Cor et Vasa

Available online at www.sciencedirect.com

ScienceDirect

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

Přehledový článek | Review article

Intracardiac thrombi during warfarin anticoagulation – A case report and a brief literature review

Irene Pescetelli, Eugenio Genovesi, Giulia Renda, Eligio Di Renzo, Raffaele De Caterina

Institute of Cardiology and Center of Excellence on Aging – "G. d'Annunzio" University, Chieti, Italy

ARTICLE INFO

Article history:
Received: 19. 5. 2016
Received in revised form: 31. 12. 2016
Accepted: 6. 1. 2017
Available online: 16. 2. 2017

Klíčová slova:
Antagonisté vitaminu K
Antikoagulancia
Dabigatran
Intrakardiální trombus
Nová perorální antikoagulancia (non-vitamin K antagonist oral anticoagulant, NOAC)
Systémová embolie
Trombóza
Warfarin

Keywords:
Anticoagulants
Dabigatran
Intracardiac thrombus
Non-vitamin K antagonist oral anticoagulants (NOACs)
Systemic embolism
Thrombosis
Vitamin K antagonists
Warfarin

SOUHRN

Na oddělení urgentního příjmu byla pro paroxysmální noční dyspnoe přivezena 78letá žena s ischemickou chorobou srdeční v anamnéze a s trvalou fibrilací síní, léčená warfarinem. Přístrojové vyšetření ukazovalo na časnou fázi akutního srdečního selhání. Poslední hodnota INR byla 3,64, přičemž všechny předchozí dostupné hodnoty INR byly v terapeutickém rozmezí (2–3). Transthorakální 2D echokardiografické vyšetření prokázalo dilataci levé komory a závažné snížení systolické funkce. V levé síni byla zjištěna přítomnost echogenního stopkatého útvaru nasedajícího na mezisíňové septum. O 12 hodin později si pacientka náhle začala stěžovat na bolest v levé paži. Byl zjištěn tromboembolický uzávěr levé pažní tepny akutně řešený embolektomií s použitím Fogartyho katétru. Během první hodiny po tomto výkonu si několik tromboembolických příhod opakujících se po sobě nakonec vyžádalo amputaci paže. Podávání warfarinu bylo přerušeno a současně byla zahájena léčba dabigatranem v dávce 150 mg dvakrát denně; následně došlo k vymizení trombotického útvaru a úpravě klinického stavu pacientky.

ABSTRACT

A 78-year-old woman with a history of ischemic heart disease and permanent atrial fibrillation, on treatment with warfarin, was admitted to the Emergency Department because of paroxysmal nocturnal dyspnoea. Instrumental findings indicated an early phase of acute heart failure. The latest INR value was 3.64, and previous available INR values were all within the therapeutic range (2–3). A transthoracic 2D echocardiographic examination showed left ventricular dilatation and a severe reduction in systolic function. An echogenic pedunculated mass was observed in the left atrium, adherent to the interatrial septum. Twelve hours later, the patient reported the acute onset of pain in the left arm. A thromboembolic occlusion of the left humeral artery was documented, and this was acutely treated with Fogarty embolectomy. In the first hour after this intervention, a series of relapsing thromboembolic events led to the final amputation of the arm. Warfarin was discontinued and treatment with dabigatran 150 mg BID enacted, followed by the disappearance of the thrombotic mass and clinical resolution.

Address: Raffaele De Caterina, MD, PhD, Institute of Cardiology, "G. d'Annunzio" University – Chieti, C/o Ospedale SS. Annunziata, Via dei Vestini, 66013 Chieti, Italy, e-mail: rdecater@unich.it
DOI: 10.1016/j.crvasa.2017.01.004

Please cite this article as: I. Pescetelli, et al., Intracardiac thrombi during warfarin anticoagulation – A case report and a brief literature review, Cor et Vasa 59 (2017) e277–e281 as published in the online version of *Cor et Vasa* available at http://www.sciencedirect.com/science/article/pii/S0010865016300510

