MÆDICA - a Journal of Clinical Medicine

STATE-OF-THE-ART

Oral anticoagulation in clinical practice

Mircea CINTEZA, MD, PhD
Andrei-Dumitru MARGULESCU, MD
Cardiology and Internal Medicine Department, University Hospital of Bucharest, and "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

MOTTO

"Any point of view is also a point of blindness."

Richard Wurmbrand

1. INTRODUCTION

Oral anticoagulation with vitamin K antagonists (VKA) is a frequently prescribed class of medication. VKA are also denoted as coumarins. Warfarin is the most commonly used coumarin worldwide, but is unavailable in Romania. Other coumarins are acenocoumarol (the only VKA used in Romania), and phenindione (rarely used). The use of VKA is generally recommended for preventing the recurrence of embolic events. However, the oral anticoagulation therapy is not without risk, especially bleeding risk, due to their narrow therapeutic window; there is a high individual variability between doses needed for achieving therapeutic effects, there are large number of interactions between VKA with various drugs and diet, and the need for a tight laboratory monitoring is mandatory, requesting an optimal patients' compliance, frequent changes in dosage and additional costs (1).

In this editorial we will present a personal perspective on when to use and when not to use VKA in the daily care of patients. Our perspective is based on the recommendations of current guidelines for anticoagulant treatment (2-5,9,10,12,13,19-21). However, it also takes into account that these recommendations might not be always suitable for clinical practice. We will not discuss the use of heparins, fibrinolytics and other forms of antithrombotic treatments. Ximelagatran, an oral direct thrombin inhibitor, have been with-drawn from the market because of the occurrence of elevated liver enzymes (in about 5% of patients) with several, yet extremely rare cases of fatal toxic hepatitis (22). Other oral direct thrombin inhibitors, with a better safety profile, are currently under clinical investigation in randomized clinical trials.

The whole process of hemostasis is an incredible complex one. Its description is not the aim of this article. However, we will point some important, yet basic facts, about the hemostatic process. Hemostasis can be academically divided into primary hemostasis and secondary hemostasis. The primary hemostasis includes the adhesion, activation and aggregation of platelets. This process lasts only seconds and leads to the formation of the platelet white thrombus. The secondary hemostasis stabilizes the fragile primary hemostatic thrombus, by forming the insoluble fibrin thrombus. This is also called the coagulation cascade, and it takes minutes to develop. The coagulation cascade has two pathways of activation (the extrinsic and the intrinsic pathway) and a final common pathway which leads to the formation of fibrin (Figure 1). Although presented as separate and consecutive processes, primary and secondary hemostasis are activated at the

same time, and in conjunction with the antagonist process of fibrinolysis. In the formation of thrombus, the synthesis of insoluble fibrin is far larger that the degradation of fibrin through fibrinolysis. This balance is later reversed and blood flow is finally reestablished through the vessel.

VKA inhibits the coagulation cascade by inhibiting the hepatic synthesize of vitamin K coagulation factors (i.e. factor II, V, VII and IX). Thus, VKA predominantly and indiscriminately inhibit the extrinsic and common final pathways of the coagulation cascade (Figure 1).

