoris, skorašnji AIM -poslednjih mesec dana, dekompenzovana srčana slabost, značajna srčana aritmija i značajna valvularna bolest) minimum preoperativne kardiološke dijagnostike pre elektivne operacije AAA podrazumeva radiografiju (RTG) grudnog koša, elektrokardiografski nalaz (EKG) i transtorakalna ehokardiografija (TTE) . Potreba za daljim neinvazivnim dijagnostičkim testovima se procenjuje na osnovu funkcionalnog kapaciteta i prisustva faktora rizika.[3]

Objektivna procena funkcionalnog kapaciteta se procenjuje testovima fizičkog opterećenja ili na osnovu sposobnosti pacijenta da obavlja različite fizičke aktivnosti. Na osnovu ciljanih pitanja o sposobnosti izvođenja određenih zadataka (hodanje po ravnom, penjanje uz stepenice, nošenje tereta…) može se proceniti funkcionalni kapacitet pacijenta. Shodno tome, mogućnost penjanja na 2 sprat bi odgovarao funkionalnom kapacitetu od 4 META (metabolički ekvivalent)

Kada je funkcionalni kapacitet dobar, progonza je dobra čak i u prisustvu faktora rizika ili stabilne ishemijske bolesti.[8]

Za procenu faktora rizika su korišćeni različiti indeksi rizika. U evropskim preporukama je korišćen indeks po Lee-ju ili revidirani srčani indeks rizika koji se zasniva na šest prediktora : vrsta hirurške intervencije, istorija ishemijske boelsti srca, istorija srčane insuficijencije, istorija cerebrovaskularne bolesti (cerebrovaskularni insult CVI ili tranzitorni ishemijski atak TIA), istorija bubrežne insuficijencije (preoperativna vrednost kreatinina > 2mg/dl) I dijabetes mellitus koji zahteva preoperativnu primenu insulina.[3]

Prema evropskim preporukama neinvazivni stres testovi kod asimptomatskih bolesnika su indikovani kod bolesnika koji su upućeni na hirurišku intervenciju visokog rizika, a koji imaju 2 ili više faktora rizika i loš funkcionalni kapacitet (<4META). (klasa preporuka I nivo dokaza C).[3] U pogledu indikacija za izvođenje neinvazivnih stres testova nema bitne razlike između evropskih i američkih preporuka koje predlažu da pacijente sa povišenim rizikom za nesrčane operacije i sa lošim funkcionalnim kapacitetom treba uputiti ili na dobutamin stresehokardiografski test ili imidžing testove miokardne perfuzije ako će to uticati na dalji način lečenja (klasa preporuka IIa nivo dokaza B).[4]

Pacijenti sa okluzivnom vaskularnom patologjom uglavnom nisu u mogućnosti da urade test fizičkim opterećenjem, tako da se ovi pacijenti najčešće testiraju farmakološkim neinvazivnim testovima. Ima samo nekoliko studija koje su poredile prognostičku vrednost različitih neinvazivnih testova u preoperativnoj proceni rizika.[9] Kertai i sar. su pokazali u svojoj studiji da senzitivnost dobutamin stresehokardiogrfije (SEHO) za procenu rizika od periproceduralne srčane smrti i nefatalnog infarkta miokarda kod pacijenata upućenih na velike vaskularne operacije iznosi 85% a specifičnost 70%, dok je senzitivnost perfuzione scintigrafije miokarda (SPECT) 83% a specifičnost 49%.[9] U publikovanim studijama i meta analizama data je blaga prednost dobutamin SEHO testu u odnosu na SPECT zbog slične senzitivnosti, ali veće specifičnosti.[9] Takođe prednost dobutamin SEHO testa je i u tome što pruža informacije i o stanju srčanih valvula i ventrikularnoj funkciji.[10] Izbor testa takođe zavisi i od raspoloživosti, ekspertize i iskustva lekara.[4]

U skladu sa evropskim preporukama pacijenti kod kojih testom nije izazvana ishemija ili je provocirana blaga do umerena ishemija upućuju se na planiranu hirurgiju. U slučaju pozitivnog stres testa neophodan je individualni pristup perioperativnoj proceni rizika uzimajući u obzir koristi predložene hirurške intervencije u odnosu na rizik od neželjenog ishoda kao i koristi od eventualne revaskularizacije.