Introduction and background

Oral anticoagulant (OAC) therapy is key in the management of most patients with atrial fibrillation (AF) [1]. Antithrombotic therapy is recommended in non-valvular AF patients with one or more risk factors for thromboembolism, according to the CHA_2DS_2-VASc score [1]. Current therapeutic options include OAC therapy with either a well-controlled vitamin K antagonist (VKA with an international normalised ratio [INR] 2–3) or one of the non-vitamin K antagonist oral anticoagulants (NOACs) [1]. For over 60 years VKAs have been the only available agents for long-term anticoagulation, and warfarin has been the most widely used [2]. VKAs exert their anticoagulant effect by interfering with the synthesis of the vitamin K-dependent coagulation factors, inhibiting the vitamin K epoxide reductase complex subunit 1 (VKORC1) in the liver [2,3]. The effectiveness of VKA anticoagulation is strictly related both to the degree of anticoagulation achieved (assessed by the INR value) and the time in therapeutic range (TTR), as well as treatment duration.

Warfarin is metabolized in the liver by a group of enzymes encoded by the cytochrome P450 (CYP) 2C9 gene, largely responsible for its hepatic metabolism [3]. Such pharmacokinetic properties account for the long-standing observation that doses required to exert the anticoagulant effect are highly variable from patient to patient. The variety of enzymes involved and, at least in part, polymorphisms in the *CYP2C9* and *VKORC1* genes, play a role in affecting the pharmacokinetics and pharmacodynamics of warfarin, with a resulting highly variable clinical response [4,5]. In addition, because CYP2C9 is involved in a large number of metabolic pathways, many foods and drugs can affect warfarin metabolism and half-life. All these characteristics explain the narrow therapeutic window of warfarin, with oscillations between the risk of thromboembolism in case of insufficient dosing and the risk of bleeding in case of excessive dosing. This has prompted the search for non-vitamin K antagonist oral anticoagulants (NOACs), with a more predictable anticoagulation profile [3]. NOACs have indeed recently emerged as an alternative for VKAs for thromboembolic prevention in patients with non-valvular AF, because of their more predictable effect, no need for routine monitoring, no food and fewer drug interactions, a shorter plasma half-life, and improved efficacy/safety ratio [6]. Among the NOACs, dabigatran is an oral direct, competitive thrombin inhibitor, ingested as a pro-drug (dabigatran etexilate), and then activated to dabigatran by intestinal and serum esterases [6]. Dabigatran is not metabolized by the CYP P450 enzymes or other oxidoreductases, while it is a substrate for P-glycoprotein, and is almost entirely excreted renally [7]. Dabigatran 150 mg twice daily (BID) was associated with lower rates of stroke or systemic embolism compared with warfarin in the RE-LY study; while dabigatran 110 mg BID was associated with rates of stroke and systemic embolism similar to warfarin, but with lower rates of major bleeding [8].

Case presentation

A 78-year-old woman with a history of ischemic heart disease was admitted to the Emergency Department of the Chieti University Hospital because of the sudden onset of shortness of breath during the night. Three years before, the patient had had an ST-elevation acute myocardial infarction (STEMI) without obstructive coronary disease documented at coronary angiography. Because of this, she had received dual antiplatelet therapy with aspirin 100 mg/day and clopidogrel 75 mg/day for one year. Because of the subsequent occurrence of permanent bradycardic AF requiring pacemaker implantation, she was currently being treated with the oral anticoagulant warfarin alone. Her blood pressure was 130/80 mmHg and her heart rate was 96 beats per minute. Her pulse was irregular. Electrocardiographic findings demonstrated AF, and were suggestive of left ventricular hypertrophy. The pulmonary auscultation revealed crackles at both lung bases, and a chest X-ray confirmed the suspicion of pulmonary congestion. Laboratory testing showed mild leucocytosis with increased neutrophil count, mild hypokalaemia, significantly elevated plasma levels of the N-terminal fragment of brain natriuretic peptide (NT-proBNP) (7774 pg/mL, normal values for women ≥75 years old: <300 pg/mL) and a mild elevation in troponin I (0.105 ng/mL, normal range: <0.045 ng/mL). The INR was 3.64, and all previous INR values available were in the therapeutic range. The

