Cor et Vasa

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/crvasa

Chlopenní a vrozené srdeční vady | Valvular and congenital heart disease

Přehledový článek | Review article

Antithrombotic therapy in valvular heart disease and artificial valves

Hana Línková, Róbert Petr

III. interní-kardiologická klinika, Kardiocentrum 3. lékařské fakulty Univerzity Karlovy a Fakultní nemocnice Královské Vinohrady, Praha, Česká republika

INFORMACE O ČLÁNKU

Historie článku:
Došel do redakce: 23. 11. 2012
Přepracován: 18. 1. 2013
Přijat: 20. 1. 2013
Dostupný online: 25. 1. 2013

Keywords:
Antiagregation
Anticoagulation
Aspirin
Bioprosthesis
Embolism
Low molecular weight heparin
Mechanical prosthesis
Native valves
Thrombosis
Unfractionated heparin

Klíčová slova:
Antiagregace
Antikoagulace
Bioprotézy
Embolizace
Kyselina acetylsalicylová
Mechanické náhrady
Nativní chlopně
Nefrakcionovaný heparin
Nízkomolekulární heparin
Trombóza chlopní

ABSTRACT

The article summarizes the current recommendations and knowledge for the treatment of patients with artificial valves. The attention is focused on antithrombotic therapy after valve replacement, including possible complications of the treatment, particularly thromboembolic and bleeding complications. We review the procedures when the anticoagulation must be interrupted. The possibilities of improving therapy in patients that require permanent anticoagulation and the outlook for the future are discussed.

SOUHRN

Článek shrnuje současná doporučení a znalosti antitrombotické léčby pacientů s chlopenními vadami a náhradami chlopní.
Pozornost je zaměřena především na antitrombotickou léčbu po náhradách chlopní, včetně možných komplikací, zvláště tromboembolických či krvácivých. Je rozebrán také postup při nutném přerušení antikoagulační léčby. V článku jsou také diskutovány možnosti zkvalitnění léčby u pacientů, kteří užívají antikoagulační léčbu, a možnosti léčby v budoucnosti.

Adresa: MUDr. Hana Línková, III. interní-kardiologická klinika, Kardiocentrum 3. lékařské fakulty Univerzity Karlovy a Fakultní nemocnice Královské Vinohrady, Ruská 87, 100 00 Praha 10, e-mail: hana.linkova@fnkv.cz
DOI: 10.1016/j.crvasa.2013.01.008

Tento článek prosím citujte takto: H. Línková, R. Petr, Antithrombotic therapy in valvular heart disease and artificial valves, Cor et Vasa 55 (2013) e158–e163, jak vyšel v online verzi *Cor et Vasa* na http://www.sciencedirect.com/science/article/pii/S0010865013000106

Table 1 – Determination of INR levels in mechanical prosthesis.

Recommended INR			
		AVR Without risk factors SR LA < 50 mm MValve Gr 0 EF normal SEC –	MVR, TVR, PVR With risk factors FS LA ≥ 50 mm M Valve Gr + EF ≤ 30 SEC +
Thrombogenicity of the valve	Low Intermediate High	2.5 (2.0–3.0) 3.0 (2.5–3.5) 3.5 (3.0–4.0)	3.0 (2.5–3.5) 3.5 (3.0–4.0) 4.0

AF – atrial fibrilation; AVR – aortic valve replacement; EF – ejection fraction; MVR – mitral valve replacement; PVR – pulmonary valve replacement; SEC – spontaneous echocontrast; SR – sinus rhytmus; TVR – tricuspid valve replacement; M Valve – mitral valve.
Risk of thromboembolism in different types of prosthesis:
Low risk: Medtronic Hall, St. Jude Medical (without Silzone), Carbomedics AVR.
Intermediate risk: Bileaflet valves with insufficient data on thrombogenicity, Bjork-Shiley.
High risk: Lillehei-Kaster, Omniscience, Starr-Edwards.

Introduction

More than 100 million patients around the world suffer from valvular heart disease, as the incidence of degenerative valvular heart disease increases with age. At the present time, each year approximately 300 000 valves are implanted, and a further increase is expected. In addition, new less invasive procedures, percutaneous aortic valve implantation – TAVI and edge to edge mitral repair – MitraClip are also being used.

