

STUDY ON THE CHRONIC ANTITHROMBOTIC TREATMENT AFTER SURGICAL REVASCULARIZATIONS IN THE PERIPHERAL ARTERIAL DISEASE

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Abstract

The article presents a prospective controlled study of postoperative follow-up for 36 months, of the effect of the antithrombotic therapy on the arterial flux and vascular graft patency.

The study included 231 patients with peripheral arterial disease, who underwent surgical interventions for lower limb revascularization during a 10-year period (1999-2008), one month after surgery, the patients were divided into two groups: group #1 (174 patients) treated with antiplatelet therapy (AT), with a free interval after the first month or without treatment with vitamin K antagonist (VKA), and group #2 (57 patients) treated with continuous VKA, associated with the antiplatelet therapy (AT) treatment. The statistically homogeneous groups presented were compared in dynamics during the first 36 postoperative months with regard to the correlation between treatment and frequency of acute coronary events (ACE), stroke, hemorrhagic events, and significant hemodynamic modifications and graft patency in the operated lower limbs.

There was no significant difference between the groups as far as ACE ($p=0.59$) or stroke ($p=0.47$) incidence was concerned. Group #1 presented a statistically higher significance of failing graft cases (43.8%) as compared to group #2 (34.5%) ($r=0.165$, $p<0.05$) and graft occlusion (20.4%) as compared to group #2 (12.7%) ($r=0.143$, $p<0.05$). In group #2, the general incidence of hemorrhages is highly significant as compared to group #1. There were no deaths in the selected groups.

Postoperative association treatment of VKA with AT in operated patients with chronic vascular conditions does not decrease the incidence of ACE or stroke in at-risk patients, it leads to a better graft patency (especially in case of low flows of distal discharge), but with significant increase of bleeding events.

Rezumat

Articolul prezintă un studiu prospectiv, controlat, de urmărire postoperatorie pe durata a 36 luni, a efectului tratamentului antitrombotic asupra fluxului arterial și patenței grafturilor, a unui eșantion de 231 pacienți cu boală arterială periferică, asupra cărora s-au efectuat intervenții chirurgicale de revascularizație la nivelul membrelor inferioare într-o perioadă de 10 ani (1999 – 2008).

Pacienții au fost împărțiți după prima lună postoperator în două grupuri: grupul 1 (174 pacienți) cu tratament antiagregant plachetar (AAP), cu interval liber după prima lună

sau fără tratament cu antivitamină K (AVK) și grupul 2 (57 pacienți) cu tratament cu AVK continuu, asociat tratamentului AAP (antiagregant plachetar). Loturile prezentate, omogene statistic, au fost comparate în dinamică în primele 36 luni postoperator în privința corelației dintre tratament și frecvența evenimentelor coronariene acute (ECA), a accidentelor vasculare cerebrale (AVC), a evenimentelor hemoragice și a modificărilor hemodinamice semnificative și patența grafturilor la membrele inferioare operate.

Nu există o diferență semnificativă între grupuri privind incidența ECA ($p=0,59$) sau a AVC ($p=0,47$). Grupul 1 a prezentat o incidență mai crescută semnificativ statistic a cazurilor de *failling graft* de (43.8%) față de grupul 2 (34.5%) ($r=0,165$, $p=0,021$) și a ocluziei graftului (20.4%) față de grupul 2 (12.7%) ($r=0,143$, $p=0,03$). În grupul 2 incidența generală a hemoragiilor este semnificativă față de grupul 1. Nu au fost decese în grupurile selectate.

Asocierea AVK postoperatorie la tratamentul cu AAP la pacienții vasculari cronici operați, nu scade incidența ECA sau AVC la pacienții cu risc, ci conduce la o mai bună patență a grafturilor (în special în cazul fluxurilor slabe de descărcare distală) dar cu creșterea importantă a evenimentelor de sângerare.

Keywords: antiplatelet therapy (AT), vitamin K antagonist (VKA), acute coronary events (ACE), stroke

Introduction

Nowadays, when the invasive endovascular treatment is accepted by most reference guidelines as a first choice therapeutic solution when the situation allows it [6,7,9], this article proposes a comeback to the classic vascular surgery ("open surgery") and proposes especially a study on the effectiveness of the postoperative antithrombotic medical therapy in chronic arteriopathies. The unanimously accepted antithrombotic therapy guidelines [3,6,7,9] recommend antiplatelet therapy (AT) as Aspirin (Level of Evidence I / Class A) in obliterating arteriopathy of the lower limbs both pre- and postoperative, while the effectiveness of vitamin K antagonist (VKA) treatment, according to some trial (Dutch Bypass Oral Anticoagulants or Aspirin) is controversial [2], and other trials (Department of Veterans Affairs Cooperative Study) actually contraindicate the VKA treatment [4].

