

CLINICAL STUDY

Arterial hypertension in patients with coronary artery disease treated with surgical myocardial revascularization

Vavlukis M, Borožanov V, Georgievska-Ismail L, Bosevski M, Taneva B, Kostova N, Peovska I

Institute for Cardiac Diseases, Clinical Centre, University St. Cyril and Methodius, Medical Faculty, Skopje, Republic of Macedonia. vavlukis@mt.net.mk

Abstract

Objectives: To evaluate the incidence and prognostic power of arterial hypertension in patients with coronary artery disease treated with surgical myocardial revascularisation, before and after the operation.

Background: Arterial hypertension is one of the leading modifiable risk factors in CAD patients who underwent CABG surgery with the major impact on clinical outcome in these patients.

Methods: 749 patients with mean age of 55±8 years, (639 male/119 female) were analyzed for their pre-operative: demographic, clinical, left ventricular morphologic and functional and angiographic, peri-operative: type of operation, type and number of applied conduits, in-hospital morbidity and mortality, and post-operative: demographic, clinical, left ventricular morphologic and functional and angiographic characteristics. Mean postoperative follow-up period was 5.97±4.27 years.

Results: Hypertension was found in 52.7 % of patients before the operation, and it was the most frequent risk factor, without any differences between different age groups, but significantly more often in females ($p=0.0001$), diabetics ($p=0.0001$), and patients with preserved LV function ($p=0.011$). Although significantly correlated with in-hospital morbidity ($r=0.085$ and $p=0.023$), HTA was not identified as independent predictor. The most predictable was the occurrence of early neurological complications. HTA was also found to be a predictor of long life prognosis in CABG patients, but not as independent prognostic factor. Significant reduction in incidence was found in post-CABG patients (30.1%), which is most likely a result of applied pharmacologic treatment. ACE-inhibitors, Ca-antagonists and B-blockers were applied in 39.44 %, 30.1 % and 33.6 % of patients respectively, with significant positive correlations found for all of them as follows: $r=0.221$, $p=0.0001$, $r=0.316$, $p=0.0001$ and $r=0.093$, $p=0.031$.

Conclusion: Hypertension is the most powerful risk factor in CAD patients who undergo CABG surgery in our country, and a powerful prognostic factor of early and late clinical outcome. There is a trend toward decreasing the incidence of HTA in post-CABG patients, as a result of improved pharmacologic treatment after the operation (Tab. 5, Fig. 1, Ref. 13). Full Text (Free, PDF) www.bmj.sk.

Key words: arterial hypertension, CAD, CABG surgery, prognostic factors, cardiac events, pharmacologic treatment, secondary prevention.

Coronary artery bypass surgery (CABG) is the treatment of choice, together with percutaneous coronary interventions (PCI) for myocardial revascularization in patients with coronary artery disease (CAD). Success of the procedure and patient status early and late after the operation is depends on many factors. Arterial hypertension is one of them, maybe the most powerful, that influences early and late clinical outcome in CABG patients.

In our study we analyzed incidence of arterial hypertension in CAD patients, treated with CABG in our country, before and after the operation, and its influence on the early and late clinical outcomes (1, 2).

Institute for Cardiac Diseases, Clinical Centre, University St. Cyril and Methodius, Medical Faculty, Skopje, Republic of Macedonia

Address for correspondence: M. Vavlukis, Bul Avnoj Nr. 64/2/4, Skopje, 1000, Republic of Macedonia.
Phone: +38922455142, Fax: +38923113116

Acknowledgment: This investigation is part of the scientific project No. 40079798/0, under the title "Clinical evaluation, follow up, prognosis and quality of life after a successful revascularisation with aortal-coronary bypass surgery in patients with coronary artery disease", carried out in the period of 1999/2002, with a grant from the Ministry of Education and Science of the Republic of Macedonia.

Tab. 1. Basal pre-operative characteristics of patients who underwent CABG.