Czech guidelines were published in 2007 and they are mainly based on the 2007 European Society of Cardiology (ESC) guidelines and the AHA/ACC guidelines published in 2006. Recently, new guidelines were published by the European Society of Cardiology as well by the American College of Chest Physicians (ACCP), which include new knowledge regarding antithrombotic therapy [1–5].

The current guidelines are in agreement in essential areas, but there are some points in which the European and American guidelines differ. This is because the recommendations are primarily based on retrospective and observational trials, as prospective randomized trials are missing. At the present time, there is much progress in cardiology in terms of new antithrombotic agents. Many questions therefore emerge:

1. How to manage antithrombotic therapy in patients with valvular disease and in patients with artificial valves?
2. What situations require dual antithrombotic therapy?
3. How to manage complications during antithrombotic therapy and in case of requirement for discontinuation of anticoagulation therapy?
4. How to manage patients with artificial valves during pregnancy?
5. Is there any place for new antithrombotics in the treatment of valvular heart disease?
6. Is it possible to improve therapy in patients who require permanent anticoagulation therapy?

Antithrombotic therapy in patients with valvular disease and with artificial valves

Oral anticoagulation therapy with warfarin

1. In patients with native diseased valves:
(a) always when atrial fibrillation is present;
(b) specific situations arise in patients with mitral stenosis, where anticoagulation therapy is indicated in the presence of atrial fibrillation (paroxysmal, persistent or permanent), further in patients with thromboembolic complications during sinus rhythm, and if a thrombus is present in the left atrium. It should be considered in patients with a severe mitral stenosis, who have sinus rhythm but significantly dilated left atrium.
2. In patients with artificial valves or valve repair:

The individual risk of thromboembolism should be determined individually before antithrombotic therapy is initiated. This is based on what type or surgery was performed – valve replacement or repair, what type of prosthesis was used (mechanical, biological, homograft, autograft), another important factor is the location of the prosthesis (mitral, aortic, tricuspid, pulmonal) [6].

There are no data from randomized trials for initial anticoagulation treatment, therefore the regimes vary. Based on observational trials, most of the embolization events occurred early after the surgery. It is therefore recommended to initiate anticoagulation as soon as possible after the surgery, as soon as the risk of bleeding decreases. Warfarin therapy is initiated 6–24 h after the operation. Unfractionated heparin or low molecular weight heparin with monitoring of aPTT and antiXa is administered simultaneously. Low molecular weight heparin is not recommended in obese patients and in patients with renal failure [7,8].

(A) Permanent anticoagulation therapy is indicated in patients with mechanical prosthesis regardless the type of prosthesis or the time of implantation. The target INR range must take into account the individual patient risk factors and the thrombogenicity of the valve (Table 1). Conventional cate-

Table 2 – Risk factors of thromboembolism.

Connected with slow blood velocity
Atrial fibrillation, dilatation of left atrium (> 50 mm), mitral stenosis
Decreased LV ejection fraction (EF) < 35 %, functional class NYHA IV
Connected with vessel disease or endothelial dysfunction
Systemic hypertension
Diabetes mellitus
Aortic and/or carotid atheromatosis
Connected with increased coagulation and/or aggregration of platelets
Diabetes mellitus
Smoking
Hyperlipidemia
Chronic inflammation/infection, chronic hemolysis
Hypercoagulation conditions
Malignancy

gorization of individual types of prosthesis differ between the European and American guidelines, on top of it the American guidelines recommend the use of warfarin with a low dose of ASA in all patients with mechanical prosthesis, as the risk of thromboembolic complications and overall mortality decreases, however, there is an increase in bleeding complications. Therefore this combination is recommended in the European as well as in our guidelines in only targeted patients with an increased risk of thromboembolism [1–5].

(B) Permanent anticoagulation therapy in patients with biological valves, after valve repair, or homografts is indicated if the patient has another indication for chronic anticoagulation, i.e. atrial fibrillation, left ventricular dysfunction with ejection fraction of less than 30%.

(C) The first 2–3 months after the implantation of a biological prosthesis in mitral position and after mitral valve repair with the annuloplastic ring. According to the 2007 Czech guidelines, a 3-month antiaggregation as well as a 3-month anticoagulation therapy can be used in the case of aortic bioprosthesis. (The ACTION and ANSWER trials are currently investigating whether antiaggregation therapy is sufficient) [9].