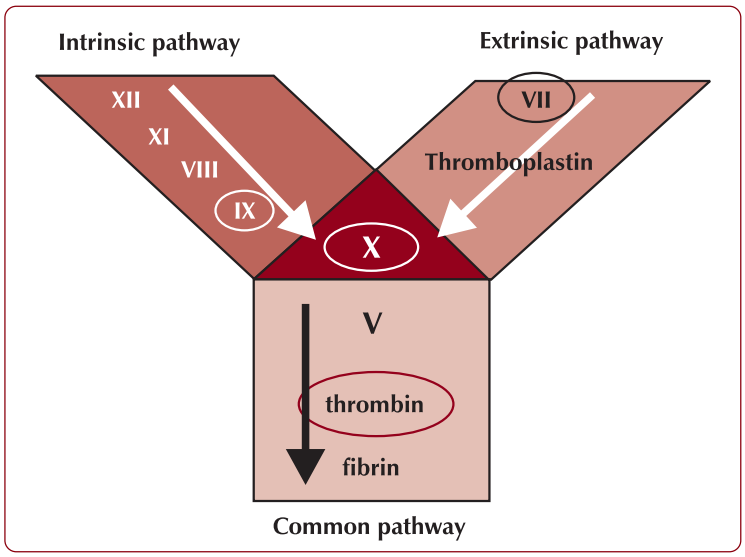

FIGURE 1. The coagulation cascade
Roman numbers denotes coagulation factors. Vitamin K dependent factors are highlighted in the figure. With the exception of factor IX, they all belong to the extrinsic and common pathway of the coagulation cascade. The extrinsic and common pathways of activation are monitored with the use of International Normalized Ratio (INR, see text).

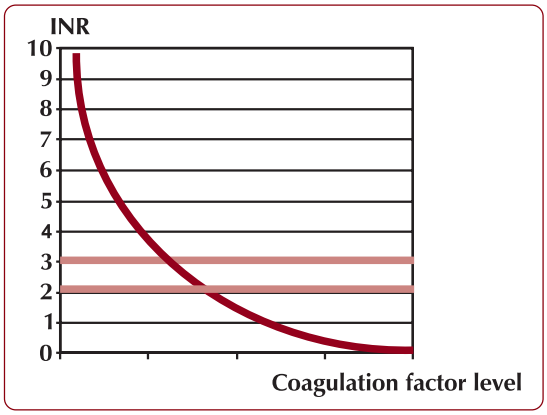

FIGURE 2. The relationship between the level of coagulation factors and INR
The horizontal lines denote the therapeutical level of INR (2-3). Small reductions in the level of coagulation factors above the lines will lead to a sharp increase of the INR value and a sharp increase of the hemorrhagic risk. On the other hand, relatively large doses of vitamin K antagonists are needed to lower the coagulation factor level enough to lead to a therapeutical INR. INR = International Normalized Ratio. Data from reference 14.

The usual way to monitor the activity of the extrinsic pathway together with the common final pathway is the International Normalized Ratio (INR) index. The INR of a blood sample represents the ratio between the time of coagulation of that blood sample divided by the time of coagulation of a blood sample from a normal control. Thus, the normal INR is about 1. A high INR value cannot point precisely which of the four vitamin K dependent coagulation factors are predominantly depleted. In most clinical situations, the therapeutic limit of VKA administration is shown by an INR of 2 to 3.

The relation between the INR and the blood level of vitamin K dependent coagulation factors is a logarithmic one (Figure 2) (14). Thus, an increase of INR from 1 (normal) to 2 (therapeutical anticoagulation) requires a far more pronounced depletion of coagulation factors than an increase of INR from 3 to 4, for example. The practical and extremely important aspect of the logarithmic relation between INR and the depletion of coagulation factors is that relatively large doses of VKA are required to get the INR into therapeutical ranges, but once there, little increase of the VKA dose can lead to large increases in INR level, therefore leading to increased risk of bleeding. Thus, VKA should never be prescribed in the absence of INR monitoring, whatever the indication. ❑

2. INDICATION OF ORAL ANTICOAGULATION

We will summarize the indications for chronic oral anticoagulation with VKA. Usually, there are 4 conditions where VKA are frequently prescribed: venous thrombembolism (VTE) with its two conditions (pulmonary thrombembolism, PTE, and deep vein thrombosis, DVT), procoagulant status (protein C or S deficit, antithrombin III deficit, factor V Leyden, antiphospholipidic syndrome), atrial fibrillation, and metallic prosthetic valves. Beside these indications, we will underline some aspects related to the indication of oral anticoagulation in acute myocardial infarction, cerebrovascular disease, peripheral artery disease and pregnancy. It is not in our intention to discuss other non-established indications for VKA treatment without proven benefit (class IIb and class III indications). ❑

2.1. Venous Thrombembolism

VTE has a 15 to 50% risk of recurrence in the first year without anticoagulation treatment (15). This risk is equal both in distal and proximal DVT. Long term treatment with low-dose low molecular weight heparin (LMWH) has been proven ineffective in preventing recurrent VTE, with a relative risk of recurrence as high as 45% (16). Short term treatment (4 to 6 weeks) with VKA is inferior to a 3 month course of VKA (17). Therefore, chronic oral anticoagulation with VKA appears as an appropriate option. The duration of such treatment depends on the location of VTE, its predisposing factors and its severity.