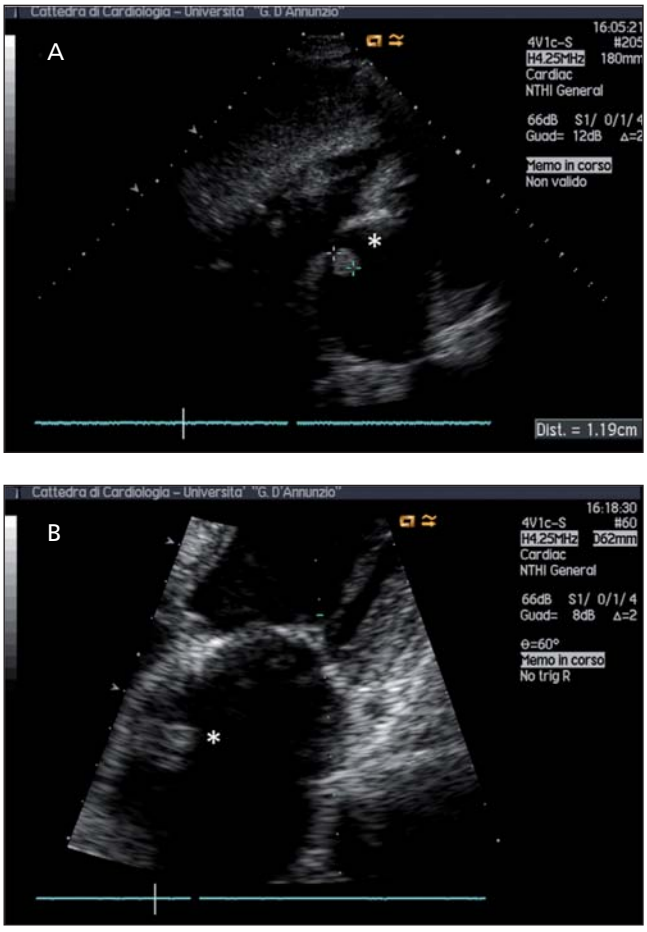

Fig. 1 – Transthoracic echocardiographic examination performed after the episode of heart failure at admission. An echogenic pedunculated, movable mass, with sharp margins, can be seen in the left atrium, adherent to the interatrial septum (*). A) subcostal 4-chamber view; B) apical 4-chamber view.