Materials and Methods

This work is a prospective, controlled study, developed in a 10-year period (1999 – 2008) on a sample of 231 patients operated in the Department of Cardiovascular Surgery of Emergency Hospital Floreasca of Bucharest, Romania, who suffered from peripheral arterial disease (aortoiliac occlusive disease and infrainguinal occlusive disease) and aims at analyzing the way in which associating the postoperative AVK medical treatment with the AT, from the very first months after surgery or at a distance, may alter, in the first 36 months of postoperative follow-up, both the clinical evolution of the operated patients and the objective

hemodynamics in the arterial circulation of the operated lower limbs, or at the graft level. Out of the total number of patients with chronic peripheral arterial disease, who underwent revascularization operations, 231 patients were selected.

The study was conducted according to the principles of Declaration of Helsinki (1964) and its amendments (Tokyo 1975, Venice 1983, Hong Kong 1989) and Good Clinical Practice (GCP) rules. The study was approved by the Ethics Committee of UMF "Carol Davila" Bucharest and patient consent was obtained for the collection and analysis of biological samples.

The inclusion criteria were:

1. patient suffering from an aortoiliac occlusive disease or infrainguinal occlusive disease with chronic evolution with correct indication of surgical treatment, in Fontaine class (II-B, III, and IV) and C or D types in TASC (TransAtlantic InterSociety Convention) classification [6], operated during the period 1999 – 2008 in the Department of Cardiovascular Surgery;
2. compliant patients, who accepted and observed the recommended postoperative treatment (including AT and/or VKA therapy), who checked and maintained, as required, the correct level of oral anticoagulant treatment (international normalized ratio: INR = 2-3.4) and who came in for all checkups 1, 3, 6, months after surgery and then every 3 months, until 36 months after surgery;
3. patients without thrombophiles or other known coagulation diseases;
4. no allergies to AVK therapy.

The exclusion criteria were:

1. patients with acute peripheral ischemia;
2. patients with immediate, multiple new surgical interventions, considered to have been subject to incorrect or technically defective surgical treatment.
3. patients with wide INR level fluctuation
4. thrombophilia or hemophilia, or other coagulation disorders known or diagnosed during follow-up;
5. patients categorized as II-A, II-B, III or IV with endovascular treatment indication (types A or B TASC classification) or without vascular surgery solution (gracil distal receptor bed);
6. patients who do not comply with the postoperative medical treatment (including AT and /or VKA): treatment taken irregularly or discontinued by the patient's own initiative, or without a rigorous control of the INR level or

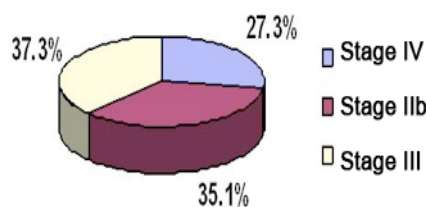
patients with absences from periodical checkups in the first 36 months according to the work protocol.

Group description: Out of the 231 operated patients, 210 were men (90.9%) and 21 were women (9.1%), the proportion men vs. women being 9:1. The patients age ranged between 41 and 82 years, the group having an average age of 60.29 ± 7.879 years. Most patients were operated before the occurrence of trophic lesions, thus, pre-op Fontaine Class was: II-B in 81 cases (35.1%), III in 87 cases (37.3%), IV in 63 cases (27.3%) (Figure 1). The associated risk factors were grouped in table I, and their distribution in the general group is presented in figure 2.

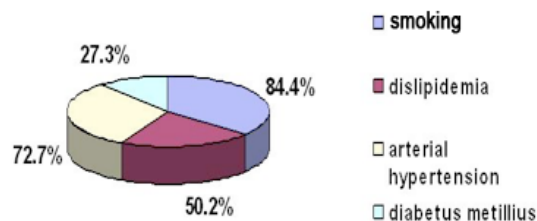
Table I

The presence of risk factors in the group of 231 patients included in the study

RISK FACTORS	YES (%)	NO (%)
Smoking	195 (84.4%)	36 (15.6%)
Essential arterial hypertension	168 (72.7%)	63 (27.3%)
Diabetes mellitus (all kinds of type 2)	63 (27.3%)	168 (72.7)
Hypercholesterolemia	116 (50.2%)	115 (49.8%)

**Figure 1**

Distribution of Fontaine Class in the general group

**Figure 2**

Distribution of risk factors in the general group

The types of vascular operations performed on the 231 followed-up patients were grouped and analyzed in table II.