The current guidelines separate the length of chronic oral anticoagulation by the number of episodes (Table 1) (2,3). If one has 2 or more episodes of VTE, regardless of the presence or absence of predisposing factors (procoagulant status, prolonged immobilization, etc), the length of VKA therapy is life-long. Only if one has a first episode of VTE, the length of VKA therapy is indicated by the presence of associated predisposing factors or diseases. However, even in this situation, life-long anticoagulation is suggested with the exception of VTE associated with reversible factors, such as temporary immobilization. In patients with VTE associated with cancer, LMWH are indicated for at least 3 months, followed by life-long oral anticoagulation. This is because the rate of recurrence of VTE in patients with cancer is lower in patients receiving LMWH therapy than in patients receiving VKA. This is one of the very few indications of chronic use of heparins (2,3). ❑

2.2 Atrial fibrillation

The benefit of oral anticoagulation in prevention of systemic thromboembolic events in atrial fibrillation (AF) has been shown in several trials, with a risk reduction of 65% (4,5). The use of aspirin did not show any benefit with the exception of SPAF trial (6), where aspirin was slightly better than placebo in prevention of systemic thromboembolic events in patients with AF. The analysis of 6 trials that compared aspirin with placebo (7) in patients with AF showed a slight significant benefit associated with aspirin, with a 22% reduction in relative risk of systemic embolism. When comparing VKA with aspirin, there is a 50% supplementary risk reduction of systemic embolization associated with VKA (4, 5). However, the risk of systemic embolization in AF is not 100%. In fact, the risk of stroke is only 6 to 7 times greater than in the general population, and is usually less than 10% per year (5). Several factors are associated with the risk of systemic embolization: prior embolic events or stroke (relative risk, RR = 2,5), mitral stenosis, prostethic valves, diabetes (RR = 1.7), hypertension (RR = 1,6), age (RR = 1,4 for every decade), left ventricular dilatation and dysfunction (ejection fraction <35%), and left atrial dilatation. The risk factors for embolic risk are classified in three groups by severity (high risk, medium risk and low or undetermined risk) and they are central in the clinical decision on the anticoagulant indication (Table 2) (5).

TABLE 1. Indications and recommended length of treatment with oral anticoagulation in proximal and distal deep vein thrombosis

No.	Predisposing factor	Months	Life-long?
1 episode	Reversible factor	3	No
	Idiopathic	6-12	Suggested
	Cancer	LMWH 3-6 months, folllowed by VKA	VKA indefinitely (or cured cancer)
	- Antiphospholipidic - ⩾ 2 thrombophilic factors	12	Suggested
	1 thrombophilic factor	6-12	Suggested
Over 2 episodes		Life-long	

Note: LMWH, low molecular-weight heparin; VKA, vitamin K antagonists
Data from references 2,3.

The risk of embolization can be lowered by 65% with anticoagulant therapy but this benefit of therapy carries the risk of bleeding. The maximal benefit with the minimal risk is obtained when the INR level is kept between 2 and 3 (8). An INR level higher than 3 is not associated with additional benefit, but is associated with a steep increase in the risk of bleeding. This is a consequence of the logarithmic relationship between the INR and the coagulation factor concentration, as shown previously (14). The risk of total bleeding associated with VKA use is about 4% per year, with a risk of fatal bleeding of about 1% per year (5). It should be emphasized that this risk is associated with controlled therapy, i.e. when the INR is in therapeutic range (Figure 3A).