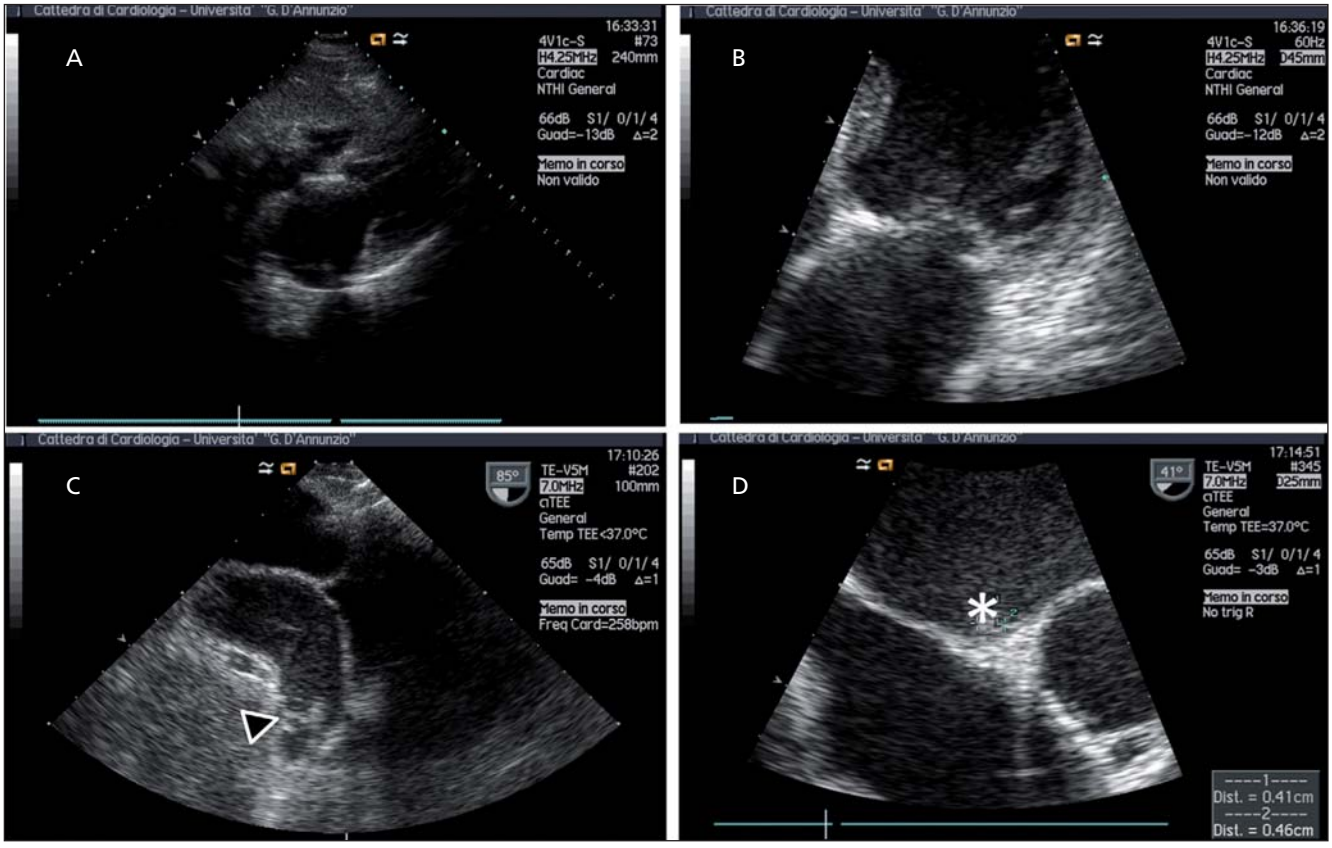

Fig. 2 – Transthoracic echocardiography (A and B) performed after the embolic episode, showing the disappearance of the mass previously adherent to the interatrial septum. A) subcostal 4-chamber view; B) apical 4-chamber view. Transoesophageal echocardiography shows the presence of thrombi (arrowhead) in the left atrial appendage (C), and the persistence, although of reduced size, of the thrombotic mass (*) in the left atrium (D).