Koronarna angiografija kao invazivna metoda se prema važećim Evropskim preporukama ne primenjuje često u proceni rizika od kardioloških komplikacija kod pacijenata kod koji se planira nekardijalna hiurgija.[3] Indikacije za preoperativnu koronarografiju i revasklarizaciju kod pacijenata sa poznatom ili suspektnom koronarnom bolešću, a koji su upućeni na nekardijalnu hirurgiju su slične kao i u slučajevima kod kojih se hirurgija ne planira.[11]

CASS (The Coronary Artery Surgery Study) studija je obuhvatila 25.000 pacijenata sa koronarnom ishemijskom bolešću, a koji su lečeni ili hirurškom revaskularizacijom mikarda ili optimalnom medikamentnom terapijom i praćeni u periodu od 10 godina.[12] Tokom praćenja kod 3.368 bolesnika je urađena nekardijalna operacija. Retrospektivna analiza je pokazala da je u grupi nerevaskularizovanih bolesnika rizik od perioperativnog infarkta miokarda i smrti bio veći u odnosu na grupu bolesnika kod kojih je prethodno urađen CABG. Ovakva protektivna uloga revaskularizacije se pokazala u barem prvih 6 godina nakon CABG naročito kod bolesnika sa trostrukom koronarnom bolešću i/ili redukovanom funkcijom leve komore i kod bolesnika koji su podvrgnuti operaciji viskog rizika. U skladu sa ovim rezultatima, prema važećim preporukama asimptomatski bolesnici kod kojih je urađena hirurška revaskularizacija miokarda u poslednjih 6 godima se upućuju na elektivnu nekardijalnu operaciju bez prethodnog rutinskog testa opterećenjem i angiografije, izuzev visoko rizičnih bolesnika.

CARP (The Coronary Artery Revascularization Prophylaxis) studija je poredila uticaj medikamentne terapije i profilaktičke revaskularizacije (perkutana koronarna angioplastika- PCI ili hirurška revaskularizacija-CABG) kod pacijenata sa stabilnom IBS pre velike vaskularne operacije.[13] U studiju je uključeno 510 bolesnika sa povišenim rizikom za nastanak kardioloških komplikacija, a što je procenjeno na osnovu faktora rizika (revised cardiac risk index) i provocirane ishemije na neinvazivnim testovima. Studija je pokazala da u ove dve grupe pacijenata nema razlike u mortalitetu niti u učestalosti perioperativnog infarkta miokarda 2.7 god nakon početka studije, te da profilaktička revaskularizacija koja prethodi vaskularnoj operaciji kod stabilnih boelsnika ne poboljšava ishod.

Evropske preporuke o opravdanosti profilakticke revaskularizacije pre planirane nekardijalne operacije predlažu revaskularizaciju miokarda u skladu sa trenutno dostupnim preporukama za dijagnozu i lečenje sta-

bilne koronarne bolesti (klasa preporuka I nivo dokaza C) kao i da se profilaktička revaskularizacija može razmotriti pre visokorizičnih operacija u zavisnosti od veličine stresom indukovanog defekta u perfuziji miokarda (klasa preporuka IIb nivo dokaza B).[3]