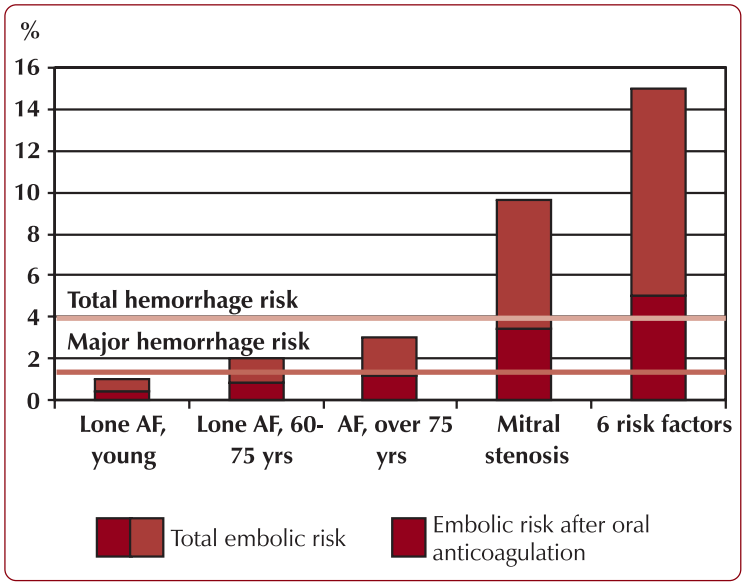

FIGURE 3A. Annual embolic risk and the benefit of oral anticoagulation in atrial fibrillation: In randomized controlled trials.
Lighter coloured bars represent 65% relative risk reduction with the use of oral anticoagulation of the risk of systemic embolization. Darker coloured bars represent the remaining risk of systemic embolization after oral anticoagulation. This is compared with the risk of major hemorrhages (horizontal darker coloured line) and the total hemorrhagic risk (horizontal lighter coloured line).
Note: AF, atrial fibrillation. Data from references 3, 5, 21.

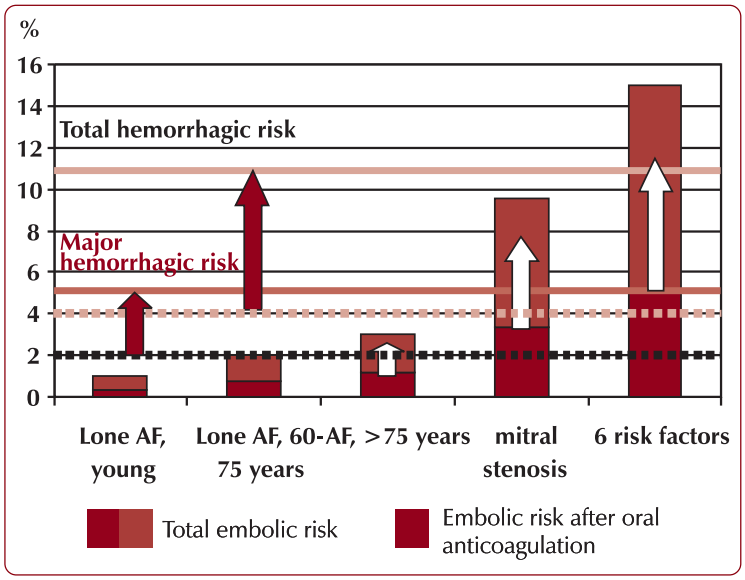

Figure 3B. Annual embolic risk and the benefit of oral anticoagulation in atrial fibrillation: In the real world.
By comparison, in the real life, the embolic risk is reduced by less than 65% with oral anticoagulation (white arrows) and the hemorrhagic risk is higher than in RCT (red arrows). Thus, in the real life, the threshold for administering oral anticoagulation should probably be higher than the recommendations of current guidelines.
Note: AF, atrial fibrillation. Data from references 3, 5, 21.

Thus, taking into account the risk of embolization versus the risk of bleeding, the current recommendations are not to use VKA in patients with lone AF (i.e. without embolic risk factors) (4,5). In these cases aspirin should be used. In case of patients with one moderate risk factor, choosing between aspirin and VKA is left at the clinician's choice (Table 2); patient's compliance with the INR monitoring should be crucial in clinical decision.