Table II

The types of vascular operations performed

No.	TYPE OF OPERATION	NO. OF CASES	%
1.	Aorto-bifemoral bypass with prosthetic "Y" graft	30	13.0 %
2.	Ilio-femoral bypass with prosthetic graft	65	28.1 %
3.	Ilio-femoral bypass with prosthetic graft and femoro-popliteal extension with reversed autologous saphenous vein graft	15	6.5 %
4.	Femoro-popliteal bypass with reversed autologous saphenous vein graft	52	22.5 %
5.	Femoro-popliteal by-pass with prosthetic graft	52	22.5 %
6.	Femoro-femoral crossover bypass with prosthetic graft	3	1.3 %
7.	Thromboendarterectomy of the femoral artery bifurcation and angioplasty with patch augmentation	12	5.2 %
TOTAL		231	100 %

After surgery, during the first month after discharge all patients received AT (Aspirin 75 – 325 mg) and VKA (Sintrom[®] or Trombostop[®]) to maintain the INR's range = 2-3.4 was accepted and rigorously controlled, initially every few days, then on a weekly basis. According to the type of antithrombotic treatment received starting from the second postoperative month, the patients were randomized and subdivided into two groups: GROUP #1 (57 patients) only with AT, no VKA treatment (or VKA-free interval treatment) and GROUP #2 (174 patients) both with AT and VKA treatment continuously associated, the latter group included patients with indication of oral anticoagulant treatment due to associated comorbidities (mechanical heart valves, atrial fibrillation etc). During follow-up, removal of risk factors was envisaged in both groups (smoking prohibited, treatment of arterial hypertension, control of diabetes and hyperlipidemia). Some of the patients in GROUP #1 were subsequently introduced to VKA treatment in evolution, in cases where there appeared significant hemodynamic modifications in the peripheral circulation, with the recurrence of symptomatic ischemic phenomena, in dysfunctions of graft permeability ("failing graft"), occlusion thereof, or as a result of other cardiovascular causes: appearance of atrial fibrillation, unstable angina or myocardial infarction, stroke of cardioembolic cause. Table III presents the distribution of treatment.

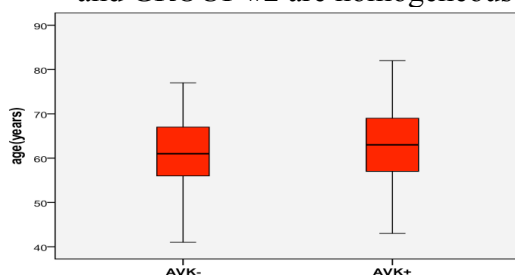
Table III

Distribution of VKA therapy during the 36 months in GROUP#1

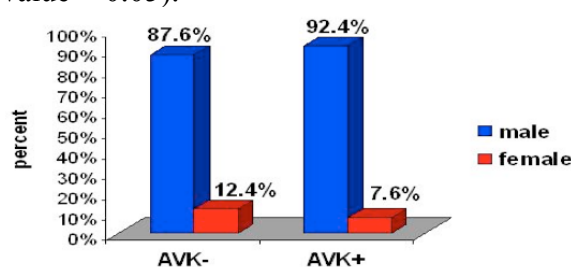
Month	1	3	6	9	12	15	18	21	24	27	30	33	36
No	0	0	0	5	11	13	16	21	25	27	31	35	50
%	0	0	0	8,8	19.3	22.8	28	36.84	43.85	47.37	54.38	61.4	87.72

(mean free VKA treatment = 24.35 months $\pm$ 4.1 months):

Thus, the structure of the two groups was schematized for a better understanding in Table IV and, from a statistical point of view, GROUP #1 and GROUP #2 are homogeneous (p value > 0.05).