Followed parameters	Values expressed as M±SD and/or n (%)
Age (years)	55.98±8.95
Gender male/female (%)	639 (84.1%)/119 (15.9%)
BMI (kg/m ²)	27.20±3.42
Obesity (BMI>30)	150 (20%)
Diabetes mellitus	25.9%
HTA	52.7%
Smoking	50.6%
HLP	36.4%
Family history of CAD	39.6%
CVD	2.5%
HOPD	3.1%
PVD	4.5%
old MI	63.8%
HF*	6.1%
Angina pectoris	80.1%

M±SD – mean±standard deviation; BMI – body mass index; HTA – hypertension; HLP – hyperlipidemia; CVD – cerebrovascular disease; COPD – chronic obstructive pulmonary disease; PVD – peripheral vascular disease; MI – myocardial infarction; HF – heart failure in anamnesis (dyspnoea, oedemas)

Methods

The study was designed as retrospective/prospective study, performed in 749 patients treated with CABG surgery for treatment of CAD, first time operated in several different cardio-surgical centres in Europe in the period of 1981–2002. Patients data were collected from a database (for CAD patients treated with CABG surgery) in our institution. Data obtained from patient's history of the disease, clinical examination and the following investigations were collected: basal ECG, laboratory analyses: (hemogram, glycaemia, urea, creatinin, electrolytes, lipid profile etc), 24-hour ambulatory ECG monitoring by Holter, 2D and Doppler echocardiography and coronary angiography. Mean postoperative follow-up period was 5.97±4.27 years.

Several groups of characteristics were analysed:

Pre-operative characteristics

– demographic and clinical characteristics: age, gender, body mass index (BMI), smoking, previous myocardial infarction (MI), previous PCI, angina pectoris (AP), according to the CCSC (Canadian cardiovascular society classification), heart failure, comorbidities: HTA, cerebrovascular disease (CVD), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD) and diabetes (DM);

– left ventricular morphologic and functional characteristics: ejection fraction, left ventricular end- diastolic and end- systolic dimensions, segmental wall motion (by using 16-segmental model and five point scoring system), valve function;

– angiographic characteristics: anatomical distribution of CAD (number of diseased vessels, localisation and degree of stenosis), calculation of PAS and Modified Gensini score.

Tab. 2. Risk factors and used medications after CABG.

Followed parameters	Patients	
	n	%
Diabetes mellitus	234	31.5%
HTA	225	30.1%
Smoking	68	9.16%
HLP	261	34.95%
Obesity (BMI>30)	162	21.6%
ACE-inhibitors	295	39.44%
Ca antagonists	255	30.10%
B-blockers	252	33.65%
Diuretics	162	21.68%

HTA – hypertension; HLP – hyperlipidemia; BMI – body mass index

Per-operative characteristics

– type of operation (on-pump, off-pump), type, number and location of conduits that were applied, additional intra-cardiac operations (aneurysmectomy, ventriculoplasty, atrioplasty, valvuloplasty or valve replacement), endarterectomy, carotid endarterectomy, occurrence of in-hospital morbidity (infections, acute renal failure (ARF), neurological complications, pericarditis, pleuritis, arrhythmias, hemodynamic complications, arterial thrombosis, acute myocardial infarction), and mortality.

Post-operative characteristics

– demographic, clinical, left-ventricular morphologic and functional, angiographic (if re-coronarography was performed), and occurrence of cardiac events including cardiac death.

Statistical analyses

Data were analysed using SPSS software (version 10,0). Continuous variables were reported as mean SD. Categorical variables were reported as counts (percentages) and compared between groups using chi-square test. Continuous variables were examined by a two-tailed t test or Wilcoxon rank-sum test. The Spearman rank correlation coefficient was used to estimate the correlation between variables. For estimation of predictive value of multiple variables in prediction of occurrence of adverse cardiac events, including cardiac death, multiple linear regression analysis was performed and coefficient of regression (R), coefficient of determination of the model (R²) and statistical significance of predictive variables were calculated. For all analyses a p value <0.05 was considered statistically significant.