In summary, in patients with AF, VKA should be considered when the embolic risk (according to the risk factors) is more than 4% per year and overweighs the risk of bleeding (Figure 3A). ❑

2.3. Prosthetic metallic valves

The current guidelines for anticoagulant therapy in patients with prosthetic metallic valves recommend a higher INR level than in AF (9). Aspirin can be considered, and in the view of some experts it is indicated, to be associated with VKA in patients with prosthetic valves with high risk of thrombosis (mitral prosthetic valves, cage-ball valves – Starr-Edwards) or prior embolic event under therapeutical anticoagulation level. In these cases the INR should be kept between 2,5 and 3,5. The VKA doses should not be raised if there is an embolic event under therapeutic INR level, because there is no additive benefit; instead the risk of bleeding is higher. Aspirin is not indicated, and the INR level can be lower (between 2 and 3) in patients with prosthetic metallic valves in aortic position, because of the high velocity of flow through the aortic valve that prevents thrombosis. ❑

2.4. Peripheral vascular disease and cerebrovascular disease

Current guidelines do not recommend oral anticoagulation in patients with peripheral artery disease (9), not even when arterial grafts

TABLE 2. Recommendation for oral anticoagulation in atrial fibrillation considering the risk of systemic embolisation.

Risk category	Recommended treatment	
Without risk factors	Aspirin 125-325 mg/day	
1 moderate risk factor	Aspirin 125-325 mg/day, or	Oral anticoagulation, INR 2-3
> 1 moderate risk factor, or any major risk factor	Oral anticoagulation, INR 2-3 (ideally 2,5) For valvular prothesis, INR > 2,5	
Embolic risk factors		
Unknown or low importance	**Moderate**	**Major**
Women	Age over 75 years	Hystory of stroke, TIA or systemic embolism
Thyreotoxicosis	Hypertension	Mitral stenosis
Age 64-75 years	Heart failure	Valvular prothesis
Ischemic heart disease	LVEF < 35%	
	Diabetes mellitus	

TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; INR, International Normalized Ratio
Adapted from reference 5.

are inserted. In the latter case, the benefit on prevention of reocclusion and graft patency is overweight by the risk of bleeding (11). Aspirin 160-325 mg daily is used; the more expensive alternative is clopidogrel.

In cerebrovascular disease (CVD), oral anticoagulation is contraindicated, when is not associated with AF (12,13). Aspirin or clopidogrel are used for secondary prevention, and aspirin for primary prevention. Addition of extended release dipiridamol to aspirin can be superior to aspirin alone for secondary prevention in CVD, but is frequently badly tolerated (18). ❑

2.5. Pregnancy

VKA are contraindicated in pregnancy due to the risk of developing warfarin-associated embriopathy between the 6th and the 12th week of gestation (19). However, this risk is around 5% and it is about the same as the risk of fetal hemorrhages and is far less than the risk of intracranial maternal hemorrhages during labor (15%) (19). For these reasons, in highly-selected cases, oral anticoagulation can be used with special caution in pregnancy, if it is compulsory (i.e. metallic prosthetic valves). ❑

2.6. Acute myocardial infarction

The source of systemic emboli in acute myocardial infarction is intraventricular thrombosis and, more importantly, atrial fibrillation (20). The risk of intraventricular thrombosis is significant in patients with left ventricular aneurism, large akinetic segments (especially anterior and apical locations) and depressed ejection fraction (18% risk for every 5% decrease of the LVEF) (20). Thus, myocardial infarctions complicated with intracardiac thrombosis, large akinetic segments or LV aneurism, are indications for oral anticoagulation for a period of at least 6 months, probably indefinitely (20). The use of aspirin, though it is associated with a higher risk of bleeding, is recommended because the benefit outweighs the risk (20). ❑

3. CONTRAINDICATIONS AND SIDE EFFECTS OF ORAL ANTICOAGULATION

The list of contraindications of VKA is long (1). They include: 1. active hemorrhage; 2. active ulcer disease; 3. known hypocoagulant status (e.g. hemophilia); 4. moderate or sever thrombocytopenia (<50,000 / mm3) or platelet dysfunction; 5. recent hemorrhagic stroke; 6. non-adherent patients; 7. patients who are not candidate due to social or psychosocial issues; 8. dementia or other severe cognitive disorders; 9. history of falls (= or > 3 in the last year, or recurrent falls with trauma); 10. alcoholism; 11. poor controlled hypertension (= or > 180 / 100 mmHg); 12. daily use of non-steroidal anti-inflammatory drugs (NSAIDS); 13. major surgery or invasive proce-

dures planned in the near future. Any of these contraindications was also an exclusion criterion in clinical studies with VKA. Thus, the results of clinical studies (the benefits and risks) with VKA can be applied only in people without contraindications for anticoagulant treatment.