**Figure 3**

Average age of the two groups does not differ statistically ($p = 0.18$)

**Figure 4**

Composition on sexes of the two groups is statistically similar ($p = 0.33$)

Table IV
The statistically homogeneous structure of the two analyzed groups

CHARACTERISTICS OF THE GROUPS		GROUP #1 Without AVK (-) INR (%)	GROUP #2 With AVF (+) INR (%)	p value
SEX	Male	50 (87.6)	160 (92.4)	0.33
	Female	7 (12.4)	14 (8)	
AGE	average (years)	61.07 +/-8.2 years	62.68 +/-7.7 years	0.18
MAJOR CARDIOVASCULAR RISK FACTORS	Smoking	49 (86)	146 (84)	0.7
	Dislipidemia	33 (58)	83 (44.7)	0.18
	Arterial hypertension	45 (79)	123 (71)	0.22
	Type 2 diabetes mellitus	19 (33)	44(25.1)	0.23
FONTAINE CLASS	Class II-B	26 (45.6)	55 (31.7)	0.8
	Class III	15 (59.6)	72 (41.4)	
	Class IV	16 (73)	47 (27)	
GRAFT TYPE	reversed saphenous vein	20 (28.2)	51 (71.8)	0.45
	synthetic	37 (23.1)	123 (76.9)	0.21
CONCOMITANT MULTIVASCULAR DISEASES	coronaries	14 (52.5)	44 (54.6)	0.8
	carotids / vertebral	8 (29)	21 (26)	
	coronaries / renal	0	2 (2.5)	
	coronaries / carotids	5 (18.3)	14 (17.3)	

The groups were rigorously monitored at 1, 3, 6 months and subsequently every 3 months for the 36 postoperative months, from the point of view of VKA treatment accuracy (INR) where applicable, and compared from the viewpoint of the correlation between the treatment and the frequency of acute coronary events (ACE) – forms of unstable angor or myocardial infarction, stroke (including transient ischemic attack), bleeding events (hematemesis, melena, epistaxis, macroscopic hematuria etc.), but also of significant hemodynamic modifications and graft patency in the operated lower limbs (evidenced clinically and by ultrasound).

Table V
Frequency of complications during the monitoring period

Complications	1	3	6	9	12	15	18	21	24	27	30	33	36
Upper GI bleeding	0.4	0	0	2.6	2.6	5.6	7.8	9.1	11.3	9.5	14.7	13.4	11.3
Stroke	0	0	2.6	1.3	1.3	3.9	2.6	3.9	3.5	2.2	1.3	0.9	0.9
ACE	0	4.3	4.3	3.5	3.5	2.6	5.2	4.3	2.6	4.3	2.6	2.2	3
Failing graft	0.9	2.6	2.6	1.3	1.3	1.3	2.6	3.9	8.2	26.4	45.5	64.9	71.4

HDS – hemodynamic stability; CVA – cerebrovascular accident; AMI – acute myocardial infarction

The hemodynamic parameters monitorisation at the level of arterial circulation in the operated lower limbs was mainly done by ultrasound examination, which analyzed: the anatomy and hemodynamic changes at the level of the arterial bed of the proximal donor, anastomoses, graft and distal receptor bed, the significant modifications of the perivascular tissue

(collections, effractions), significant modifications of velocities. A small subgroup of patients with failing graft or occlusions was subjected to subsequent arteriographic investigation. The presence of stenoses or early occlusions (after the first month of postoperative monitoring was a criterion for exclusion and does not make the object of discussion in this work). The significant hemodynamic modifications, the stenoses and occlusions occurred starting from the third follow-up month up to two years are caused by intimal hyperplasia, and the hemodynamic changes, the stenoses and occlusions occurred later on (after 2 years) were due to the atherosclerotic process [1,5]. The most important data for diagnosing stenoses, failing graft and occlusions were brought up by the pulsed Doppler investigation, which quantifies the cumulated hemodynamic effect of apparently unimportant serial stenoses, with values of 20-30% in the planimetric determination and which, added up on the length of the arterial axis, significantly alters the distal flux, producing a hemodynamic effect equivalent to a 60-70% stenosis [5]. Moreover, the evolution of arterial wall atheroma with prothrombogenic potential in the presence of an ineffective medical treatment leads to stenoses with progressive evolution from an ultrasound exam to another [5]. The classification of stenoses was the classical one [1]. Thus, there were taken into consideration:

- minimal hemodynamic changes — with an increase of systolic velocity by maximum 30%, which determined a slight spectral alteration, presented in the graph by a thickened line of complexes; no alteration of diastolic velocity, or 20% isolated stenosis [1,5].
- moderate hemodynamic changes – with an increase of systolic velocity up to almost 100%, with further thickening of the line of complexes, but even in this case there were no modifications of the diastolic velocity, or 20-50% isolated stenosis [1,5].
- severe hemodynamic changes - with an increase of systolic velocity over 100%, producing such an extensive spectral alteration, that it obturates the systolic gap, positivizes the diastolic velocity or stenosis (over 50% of the diameter) [1,5].
- failing graft - very severe hemodynamic changes, when a *tardus et parvus* curve is produced, mainly characterized by the fall of the maximum systolic velocity (20–30 meters per second), as a sign of insufficient hemodynamic contribution [1,5].