Results

Incidence/prevalence of HTA

Hypertension was found to be the most common factor occurring *before CABG operation* in our study population, present in 394 (52.7 %) patients, before smoking (50.6 %), HLP (36.4 %) family history for CAD (39.6 %), diabetes mellitus (25.9 %), and obesity (BMI >30) in 20 % of patients (Tab. 1). Distribution

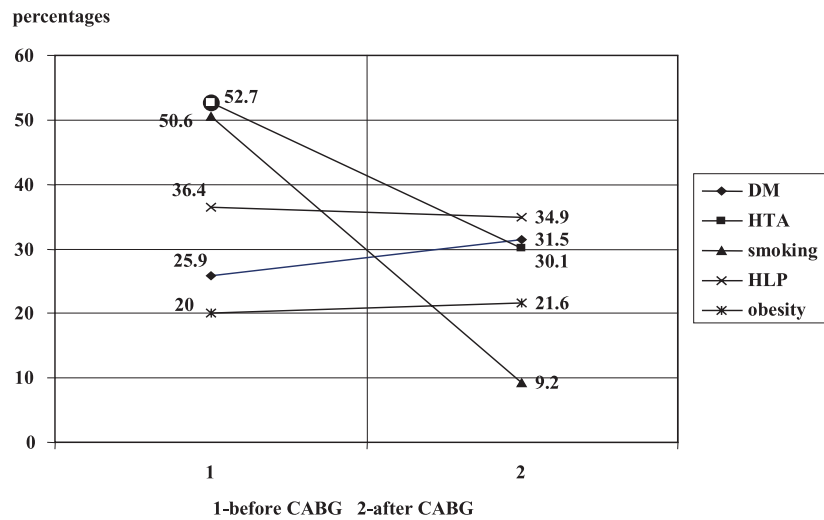


Fig. 1. Comparative distribution of risk factor before and after CABG.

of hypertension was without differences in different age groups, but was significantly more frequent in females (p=0.0001), diabetics (p=0.0001), patients with preserved left ventricular function (p=0.011), and smokers. The data on the type of medications the patients were receiving before the operation were incomplete (Tab. 1).

In the *post-CABG period* prevalence of hypertension was 30.1 %, of HLP 34.9 %, 31.5 diabetics were found, 21.6 % patients were obese, and only 9% continued smoking (Tab. 2).

We performed comparison of pre and post-operative incidence of the major modifiable risk factors in our patients. The most obvious was the reduction of smoking and hypertension,

hyperlipidemia was insignificantly reduced, as for diabetes, and obesity, increased incidences were registered (Fig. 1).

Other pre-operative (left ventricular morphologic, functional and angiographic characteristics) and peri-operative characteristics are presented in Table 3. In average patients had slightly reduced LV ejection fraction, but 45.3 % of patients had the left ventricular function preserved, and 26.4 % had left ventricular dysfunction, defined as LVEF <40 %. Patients who underwent CABG in our country were with moderate to severe CAD and that's why 89 % of them underwent on-pump CABG with an average 2.74 graft applied.

Incidences of early and late cardiac events including cardiac death and progression of the atherosclerotic disease in grafts and

Tab. 3. Pre-operative (left ventricular morphologic, functional and angiographic) and peir-operative characteristics of patients who underwent CABG.

Followed parameters	Values expressed as M SD or %
EF (%)	48.81±16.18
WMSS	1.38±1.93
MR	16.2%
Mean number of diseased CA	2.43±0.68
PAS score index	4.54±1.93
Modified Gensini score	19.62±7.71
LV aneurysms	8.2%
On-pump/off-pump	671/76
Mean number of applied grafts	2.74±0.94
Aneurysmectomy	30 (4.0)
LV repair by Batista	37 (4.9)
Endarterectomy	64 (8.5)
Anuloplasty of MV/TV	36 (4.8)

EF – ejection fraction; WMSS – wall motion summed score; MR – mitral regurgitation; AoR-aortic regurgitation; TR – tricuspid regurgitation; PAH – pulmonary artery hypertension; CA – coronary arteries; PAS – proximal artery segment score; LV – left ventricle

Tab. 4. Incidence of early (in 749 patients) and late cardiac events including cardiac death (in 563 patients), and coronary arteriography findings (in 102 patients) mean 5, 97+4, 27 years after CABG.

Followed parameters	Values M±SD or n (%)
In-hospital morbidity	173 (23.1 %)
In-hospital mortality	23 (3.1%)
AP after CABG	158 (28.1%)
HF	82 (14.6 %)
PCI after CABG	22 (3.9 %)
Re-Do CABG	10 (1.9 %)
CD	16 (2.8 %)
NCD	26 (4.6 %)
N-r of pts with graft occlusion	72 (70.6 %)
N-r of occluded grafts per patient	1.12±0.98 (0-4)
N-r of pts with patent-diseased grafts	33 (32.4 %)
N-r of patent-diseased grafts per patient	0.37±0.58 (0-2)
Progression in native CA	79 (77.4 %)

AP – angina pectoris; HF – heart failure; PCI – percutaneous coronary intervention; CD – cardiac death; NCD – non cardiac death

Tab. 5. Statistically significant correlations of analysed variables and in-hospital morbidity.