In any given patient the risk of anticoagulation has to be weight against the benefit. Knowing these two parameters (benefit and risk) is essential for the correct use of VKA.

VKA have a long list of drug interaction (1). The anticoagulant effect is raised by numerous drugs, including NSAIDS, antibiotics (cefamandole, cefazolin, co-trimoxazole, macrolides, metronidazole, quinolones, tetracyclines), antifungals, and antiarrhythmics (class Ia, Ic and III). However, several NSAIDS do not interact with VKA: naproxen, ibuprofen (1). Drugs that do not exibit an effect on VKA metabolism are: betablockers (with the exception of propranolol), antiacids, alcohol, fluoxetine, famotidine, diltiazem and vancomycin. Barbiturates, carbamazepine, rifampin, azathioprine, sucralfate and high vitamin K content in food or enteral feedings inhibit VKA activity (1).

The most frequent side effect of VKA is hemorrhage. The risk for severe hemorrhage (that necessitates blood transfusion) is 2 to 4% per year, and the risk of fatal bleeding is about 0.7% per year (21). These figures are described for therapeutical levels of INR, and in patients that where considered eligible for anticoagulant treatment. Other side effects are skin necrosis, blue-toe syndrome, osteopenia, indigestion.

The emergency treatment of VKA overdose depends on the presence and severity of bleeding (table 3) (21). There are several algorithms of treatment. In general, if severe hemorrhage is present, whatever the INR level, fresh frozen plasma plus vitamin K (10mg i.v.) should be used, and the INR repeated after 6 to 24 hours. If severe hemorrhage is not present, fresh frozen plasma should not be used with the exception of patients with very high INR level. When hemorrhage is not present, VKA overdose is treated with oral vitamin K (5mg) and the INR repeated 24 hours later. ❑

4. POINTS OF VIEW

All the conclusions about the benefits and risks of anticoagulant treatment are based on randomized clinical trials (RCT). However, RCT represent an ideal world, not the real one. In RCT, patients are carefully selected and carefully followed-up, at stringent intervals of time. If a patient does not fulfill this stringent follow-up (for example, if he does not present at one visit) then the patient will be taken out of the study and he will not be present in the final data base that will be analyzed. Thus, the final analysis will only contain patients which were not lost to follow-up and fulfilled all the criteria of the study. Therefore, the final results of a RCT are maximal and ideal for that treatment. Applying this principle to anticoagulant RCT, we conclude that these RCT show the maximal benefit with the minimal risk for anticoagulation. In the real world, which is less than ideal, our patients will have a benefit which will always be less, and a risk which will always be higher than the one shown in the data from RCT. This is extremely important to consider when administering drugs that have a very narrow therapeutic windows, like VKA. In practical terms, in the real world, the use of VKA will lower the risk of embolism with an unknown percentage which is always less than 65%, and it will be associated with an unknown risk of fatal bleeding which is always higher than 0.7% per year (Figure 3B).

A much safer alternative to VKA in respect to the hemorrhagic risk is aspirin. However, the benefit of aspirin in reducing the embolic risk is marginal. Aspirin can become an alternative to VKA in patients with high risk of bleeding and

TABLE 3. Treatment of vitamin K antagonist overdosing

Severity	INR	Vit K	FFP	Next INR
1. Without important hemorrhage	<5	–	–	
	5-9	2,5 mg orally	–	24 h
	9-20	5 mg orally	–	24 h
2. No recent surgery	≥ 20	10 mg i.v.	Yes	After PPC + 12-24 h
Severe hemorrhage	Any INR (≥5)	10 mg i.v.	Yes	6-24 h

Adapted from reference 21.

in patients where strict compliance to treatment and INR dosing is not accomplished. ❑

5. CONCLUSION

A single point of view can also become a point of blindness. In the case of oral anticoagulation with VKA the indications stated in the current guidelines, based on ideal data for benefits and risks from RCT, can become a point of blindness if one does not take into account the individual patient, the individual risk and the individual compliance with treatment. For drugs with very narrow therapeutic windows individualization of treatment is essential.