The presence of significant hemodynamic modifications, diagnosed by Doppler exam during the 36 months of postoperative monitoring is described in Figure 5, which outlines the evolution of the percentage of ultrasound exams within normal parameters, the percentage of ultrasound

results with significant hemodynamic alteration and the percentage of hemodynamic improvement after previous significant alterations. The frequency of global complications is shown in Figure 6.

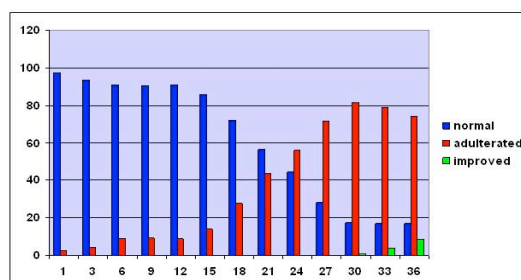


Figure 5

The evolution of Doppler hemodynamic modifications

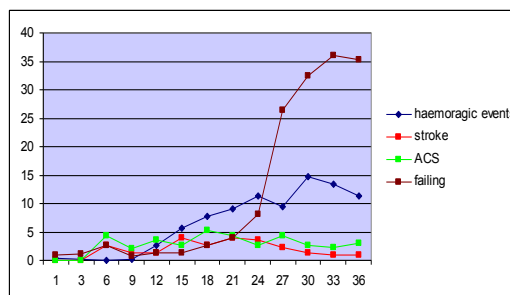


Figure 6

The statistic distribution of global complications during monitoring

Results and Discussion

In the study group there were 164 cases of synthetic graft and 67 cases only with saphenous vein graft. Out of those with prosthetic graft 127 (77.4%) benefited from continuous VKA treatment, as compared to 47 (82.1%) cases of patients with venous graft; such difference did not reach the threshold of statistical significance ($p = 0.4$). In conclusion, we can say that the proportion of patients with continuous anticoagulation was similar, whatever the type of graft used. There is no significant difference between the two groups with regard to the incidence of ACE incidence ($p = 0.59$) or stroke ($p = 0.47$). In Group #1 where the subjects did not receive VKA therapy for the whole follow-up period there were recorded 9 cases of stroke out of 57 (15.8%) as compared to 35 cases out of 174 (20.1%) in Group #2. The difference is not statistically significant, as the risk value obtained was O.R. = 0.73 (0.3-1.6, C.I = 95%) (see Table VI).

Table VI

The distribution of the complications in the two groups according to the treatment, correlated with the statistical significance

COMPLICATIONS	GROUP #1 Without AVK (-)	GROUP #2 With AVK (+)	<i>p</i> value
	INR (%)	INR (%)	
Total bleeding events	16 (28.1)	65 (37.35)	0.04
AMI / unstable angina	14 (24.5)	49 (28.1)	0.59
Stroke	9 (15.7)	35 (20.5)	0.47
Failing graft	25 (43.8)	60 (34.4)	0.021
Graft occlusion	12 (21.4)	22 (12.6)	0.03

The incidence of failing graft after 36 months recorded higher values in GROUP #1, with AVK-free interval, in 25 cases (43.8%), as compared to 60 (34.4%) cases in Group #2, with continuous AVK, the difference being statistically significant ($r = 0.35$, $p = 0.021$). The presence of the AVK-free interval in Group #1 is associated with a higher incidence of graft occlusion after 36 months, in 12 cases out of 57 (21.4%), as compared to Group #2 with 22 cases out of 174 (12.6%), the difference being statistically significant ($r = 0.143$, $p = 0.03$ at a significance threshold of 0.05).