(D) 6 months after MAZE procedures, the therapy is prolonged if atrial fibrillation persists.

Antiaggregation therapy in patients with artificial valves

Permanent antiaggregation therapy (ASA) is recommended after the discontinuation of anticoagulation therapy in patients with biological prosthesis in the mitral and tricuspid position as well as in patients after mitral repair and MAZE procedures. According to the current European guidelines, ASA should also be used in the first 3 months in patients with aortic bioprosthesis, however, these guidelines do not clearly specify treatment after the initial 3-month period. In the other guidelines, antiaggregation therapy is recommended permanently [10,11].

Patients undergoing homograft implantation or aortic valve preserving surgery should be on ASA treatment for three months.

Regardless of lack of data in patients undergoing TAVI or percutaneous edge to edge repair, dual antithrombotic therapy with ASA and a thienopyridine is given for 3 months, followed by monotherapy with either ASA or a thienopyridine [1–4].

In patients with atrial fibrillation undergoing TAVI, a combination of warfarin and aspirin or thienopyridine is generally used. It is important to consider increased risk of bleeding in older and high risk patients. There is a lack of data from randomized trials, but in our clinical practice the patients usually use dual therapy (warfarin and thienopyridine) for 1 month and then they use warfarin alone.

Dual antithrombotic therapy in patients with valvular disease and artificial valves

The combination of warfarin and low-dose ASA (75–100 mg) should be considered in patients with high risk of thromboembolism, namely in patients with thromboembolic complications during effective anticoagulation therapy, patients with hyper-coagulation conditions or patients with artificial valves if significant coronary artery disease or significant atherosclerosis is present.

Triple therapy (warfarin plus antiplatelet therapy) is associated with high bleeding risk. Therefore dose of ASA should be 100 mg daily or less. In addition, dual antithrombotic therapy with warfarin and clopidogrel (without ASA) is as effective as triple therapy, but far more safe as shown in the recently presented WOEST trial [12].

In patients with mechanical prosthesis, the use of drug eluting stents should be avoided.

If valve surgery is recommended while the patient is on dual antithrombotic therapy, the surgery should be postponed for one year if possible, or a biological valve should be used [13–15].

Complications of antithrombotic therapy

The complications include excessive anticoagulation and bleeding and on the other side thromboembolic events or valve thrombosis.

Excessive anticoagulation and bleeding

In warfarin overdose, the risk of bleeding is increased with an INR level of > 4.5, and exponentially increases in INR > 6. Excessive anticoagulation with INR > 5 considerably increases the risk of bleeding, however, a quick decrease of INR increases the risk of thromboembolic complications. Patients with an INR > 6 and clinically suspected bleeding should be hospitalized and warfarin should be discontinued temporarily. The INR levels should be monitored daily, as the INR should decrease gradually. In urgent situations and if bleeding occurs, fresh frozen plasma ev. Protromplex instead of vitamin K should be given. Prothrombin factors as well as higher doses of vitamin K increase the risk of thrombosis of the valve due to

Table 3 – Risk of bleeding in individual procedures.
Low risk:
Diagnostic endoscopy, cataract surgery, dermatology surgery, teeth extraction, operation of hernia and scrotum, arthrocentesis, coronary angiography
High risk:
Large orthopedic operations, abdominal operations, vascular surgery, urological procedures (PE, operation of urinary bladder), thoracic operations, neurosurgical operations, cardiac operations, operation of tumors, puncture of arteries without the possibility of compression, biopsies without the possibility of compression, implantation of pacemaker.

the possibility of hypercoagulation. A small dose of vitamin K (up to 1 mg) should be safe [10,11].

Thromboembolic complications and valve thrombosis

Thromboembolic complications including systemic embolizations occur in between 0.7–6% per year and they can occur even during the recommended anticoagulation scheme. In case of such complication it is mandatory to locate the source of the embolization. The most frequent source is the prosthesis alone, but other sources (thrombus in left ventricle or atrium, carotid stenosis etc.) must also be excluded. Apart from risk factors of thromboembolism (Table 2), triggers of thromboembolism can also be identified. For example dehydration associated with increased blood viscosity, pulmonary infection (with the presence of prothrombic mechanisms), sudden occurrence of atrial fibrillation, a decrease of INR level below the therapeutic value. If the risk and trigger factors are treated, an increase of anticoagulation therapy associated with high bleeding risk can be avoided.