In our opinion, one should never administer oral anticoagulation with VKA in the absence of strict control of INR, at regular intervals of at least one month when the INR is stable. If this desiderate can not be accomplished, the use of VKA is extremely dangerous. Given the logarithmic relationship between INR and coagulation factor level, the chance for a given dose of VKA to lead to a therapeutic value of INR is very low. The patients will either be under-anticoagulated (meaning they will not receive treatment) or, far more often, they will be over-anticoagulated (meaning they will have a very high risk of bleeding). When strict compliance with anticoagulant treatment cannot be accomplished, aspirin is a far safer alternative, at the cost of lower benefit. ❑

REFERENCES

1. **Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E** – The Pharmacology and Management of the Vitamin K Antagonists: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:204-233
2. **Butller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, and Raskob GE** – Antithrombotic Therapy for Venous Thromboembolic Disease: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:401-428
3. **Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW and Ray JG** – Prevention of Venous Thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:338-400
4. **Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL and Manning WJ** – Antithrombotic Therapy in Atrial Fibrillation: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:429-456
5. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation – Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). Circulation published online Aug 2, 2006; DOI: 10.1161/CIRCULATIONAHA.106.177031
6. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991; 84:527-539
7. **Hart RG, Benavente O, McBride R, Pearce LA** – Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; 131:492-501
8. **Odén A, Fahlén M, Hart RG** – Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal. *Thromb Res* 2006; 117:493-499
9. **Salem DN, Stein PA, Al-Ahmad A, Bussey HI, Horstkotte D, Miller N, and Pauker SG** – Antithrombotic Therapy in Valvular Heart Disease—Native and Prosthetic: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:457-482
10. **Clagett GP, Sobel M, Jackson MR, Lip GYH, Tangelder M and Verhaeghe R** – Antithrombotic Therapy in Peripheral Arterial Occlusive Disease: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:609-626
11. **Cosmi B, Conti E, Coccheri S** – Anticoagulants (heparin, low molecular weight heparin and oral anticoagulants) for intermittent claudication. *Cochrane Database Syst Rev* (database online). Issue 2, 2002
12. **Albers GW, Amarenco P, Easton JD, Sacco RL and Teal P** – Antithrombotic and Thrombolytic Therapy for Ischemic Stroke: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:483-512
13. Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Council on Stroke: Co-Sponsored by the Council on Cardiovascular Radiology and Intervention: The American Academy of Neurology affirms the value of this guideline. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH and Tomsick T. *Stroke* 2006; 37:577-617
14. **Watala C, Golanski J, Kardas P** – Multivariate relationship between international normalized ratio and vitamin K-dependent coagulation-derived parameters in normal healthy donors and oral anticoagulant therapy patients. *Thromb J* 2003; 30:1-7
15. **Research Committee of the British Thoracic Society** – Optimum

duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. *Lancet* 1992; 340:873-876
16. **Hull R, Delmore T, Genton E et al.** – Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. *N Engl J Med* 1979; 301:855-858
17. **Levine MN, Hirsh J, Gent M et al.** – Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. *Thromb Haemost* 1995; 74:606-611
18. **Norrving B** – Dipyridamole with aspirin for secondary stroke prevention. *Lancet* 2006; 367:1638-1639
19. **Bates SM, Greer IA, Hirsh J and Ginsberg JS** – Use of Antithrombotic Agents During Pregnancy: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:627-644
20. ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). www.acc.org
21. **Levine MN, Raskob G, Beyth RJ, Kearon C and Schulman S** – Hemorrhagic Complications of Anticoagulant Treatment: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:287-310
22. **Arora N, Goldhaber SZ** – Anticoagulants and Transaminase Elevation. *Circulation* 2006; 113:698-702

Address for correspondence:
Andrei-Dumitru Margulescu, University Hospital of Bucharest, 169 Splaiul Independentei, SE 5, Bucharest, Romania
email address: andrei_marg@yahoo.com