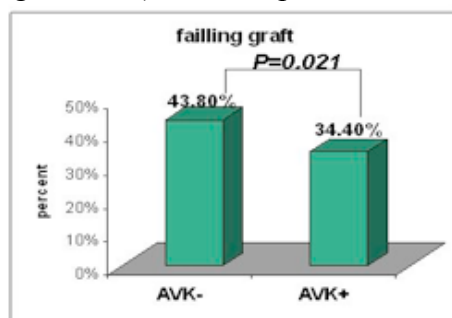


Figure 7

Incidence of failing graft in the two analyzed groups

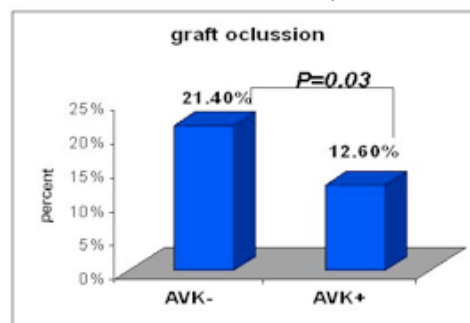


Figure 8

Incidence of graft occlusion in the two analyzed groups

The cumulative bleeding events (hematemeses, melena, epistaxis, macroscopic hematuria, etc) was in Group #2 of 65 cases out of 174 (37.35%) as compared to 16 cases out of 57 (28.1%) in Group #1, a statistically significant difference with test value $r = 0.136$, $p = 0.04$ (Figure 9).

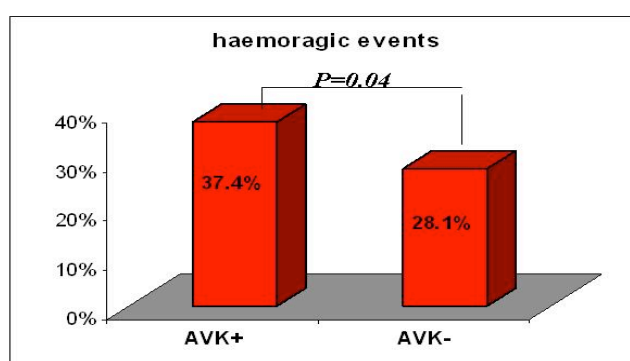


Figure 9

Incidence of bleeding events in GROUP #1 (AVK+) versus GROUP #2 (AVK-)

Most bleeding events were minor in Group #2 (haematemesis, melaena, epistaxis, hematuria macroscopic), but only 6 cases (3.44%) were serious upper gastrointestinal bleeding with haemodynamics instability even shock (with INR in range = 2-3), which required intensiv care measures, temporary interruption of VKA therapy, correction of anemia, endoscopic control and treatment, starting the proton-pump inhibitors therapy and replacing for long term Aspirin therapy with Clopidogrel 75 mg / day, with less gastric aggressive effect. There were no deaths in the selected groups.

Conclusions

This study starts from the presupposed obligatory treatment with Aspirin after surgical revascularizations of lower limbs (Level of Evidence I / Class A) [6,7,9]. The postoperative association of VKA therapy with AT in operated chronic vascular patients does not decrease the incidence of ACE or stroke in at-risk patients. In the randomized multicentric trial entitled "The Dutch Bypass Oral Anticoagulants or Aspirin Study" [2] it was used a higher level of oral anticoagulation (INR 3-4.5) and it presented the effectiveness of the AT as compared to VKA therapy on graft patency, but did not find a significant difference of the general patency, however the subgroup with autolog infrainguinal saphenous vein graft has a better patency with VKA therapy (Level II / Class II-b) [2,9] while the group of operated patients where synthetic graft was used in the infrainguinal area has a better patency with combined AT (Aspirin and Clopidogrel) (Level of Evidence II-b \ Class B) [2,9]. The purpose of this work is not such a comparison of the two types of antithrombotic treatments (AT as compared to VKA therapy), on the contrary, it tries to find the effect of the association thereof. The conclusion of this work is that the VKA therapy associated with AT leads to a better graft patency as compared to the AT alone (especially in cases of weak flows of distal discharge), but with an importantly increased occurrence of bleeding events. The results of this study contradict the prospective randomized trial of the "Department of Veterans Affairs Cooperative Study" [4], which uses a lower level of anticoagulation (INR = 1.4 – 2.8) and which does not identify an improvement of infrainguinal graft patency after 3 years, but just a doubling of hemorrhagic events. Nevertheless, the results of this work confirm the results published by Sarac TP [8], whose study done on 56 randomized patients where the association of VKA therapy (for INR = 2-3) with Aspirin (325 mg) as compared to the treatment with Aspirin alone leads to a better patency after 3 years of high risk venous grafts (defined as grafts with distal arterial bed with precarious discharge, suboptimal venous conduct and

repeated interventions). As in this work, the rescue rate was significantly higher in patients who received VKA and Aspirin therapy, but, with higher bleeding rates for this association [1,9]. The continuous postoperative association of AVK with PAA treatment leads to a better graft patency. The patients should be carefully monitored with regard to the INR level (optimum range = 2-3) and potential associated diseases, by preventing unwanted bleeding.

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