Safena vena graftovi nakon operacije aorto koronarnog bypassa pokazuju sklonost ka degenerativnim ateroskelrotskim promenama koje vode stenozi i okluziji. Dugoročna korist od hirurške revaskularizacije miokarda je upravo limitirana visokom incidencom okluzije venskih graftova. Nakon 10 god od operacije okluzija venskog grafta se viđa u 41-50% slučajeva.[14-16] Fitzgibbon i sar. (15) su na populaciji od 222 pacijenta zaključili da je najveća incidenca okluzije grafta u periodu između pet i sedam ipo godina nakon revaskularizacije. Grondin i sar. (16) su ustanovili da je stopa okluzije 12-20% u prvoj godini nakon CABG a da narednih 5 godina se stopa uvećava za 2-4% godišnje da bi nakon 10 godina iznosila 50%. U evropskim preporukama za revaskularizaciju miokarda iz 2014god navodi se da je prohodnost venskih gaftova nakon 10 godina 32-71%, a arterijskog LIMA grafta 88-95%.[17]

Obe metode lečenja venskog grafta (re do CABG i PCI SVG) su tehnički veoma zahtevne i pokazale su se lošim u pogledu dugoročne prognoze. Ponovna revaskularizacija je indikovana samo kod bolesnika sa značajnom simptomatologijom i pored agresivne medikamentne terapije i kod asimptomatskih bolesnika kod kojih je objektivnim metodama potvrđena miokardna ishemija (vise od 10% LV).[18,19] Mehanička revaskularizacija miokarda u poređenju sa medikamentnom terapijom ne utiče na preživljavanje pacijenata kod kojih je graft LIMA-LAD prohodan a sa ishemijom u zoni koju vaskularizije RCA odnono Cx koronarna arterija.[20]

Analiza slučaja kroz postojeće preporuke

Kod našeg pacijenta je planirana visoko rizična hirurška inetrvencija. Pacijent je asimptomatičan. Od faktora rizika prema revidiranom srčanom indeksu rizika (RCRI) prisutan je su jedan: ishemijska bolest srca (prethodni IM i CABG) . Funkcionalni kapacitet je 4 META. Međutim, bolesnik je bez prethodne neinvazivne dijagnostike upućen na koronarografiju. Nalaz koronarografije je pokazao da je LIMA LAD velikog kalibra i da je prohodna celom dužinom, a da je venski graft SVG RCA okludiran. Nativna Cx je okludirana proksimalno, ali se preko epikardijalne kolaterale puni zavrsna Cx i OM grana velike distribucije. Obzirom na ovakav nalaz postojala je dilema da li pacijenta uputiti na ponovnu revaskularizaciju miokarda, neinvazivnu stres dijagnostiku ili vaskularnu hirurgiju. Prema važećim preporukama, a u cilju procene značajnosti ovih lezija, bolesnik je upućen na SEHO test sa dobutaminom. Testom nisu izazvane nove ishemijske promene i bolesnik je upućen na hiruršku intervenciju operacije AAA. Operacija je protekla bez komplikacija i u daljem toku bolesnik se oseća dobro.

Zaključak

Ovim prikazom slučaja smo hteli da ukažemo na značaj neinvazivnih testova opterećenjem u kardiološkoj evaluaciji bolesnika u sklopu pripreme za nekardijalnu hiruršku intervenciju. Dobutamin SEHO test je dostupna i bezbedna metoda koja se pokazala dobrom u identifikaciji bolesnika sa umerenim do visokim rizikom od kardioloških perioperativnih komplikacija. Postupanje u skladu sa vazećim preopukama i pravilna interpretacija neinvazivnih dijagnostičkih testova može nam pomoći da izbegnemo odlaganje hirurške intervencije i invazivnu koronarografiju u slučajevima kada ona nije neophodna, kao i uštedu resursa.