When the risk of thromboembolism cannot be eliminated, it is recommended to intensify antithrombotic treatment if possible.

1. If the INR is 2.0–3.0, target INR level should be increased to 2.5–3.5.
2. If the INR is 2.0–3.5, target INR level should be increased to 3.5–4.5.
3. If the patient is not on ASA treatment, a dose of 75–100 mg per day should be added.
4. If the patient is on warfarin and ASA, the dose of ASA should be increased to 300 mg/day, if higher target INR does not have sufficient clinical effect.
5. If the patient is on ASA monotherapy, higher dose (up to 300 mg/day), or 75 mg dose of clopidogrel or warfarin with target INR between 2.0 and 3.0 should be added.

The addition of ASA to anticoagulation therapy is relatively contraindicated in patients with a history of gastrointestinal bleeding, in patients with difficultly managed hypertension on combination therapy and in patients with poorly controlled INR levels (fluctuations in INR, frequent episodes of high INR levels).

Valve thrombosis is a rare but severe complication. The obstruction on mechanical valves oscillates approximately between 0.3–1.3% per year. Non-obstructive valve thrombosis occurs more frequently in the early postoperative time period (10% of patients). The morbidity and mortality usually depends on how fast the diagnosis is made. The death rate is approximately 10% regardless of the type of treatment. Making the diagnosis can be challenging due to heterogeneous clinical manifestation. Thrombosis on bioprosthetic valves is less frequent and it also usually occurs in the early postoperative period, when the endothelization of sutures is not yet finished. The diagnosis is based on transthoracic echocardiography and fluoroscopy (in patients with mechanical valves). Transesophageal echocardiography is valuable for further assessment. Invasive hemodynamic examination is not frequently needed. The treatment depends on the clinical condition, location of the prosthesis and extent of the thrombosis rather than the type of valve (artificial or biological) [11,16,17].

The therapy includes the following options: optimization of anticoagulation and antiaggregation therapy, heparin therapy, fibrinolysis or surgical treatment.

In obstructive thrombosis, urgent or emergent surgical treatment of the valve is the first method of choice in patients in critical condition without severe co-morbidities (operation mortality in patients with NYHA I–III is about 4% and in patients with NYHA functional class IV it is approximately 17.5%). There are many types of surgical procedures, varying from basic thrombectomy to re-implantation of the valve if the main cause of the thrombosis was thrombogenicity of the valve. In this case a less thrombogenic valve should be used. Fibrinolysis can be used in patients in functional class NYHA III–IV if they have high operative risk or have contraindications to the surgical procedure. It can also be used in patients with functional class NYHA II, if the thrombus is small and anticoagulation therapy with heparin has failed. In patients treated by thrombolysis, systemic embolizations occur in approximately 12% and the mortality rates vary around 10%. In case of haemodynamic instability a short protocol is recommended, using either intravenous recombinant tissue plasminogen activator 10 mg bolus + 90 mg in 90 minutes with UFH, or streptokinase 1,500,000 U in 60 minutes without UFH. Longer duration of infusions can be used in stable patients [1].

Fibrinolysis should also be considered in thrombosis of tricuspid and pulmonary valve prosthesis as the risk of thromboembolism is lower. Fibrinolysis is less effective in thrombosis of mitral prosthesis, in case of chronic thrombosis and in the presence of a pannus, that can be difficult to distinguish from a thrombus echocardiographically.

The diagnosis of non-obstructive thrombosis of an artificial valve is made by transesophageal echocardiography that is performed after a thromboembolic event.

The size of the thrombus and the occurrence of a thromboembolic event are the key factors for selecting therapy.

Heparin therapy should last for one week, further treatment is based on a follow-up transesophageal echocardiography exam. In some cases, the increase in the dose of warfarin with the addition of a low dose of antiaggregation therapy (ASA 100 mg daily) is sufficient. Surgical therapy is recommended in thrombi ≥ 10 mm, in non-obstructive thrombosis complicated by an embolization, or if the thrombus remains even after optimal anticoagu-

lation therapy. If fibrinolysis is used when small thrombi are present, it is important to consider higher risk of systemic embolization. Therefore it should be used very cautiously.