CHA_2DS_2-VASc score was 6 (1 point for heart failure, 1 for hypertension, 2 points for age >75, 1 point for female sex, and 1 point for a coexisting carotid vascular disease and the previous STEMI). A transthoracic echocardiography (TTE) showed left ventricular dilatation and a severe reduction in systolic function (ejection fraction, EF, 35%). An unexpected echogenic pedunculated mass was observed in the left atrium, adherent to the interatrial septum, with echogenic characteristics of a fresh thrombus (Fig. 1). Because of the high INR value, a decision was taken to delay the treatment, not administering any additional anticoagulant. Twelve hours later, the patient suddenly complained of acute pain in the left arm, accompanied by paleness and coldness of the arm in the absence of radial or ulnar pulses. Colour-Doppler echography of the left arm documented the absence of blood flow in the humeral artery and downstream, supporting the diagnosis of acute peripheral embolism. The thrombosis of the humeral artery was rapidly and successfully treated with a Fogarty catheter embolectomy. Anticoagulation therapy with a low-molecular weight heparin (LMWH, parnaparin 0.6 mL = 6400 international units twice daily [BID]) was started soon after surgical procedure. However, within the first hour after the procedure, a recurrence of pain in the left arm occurred, caused by a new thromboembolic event. This was again treated with embolectomy. At this point, a humeral-to-radial graft was positioned. The surgical intervention was, however, complicated by a dissection of the left subclavian artery, prompting a percutaneous transluminal balloon angioplasty (PTA) with implantation of a bare metal stent. An early in-stent thrombosis a few hours later led to a new interventional procedure with thrombus aspiration and a subclavian artery PTA, with the implantation of 2 new overlapping bare metal stents (6 mm × 80 mm and 6 mm × 59 mm). Despite this, a new thrombotic occlusion in the subclavian artery occurring 4 h later led to the amputation of arm. A control TTE showed the disappearance of the left atrial mass, but a transoesofageal echocardiography (TOE) documented the persisting presence of thrombi in the left atrial appendage, with diffuse smoke-like effect, and also showed the persistence of the left atrial thrombotic mass, although of a reduced size compared with the previous examination (Fig. 2). At that point, warfarin was discontinued, and dabigatran 150 mg BID started. After 1 week, a pre-discharge TOE showed a reduction of the atrial thrombosis. A 1-month post-discharge TOE showed a complete resolution of the left atrial thrombosis (Fig. 3).

Discussion

Resistance to the anticoagulant effect of warfarin (warfarin resistance) is a rare phenomenon, and most of the related literature consists of case reports. Resistance to warfarin has been described as the inability of warfarin

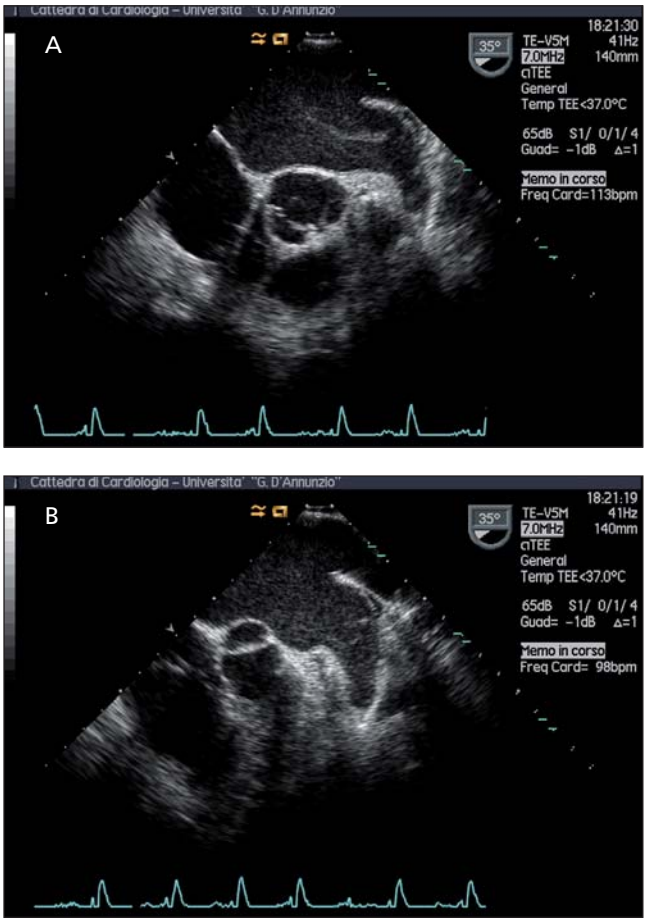

Fig. 3 – Transoesophageal echocardiography performed after 1 month of therapy with dabigatran etexilate. No thrombotic masses are evident in the atrial appendage and over the left atrial septum, documenting the complete resolution of the previous thrombus.