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Case report

Differential Diagnosis and Management of Chronic Pericarditis in the Context of 2015 ESC Guidelines on Pericardial Diseases

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A 52 years old patient was admitted to our hospital because of the recurrent large pericardial effusion, only four weeks after previous pericardiocentesis and drainage of 1600 ml of serous, initially idiopathic pericardial effusion. Five months before, he felt slowly progressing fatigue, dyspnea on effort and productive cough (but no hemoptysis). ECG revealed atrial fibrillation with low voltage and tachycardia and echocardiography demonstrated signs of an imminent cardiac tamponade and a foreign mass on the visceral layer of the pericardium in front of the right ventricle. Computed tomography verified epicardial infiltration of benign features in front of the right ventricle. The patient was initially stable after the first pericardiocentesis. However, soon after the hospital discharge, a large pericardial effusion slowly recurred, followed with dyspnea on effort. His medical history also includes arterial hypertension, well treated with ACE inhibitors.

Physical examination on his second admission revealed no fever, distended neck veins, and distant heart sounds. His heart rate was rapid but now regular (110 b/min, no atrial fibrillation any more) and there was no severe hypotension (BP 120/80 mmHg). In addition to the rapid heart rate, ECG revealed low voltage and electrical alternans, with a leftward axis deviation (QRS vector -26°). After repeated pericardiocentesis his heart rate returned to 70-80/min. However, a brief paroxysm of atrial fibrillation with a rapid ventricular rate of 180 b/min occurred again immediately after pericardiocentesis.

Laboratory analyses revealed increased sedimentation rate during the course of hospitalization (46... 38... 80... 50... 100... 69) with a slight syderopenic anemia (hemoglobin 111-122, serum iron 7.3). All other routine laboratory analyses were normal including serum cholesterol 4.19, HDL 1.41, LDL 2.22 and triglycerides. Although other parameters of the liver function were normal, gamma GT was significantly increased (132) probably due to the previous alcohol abuse.

Chest X-ray demonstrated small pleural effusion at the left side and an enlarged "water-bottle" heart shadow. Echocardiography revealed a very large, Horowitz type D pericardial effusion with the diastolic separation of pericardial layers of 24-30 mm in front of the right ventricle and 33-36 mm behind the left ventricle. Interestingly, there was a 15-20 mm thick, pear-like formation at the visceral pericardium in front of the right ventricle. Despite the huge size of the effusion, there were no signs of cardiac tamponade. Remaining echocardiography findings were normal, with the normal size and contractility of all cardiac structures.

Abdominal ultrasonography has shown normal size and shape of the liver with no focal lesions, but diffusely non-homogenous structure. Portal vein was normal, with no thrombosis. Gall bladder was of normal size and position, but bended, with increased wall thickness and with an infundibular content of high density but no calculosis. Choledochus was of regular luminal size, with no calculosis. Pancreas was normal, as well as the spleen and the kidneys. No ascites could be detected.

As a part of the initial management, pericardiocentesis and drainage of 1700 ml of hemorrhagic pericardial effusion was performed using fluoroscopic control in the cardiac catheterization laboratory, a flexible 7F catheter and the subxiphoid approach. Pericardial fluid analyses revealed the following findings: glucose 2.6, total proteins 44, albumins 27, alpha amylase 37, LDH 745 U/l, pH 8. All cultures for aerobic and anaerobic bacteria remained sterile. Direct microscopy and cultures for tuberculosis were negative as well. Cytological examination of the pericardial effusion has demonstrated coagulated proteins, scarce lymphocytes, granulocytes, and rare solitary cells with week expression of anisomorphism.

Cardiac catheterization was performed in the second session, in order to exclude presence of any pathological vascularisation of the timorous formation on the visceral layer of the pericardium in front of the right ventricle. However, coronary arteries were normal, as well as the left ventricle with the LVEF of 65%. Right-heart catheterization revealed normal pressures in the pulmonary circulation and the right-heart chambers.

In order to additionally visualize the tumor formation, intracardiac echocardiography was performed (Accu-Nav,

Siemens, Germany). Scanning from the right atrium, it was possible to visualize pear-like tumor on the visceral pericardium in front of the right ventricle, 3x5 cm, arising from the epicardium on the wide basis, with distinct borders and no signs of infiltration of the myocardium. Small, thick, residual pericardial effusion was also detectable, despite the previous drainage of the effusion and the presence of a functional pericardial catheter.