Antithrombotic therapy before dental and surgical procedures

In patients with a high risk of thrombosis, and in all mechanical prosthesis, warfarin is discontinued approximately 5 days before the procedure, and unfractionated heparin is given when the INR level is below 2. Heparin is given up to 5–6 h before the procedure and it is restarted as soon as possible after the procedure. The treatment is continued until INR is in the therapeutic range. LMWH can also be used, but in patients in a critical condition, where an urgent procedure is possible, unfractionated heparin is preferred. aPTT or ACT should be monitored every 4 h. When LMWH is used, the last dose is given 12 h before the procedure and the next dose is given 12 h after the procedure, after correction of hemostasis. In patients on anticoagulation therapy, frozen plasma is given prior to emergent procedures and is preferred over vitamin K [11].

In low bleeding risk procedures or in surgery where bleeding can be controlled easily such as dental procedures, discontinuation of antithrombotic therapy is not required (Table 3).

Anticoagulation therapy during pregnancy

Pregnancy in patients with mechanical valves is associated with high risk. There is no ideal anticoagulation treatment. Warfarin passes through the uteroplacental unit and administration of higher doses (> 5 mg) in the 1st trimester causes spontaneous abortions and embryopathies (mostly between 6th and 12th week of pregnancy). Warfarin is relatively safe to use during the 2nd and 3rd trimester (according to some authors in the 1st trimester with the dose up to 5 mg). The administration of warfarin must be discontinued 2–3 weeks before delivery (risk of intracerebral bleeding of the fetus during delivery). Unfractionated heparin does not pass through the placenta and is therefore safe for the fetus. aPTT monitoring is needed (2× daily), and the level should be prolonged 2–3 times. The value of aPTT can be low due to a higher concentration of fibrinogen and factor VIII during pregnancy. Low molecular weight heparin can also be used in the therapeutic dose (2× daily), but the levels of antiXa must be measured 4–6 h after the morning dose, with the target levels of 0.7–1.2 u/ml. Unfractionated heparin should be given intravenously 4–6 h after delivery, aPTT must be monitored. Warfarin treatment should be restarted after the bleeding risk ceases. Warfarin is not contraindicated during breastfeeding [18–20].

The use of new antithrombotics in patients with valvular disease

Currently, anticoagulation therapy in patients with valvular heart disease is limited to oral vitamin K antagonists. The well-known disadvantages of coumarins limit their clinical use: a narrow therapeutic window, an unpredictable biological response, and numerous interactions with medications and food impose strict monitoring of the INR. Insufficient anticoagulant effect may result in thrombosis, whereas overdosing is associated with an increased risk of bleeding complications. At best, the incidence of major bleeds with coumarins is between 2% and 4% and should be balanced against the risk of thrombosis. New antithrombotics are not recommended in the use of valvular heart disease at this time [1,5,21].

Possibilities of improving therapy in patients that require permanent anticoagulation, an outlook into the future

After valve surgery, 75% of complications are due to bleeding or thromboembolism. An ideal (absolutely non-thrombogenic) mechanical prosthesis is not yet available and the new promising anticoagulation drugs were not yet tested in patients with valvular heart disease.

The recent understanding of the importance of cytochrome P450 2C9 (CYP2C9) and vitamin K oxidoreductase complex 1 (VKORC1) polymorphisms in the individual response to coumarins opens a perspective for a dosing algorithm incorporating CYP2C9 and VKORC1 genotyping that could improve initial warfarin dose selection and reduce related complications. One possibility of optimization of therapy is self-monitoring of INR levels, as it unambiguously aids in improving the quality of anticoagulation and therefore lowers the risks of anticoagulation therapy. It is unfortunately not very common in our patients. Careful education of patients is also important [22–24].

References

[1] A. Vahanian, O. Alfieri, F. Andreotti, et al., Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS), Guidelines on the management of valvular heart disease, European Heart Journal 33 (2012) 2451–2496.

[2] A. Vahanian, H. Baumgartner, J. Bax, et al., The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology,Guidelines on the management of valvular heart disease, European Heart Journal 28 (2007) 230–268.