to prolong the prothrombin time or to increase the INR to within the therapeutic range [9]. Warfarin resistance may develop as a result of non-compliance, the exogenous consumption of vitamin K, or the concurrent administration of other drugs known to interfere negatively with warfarin effects [10]. The cause of this resistance can, however, also be genetic, and related to how the body processes warfarin. In this context, 2 different types of warfarin resistance can be identified: complete and incomplete. Subjects with *complete* warfarin resistance cannot achieve the therapeutic INR in response to warfarin treatment despite the use of even large doses. Subjects with *incomplete* warfarin resistance, conversely, can achieve the target INR with the use of doses of warfarin higher than normal subjects. Subjects with complete warfarin resistance do not respond at all to the drug. Most subjects with incomplete warfarin resistance – the vast majority of cases – rapidly metabolize warfarin, so that the drug is quickly eliminated. These individuals are classified as "fast metabolizers" or "rapid metabolizers". The severity of these abnormalities determines whether warfarin resistance is complete or incomplete. Single nucleotide polymorphisms (SNPs) in the *VKORC* subunit 1 (*VKORC1*), one of the warfarin target enzymes, have been shown to be associated with the dose of warfarin required to achieve a target INR value [11]; also, genetic variants of *CYPP450* have been shown to affect warfarin dose requirements [12].

Since our patient had INR values in the target range, this was not actually a case of warfarin resistance, as defined by coagulation tests. In such a case, warfarin did not provide a clinically successful thrombosis prevention – a condition to be labelled "therapeutic failure". Such an occurrence is described for patients with the antiphospholipid antibody syndrome (APS), whereby the presence of a lupus anticoagulant can influence results of the prothrombin time and lead to an elevated INR that does not reflect the true level of anticoagulation [13], resulting in a falsely adequate anticoagulation. A small randomized clinical trial has also shown that high-intensity warfarin (INR range 3.0–4.5) was not superior to standard treatment (INR 2.0–3.0) in preventing recurrent thrombosis in such patients [14,15], pointing out that other mechanisms, not recognizable by conventional anticoagulation markers, are here responsible for the tendency to thrombosis. Currently available data suggest that also in patients with malignancies, the use of VKAs is associated with incidences of thrombotic and bleeding complications higher than in patients without malignancies, despite INR values in the therapeutic range [16]. In this setting, a NOAC, either an oral direct thrombin inhibitor or one of the oral direct factor Xa inhibitors, with their more predictable anticoagulant responses, may be a better treatment option [13].

Previous studies have suggested that left atrial thrombosis in patients receiving warfarin is still present by TOE in 8% of cases despite optimal INR control during the previous 3 weeks [17], and that prolongation of warfarin treatment beyond 7 weeks results in limited additional benefit in terms of thrombus resolution compared to 7-week anticoagulation [18]. There is also increasing evidence that VKAs have a poor capacity to resolve large masses of intracardiac thrombi [19], that thrombi in the left atrial appendage persist in up to 40% of patients under VKA treatment, and that they are associated with a poor prognosis [20].

In the case reported here, we also found the rare presentation of left atrial thrombosis outside of the left atrial appendage in the absence of organic mitral valve disease of considerable interest. Indeed, most literature reports of giant atrial thrombi outside of the left atrial appendage are mostly concomitant with the presence of a giant left atrium in the presence of mitral stenosis (reviewed in [21]). Moreover, we excluded both the presence of an APS and of malignancies in our patient, but we hypothesized some analogous mechanism here occurring. Because of this, we attempted an anticoagulation strategy with dabigatran, which, by acting on thrombin activity, at the level of the final enzyme of the coagulation cascade, could halt the recurrences of arterial thromboembolism, and also eventually achieve the result of dissolving the previously persisting intracardiac thrombotic mass.

Conflict of interest
None declared.

Funding body
None.

Ethical statement

Authors state that the research was conducted according to ethical standards.

References

[1] A.J. Camm, G.Y. Lip, R. De Caterina, et al., 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation – developed with the special contribution of the European Heart Rhythm Association, Europace 14 (2012) 1385–1413.