In an attempt to clarify the etiological diagnosis, after 12 days of prolonged drainage of the pericardial effusion with a daily drainage of 200-300 ml of sero-hemorrhagic effusion, the patient underwent pericardioscopy and pericardial biopsy: (16.5 F Olympus HYF-1T flexible endoscope) (Figure 1). Endoscopic evaluation revealed signs of hemorrhagic inflammation on both pericardial layers. As expected according to the echocardiography and computed tomography findings, a large, solitary tumor formation, with macroscopic features of a lipoma, was visualized on the epicardial layer in front of the right ventricle. Six biopsy samples were taken from the borderline area of the tumor and surrounding epicardium and pericardium. The procedure was completed without any complications.

Patohistological examination has revealed lymphocyte infiltration and changes specific for cholesterol pericarditis as depicted in the Figure 1.

Due to the continuous production of large amounts of sero-hemorrhagic fluid the patient was referred to pericardiectomy. Subtotal pericardiectomy was performed, but surprisingly 5x3 cm large tumor, previously confirmed by echocardiography, computed tomography, intracardiac echocardiography, and pericardioscopy was not present at the time of surgery any longer. Perhaps, a lipomatous content of the tumor was drained after the biopsy. However, several similar tumors (Figure 2) were detected in the left pleura and removed during the same surgical procedure. In addition, 300 ml of thick chylous effusion was evacuated from the left pleura. The final diagnosis established from the biopsy samples taken by pericardioscopy and the samples taken during the surgery was cholesterol pericarditis with the chronic inflammation (foreign body granulomatous inflammation around the cholesterol crystals) as well as the benign pleural lipoma. Pear-like infiltration of the visceral pericardium in front of the right ventricle was most probably also a lipoma which collapsed after taking several biopsy samples. After the surgery, there was no relapse of either pericardial or pleural effusion and the patient was discharged from the hospital on antihypertensive medication and statins. The patient remained stable, with no symptoms, no pericardial or pleural effusion and no recurrences of lipomatous tumors during the 10-years of follow-up. He was even able to return to his previous profession – acting in the classical drama theatre.

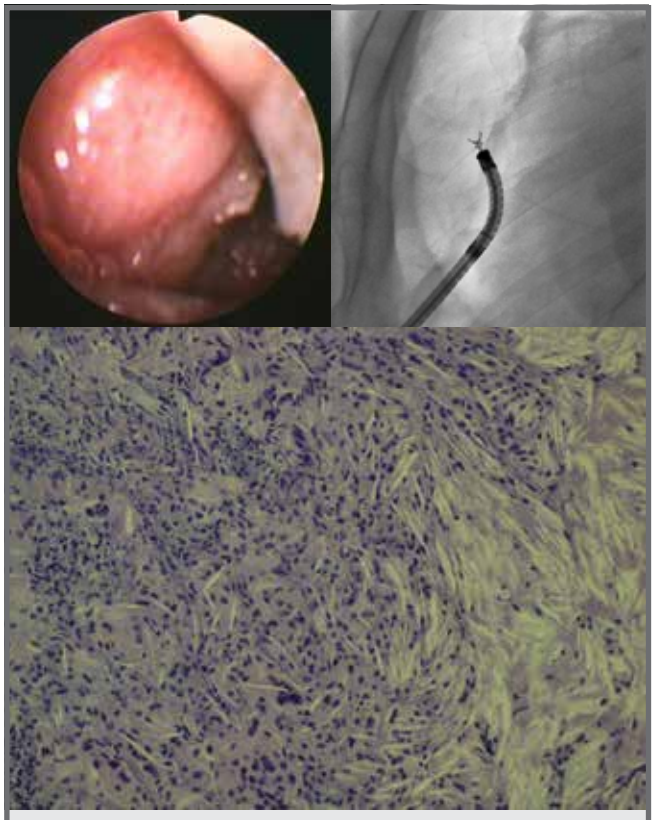

Figure 1. Pericardioscopy and pericardial biopsy in a patient with recurring cardiac tamponade and extensive prolonged production of sero-hemorrhagic pericardial effusion of unclear etiology. Patohistology revealed changes specific for cholesterol pericarditis.