[3] R.O. Bonow, B.A. Carabello, K. Chatterjee, et al., American College of Cardiology, American Heart Association Task Force on Practice Guidelines, ACC/AHA 2006 guidelines for the management of patients with valvular heart disease, Journal of the American College of Cardiology 48 (2006) e1–e148.

[4] J. Popelová, M. Brtko, M. Benešová, et al., Doporučené postupy pro diagnostiku a léčbu chlopenních srdečních vad v dospělosti, Cor et Vasa 49 (7–8) (2007) K195–K234.

[5] G.H. Guyatt, E.A. Akl, M. Crowther, et al., Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed., American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest 141 (2 Suppl) (2012) 7S–47S.

[6] J.C. Sun, M.J. Davidson, A. Lamy, et al., Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends, Lancet 374 (2009) 565–576.

[7] G. Laplace, S. Lafitte, J.N. Labeque, et al., Clinical significance of early valve thrombosis after prosthetic mitral valve replacement, Journal of the American College of Cardiology 43 (2004) 1283–1290.

[8] P. Meurin, J.Y. Tabet, H. Weber, et al., Low-molecular-weight heparin as a bridging anticoagulant early after mechanical heart valve replacement, Circulation 113 (2006) 564–569.
[9] A. Colli, J.P. Verhoye, R. Heijmen, et al., Antithrombotic therapy after bioprosthetic aortic valve replacement: ACTION Registry survey results, European Journal of Cardio-thoracic Surgery 33 (4) (2008) 531–536.
[10] E.D. Butchart, Antithrombotic management in patients with prostetic valves. A comparsion of American and European Guidelines, Heart 95 (2009) 430–436.
[11] E.G. Butchart, C. Gohlke-Bärwolf, M.J. Antunes, et al., Recommendations for the management of patients after heart valve surgery, European Heart Journal 26 (2005) 2463–2471.
[12] W. Dewilde, T. Oirbans, F. Verhauf, et al., WOEST trial, ESC 2012 Hotline, www.escardio.org
[13] D.N. Salem, P.D. Stein, A. Al-Ahmad, et al., Antithrombotic therapy in valvular heart disease, native and prosthetic, Chest 126 (2004) 457S–482S.
[14] D.R. Holmes, D.J. Kereiakes, N.S. Kleiman, et al., Combining antiplatelet and anticoagulant therapies, Journal of the American College of Cardiology 54 (2009) 95–109.
[15] M. Rossi, G.F. Serraino, A. Spadafora, et al., What do you do with the antiplatelet agents in patients with drug eluting stents who then receive a mechanical valve?, Interactive Cardiovascular and Thoracic Surgery 15 (2012) 115–121.
[16] D. Hering, C. Piper, D. Horstkotte, Management of prosthetic valve trombosis, European Heart Journal Supplements 3 (Supplement) (2001) Q22–Q26.
[17] J. Dunning, M. Versteegh, M. Fabbri, et al., Guideline on antiplatelet and anticoagulation management in cardiac surgery, European Journal of Cardio-thoracic Surgery 34 (2008) 73–92
[18] W.S. Chan, S. Anand, J.S. Ginsberg, Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature, Archives of Internal Medicine 160 (2) (2000) 191–196.
[19] J.S. Ginsberg, W.S. Chan, S.M. Bates, S. Kaatz, Anticoagulation of pregnant women with mechanical heart valves, Archives of Internal Medicine 163 (6) (2003) 694–698.
[20] G. Hanania, Management of anticoagulants during pregnancy, Heart 86 (2) (2001) 125–126.
[21] L. Maegdefessel, J.M. Spin, J. Azuma, et al., New options with dabigatran etexilate in anticoagulant therapy, Vascular Health Risk Management 6 (2010) 339–349.
[22] H. Koertke, A. Zittermann, G. Tenderich, Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II, European Heart Journal 28 (20) (2007) 2479–2484.
[23] P. Herijgers, P. Verhamme, Improving the quality of anticoagulant therapy in patients with mechanical heart valves: what are we waiting for?, European Heart Journal 28 (2007) 2424–2426.
[24] M. Benešová, Antitrombotická terapie po operacích chlopní – současná doporučení a budoucí trendy, Časopis lékařů českých 150 (2011) 229–235.