[2] R. De Caterina, S. Husted, L. Wallentin, et al., Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease, Thrombosis and Haemostasis 110 (2013) 1087–1107.

[3] S. Mundi, A. Distante, R. De Caterina, [Genetic determinants of response to vitamin K antagonists], Giornale Italiano di Cardiologia (Rome) 15 (2014) 482–493.

[4] G. D'Andrea, R.L. D'Ambrosio, P. Di Perna, et al., A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin, Blood 105 (2005) 645–649.

[5] M. Moridani, L. Fu, R. Selby, et al., Frequency of CYP2C9 polymorphisms affecting warfarin metabolism in a large anticoagulant clinic cohort, Clinical Biochemistry 39 (2006) 606–612.

[6] H. Heidbuchel, P. Verhamme, M. Alings, et al., EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary, European Heart Journal 34 (2013) 2094–2106.

[7] G.J. Hankey, J.W. Eikelboom, Dabigatran etexilate: a new oral thrombin inhibitor, Circulation 123 (2011) 1436–1450.

[8] S.J. Connolly, M.D. Ezekowitz, S. Yusuf, et al., Dabigatran versus warfarin in patients with atrial fibrillation, New England Journal of Medicine 361 (2009) 1139–1151.

[9] O. Osinbowale, M. Al Malki, A. Schade, J.R. Bartholomew, An algorithm for managing warfarin resistance, Cleveland Clinic Journal of Medicine 76 (2009) 724–730.

[10] M.L. Hulse, Warfarin resistance: diagnosis and therapeutic alternatives, Pharmacotherapy 16 (1996) 1009–1017.

[11] M.J. Rieder, A.P. Reiner, B.F. Gage, et al., Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose, New England Journal of Medicine 352 (2005) 2285–2293.

[12] G.P. Aithal, C.P. Day, P.J. Kesteven, A.K. Daly, Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications, Lancet 353 (1999) 717–719.

[13] M. Balaban, V. Stanric, G. Rincic, et al., Recurrent venous thrombosis despite 'optimal anticoagulation therapy' for antiphospholipid syndrome – could new oral anticoagulants solve the problem? Acta Clinica Croatica 49 (2010) 469–477.

[14] G. Finazzi, R. Marchioli, V. Brancaccio, et al., A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS), Journal of Thrombosis and Haemostasis 3 (2005) 848–853.

[15] M.A. Crowther, J.S. Ginsberg, J. Julian, et al., A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome, New England Journal of Medicine 349 (2003) 1133–1138.

[16] B.A. Hutten, M.H. Prins, M. Gent, et al., Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis, Journal of Clinical Oncology 18 (2000) 3078–3083.

[17] K. Seidl, M. Rameken, A. Drogemuller, et al., Embolic events in patients with atrial fibrillation and effective anticoagulation: value of transesophageal echocardiography to guide direct-current cardioversion. Final results of the Ludwigshafen Observational Cardioversion Study, Journal of the American College of Cardiology 39 (2002) 1436–1442.

[18] C.R. Thompson, C.E. Buller, L.A. Sleeper, et al., Cardiogenic shock due to acute severe mitral regurgitation complicating acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we use emergently revascularize Occluded Coronaries in cardiogenic shocK? Journal of the American College of Cardiology 36 (2000) 1104–1109.

[19] C. Hammerstingl, B. Potzsch, G. Nickenig, Resolution of giant left atrial appendage thrombus with rivaroxaban, Thrombosis and Haemostasis 109 (2013) 583–584.

[20] P. Bernhardt, H. Schmidt, C. Hammerstingl, et al., Fate of left atrial thrombi in patients with atrial fibrillation determined by transesophageal echocardiography and cerebral magnetic resonance imaging, American Journal of Cardiology 94 (2004) 801–804.

[21] R. De Caterina, A. John Camm, Non-vitamin K antagonist oral anticoagulants in atrial fibrillation accompanying mitral stenosis: the concept for a trial, Europace 18 (2016) 6–11.