Chronic pericarditis as a diagnostic and therapeutic challenge

The most important prerequisite for successful management of patients with chronic pericarditis is determination of the background etiology. Therefore, extensive etiological search may be needed in order to uncover the specific disease affecting the pericardium, sometimes, including pericardial fluid analyses and targeted pericardial biopsies. Although indications for pericardiectomy are well-established in constrictive pericarditis, referral of patients with chronic pericardial effusion for surgery is still a matter of debate, despite the clear instructions from the ESC Guidelines [1-3] and the American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease [4].

Figure 2. Intraoperative findings demonstrating extensive inflammatory changes on the visceral and parietal pericardium, thickened parietal pericardium and infiltration in the left pleural space (white arrow). Surprisingly, no timorous infiltration of the visceral pericardium could be visualized in front of the right ventricle any more. Right-sided image reveals histological examination from the pleural tumor – pleural lipoma.

Discussion

When a pericardial effusion is detected, the first step is to assess its size, hemodynamic importance (especially the presence of cardiac tamponade) and possible associated diseases (either cardiovascular or systemic diseases). Pericardial effusion is often associated with known or unknown (e.g. hypothyroidism) medical conditions (up to 60% of cases). If inflammatory signs are present, the clinical management should be that of pericarditis. Cardiac tamponade without inflammatory signs is associated with a higher risk of a neoplastic etiology (likelihood ratio 2.9), whereas a severe effusion without cardiac tamponade and inflammatory signs is usually associated with a chronic idiopathic etiology (likelihood ratio 20)[1].

Therapy of pericardial effusion should be targeted at the etiology as much as possible. In about 60% of cases, the effusion is associated with a known disease and the essential treatment is that of the underlying disease. When a pericardial effusion becomes symptomatic without evidence of inflammation, drainage of the effusion should be considered since there are no proven effective medical therapies to reduce an isolated effusion. In the absence of inflammation, NSAIDs, colchicine and corticosteroids are generally not effective. The major specific causes to be ruled out are bacterial pericarditis, neoplastic infiltration and pericarditis associated with a systemic autoimmune or metabolic disease. Each of these specific causes has a frequency of <5% of all unselected cases of pericarditis from developed countries while frequencies increase in moderate to large pericardial effusions. The etiological spectrum is different in developing countries with a high prevalence of tuberculosis (e.g. 70–80% of pericarditis in sub-Saharan Africa, and often associated with HIV infection). Rare patients with relapsing pericarditis can also benefit from pericardiectomy[1-3].

Table 1. Algorithm for diagnostic evaluation of patients with chronic pericarditis according to the 2015 ESC Guidelines: First and second level investigations for pericarditis[1].

Diagnostic tools	Investigation
1st level methods	Markers of inflammation (ESR, CRP, WBC). Renal function and liver tests, thyroid function. Markers of myocardial lesion (troponins, CK) ECG Echocardiography Chest X-ray
2nd level methods	CT and/or CMR, pericardiocentesis, or surgical drainage, for (i) cardiac tamponade or (ii) suspected bacterial, neoplastic pericarditis, or (iii) symptomatic moderate to large effusions not responding to aetiologies according to clinical presentation (presence of high risk clinical criteria).

CK - creatine kinase; CMR - cardiac magnetic resonance; CRP - C-reactive protein; CT – computed tomography; ECG - electrocardiogram; ESR -erythrocyte sedimentation rate.

Cholesterol pericarditis is a rare complication of chronic pericardial effusion or chronic scarring of the pericardium[5] and is exacerbated by cholesterol crystals. Common underlying causes include tuberculous pericarditis, autoimmune rheumatic diseases, and pericardial trauma [6, 7]. When a pericardial effusion is relatively acute, its cholesterol content remains in solution. However, when the pericardial effusion is chronic, the normal ability to dissolve cholesterol is impaired and cholesterol crystals are deposited in the pericardium and effusion[8-10]. The fluid is clear, in contrast to chylopericardium, and classically is said to have a glittering "gold paint" appearance, as it was the case with our patient at the first pericardiocentesis[11,12]. However, any other macroscopic appearance of pericardial effusion apart from the "gold paint" is not excluding the diagnosis.

The effusions tend to be large. The concentration of cholesterol equals or exceeds that of the blood, often attaining values above 500 mg/dL (13 mmol/L)[12,13]. Unfortunately, estimation of cholesterol level was not a part of our routine evaluation of the pericardial effusion, which turned out to be wrong in this specific case. The pericardial effusion associated with myxedema also has a high cholesterol concentration, but crystals are usually absent.

Blood associated with inflammation is thought to be the source of cholesterol in the pericardial fluid, and evidence of current or previous hemorrhage is usually evident. The pericardium is thicker than normal (Figure 2 left) and its inner surface is lined with plaques and cholesterol deposits. The histological findings include fibrosis, inflammatory cells, cholesterol clefts and crystals of variable geometry, and giant cell granulomata.

Treatment includes pericardiocentesis, which is seldom effective over the long-term because the effusions tend to recur and can cause tamponade at any time[13]. This procedure also fails to address the thick, scarred pericardium and does not prevent the late development of constrictive pericarditis. Thus, optimal therapy is radical pericardiectomy with additional treatment of the underlying cause of chronic pericarditis[1-3].

Conclusion

Differential diagnosis may be complex in patients with chronic pericarditis and according to both 2015 ESC guidelines and American Society of Echocardiography clinical recommendations require systematic application of multimodality imaging including targeted pericardial biopsies. In patients poorly responding to medical treatment or with specific etiology highly prone to constriction, pericardiectomy should be also considered as the ultimate treatment option.

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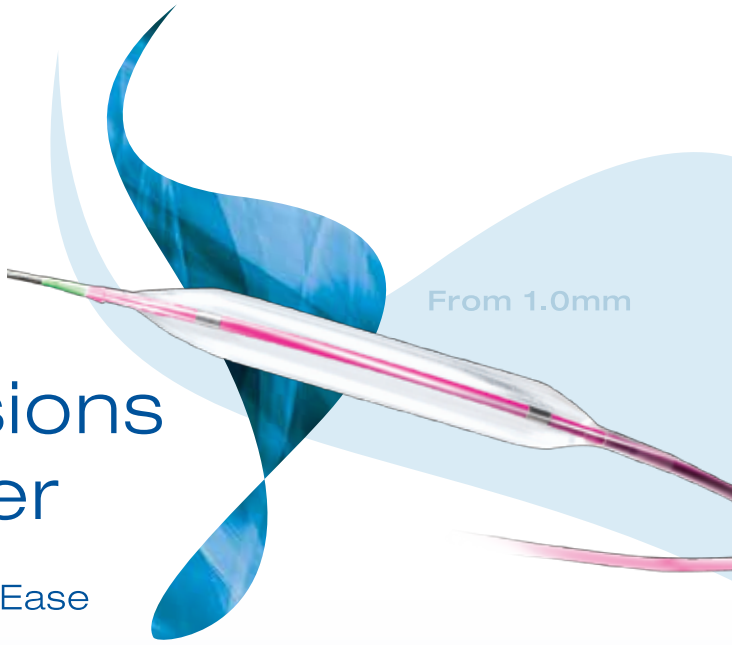

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