Variable	Correlation coefficient (r)	Statistical significance (p)
Age	-0.162	0.0001
CVD	0.073	0.047
PVD	0.089	0.018
HOPD	0.082	0.029
HTA	0.085	0.023
HF	0.128	0.00123
Mod Gensini score	-0.099	0.007
LVEDd	-0.164	0.012
EF	0.155	0.005
WMSS	-0.116	0.044
Type of conduit	0.114	0.002
Ventriculoplasty	0.084	0.021

CVD – cerebrovascular disease; PVD – peripheral vascular disease; HOPD – chronic obstructive pulmonary disease; HTA – arterial hypertension; HF – heart failure; EF – ejection fraction; LVEDd – left ventricular end diastolic dimension; WMSS – wall motion summed score

native coronary arteries are presented in Table 4. The incidence of in-hospital morbidity was 3.1 %, and of cardiac death during the mean follow-up period was 2.8 %. In 28 % of patients recurrence of angina was registered, 4.6 % of whom were re-vascularized. 14.6 % of patients experienced symptoms of heart failure.

Prognostic implication of HTA

HTA was significantly associated with in-hospital morbidity ($p=0.001$), especially predictable for appearance of neurological complications. Significant correlation ($r=0.085$ and $p=0.023$), was found for HTA as risk factor and in-hospital morbidity, same as for advanced age, CVD, PVD, HOPD (Tab. 5), but with linear regression analysis of these risk factors, only advanced age was identified as independent predictor. We failed to find significant correlation for HTA and in-hospital mortality.

HTA was found to be a predictor of long life prognosis in CABG patients, but linear regression analysis of non-modifiable and modifiable risk factors (age, gender, obesity, HTA, HLP, DM and smoking), that were found to be significantly associated with adverse cardiac events, identified as independent predictors only diabetes and smoking ($F=2.201$; $p=0.027$). Surprisingly, we found no significant correlation between graft disease/native coronary artery disease progression and pre/post-operative presence of risk factors, including HTA.

Medical treatment of hypertension after CABG

The most often used antihypertensive medications after the operation were:

- ACE-inhibitors – in 295 (39.44 %) patients;
- Calcium channel blockers – in 255 (30.10%) patients;
- B-blockers – in 252 (33.6 %) patients;
- Diuretics – in 162 (21.68 %) patients (Tab. 2).

Arterial hypertension was highly significantly positively correlated with ACE-inhibitors ($r=0.221$, $p=0.0001$), Ca-antagonists ($r=0.316$, $p=0.001$), and Beta-blockers ($r=0.093$, $p=0.031$) therapy. ACE-inhibitors were more frequently used in hypertensive patients with diabetes ($r=0.110$, $p=0.007$), hyperlipidemia ($r=0.138$, $p=0.001$), LV dysfunction manifested with low LVEF and high WMSS ($r=0.174$, $p=0.015$; $r=-0.224$, $p=0.002$ respectively), and in patients who underwent aneurismectomy and/or ventriculoplasty together with CABG ($r=0.094$, $p=0.030$ and $r=0.144$, $p=0.001$ respectively), accompanied with digitalis and diuretic therapy. Ca-antagonists were widely used in patients who had arterial conduits, but LV dysfunction manifested with low LVEF and high WMSS reduced their usage ($r=-0.172$, $p=0.016$; $r=0.162$, $p=0.024$ respectively). Beta-blockers were used in hypertensive patients, but rarely ($r=-0.106$, $p=0.014$ and $r=-0.125$, $p=0.004$), in patients with low LVEF and high WMSS respectively-as parameters of left ventricular dysfunction, and after the operation-aneurismectomy and ventriculoplasty ($r=-0.106$, $p=0.014$; $r=-0.125$, $p=0.004$, respectively). ACE-inhibitors were the preferred medications in these patients.

Discussion

Incidence/prevalence of HTA

Coronary artery disease is a multifactor disease, with employment of multiple risk factors, resulting in atherosclerotic process of coronary arteries. Arterial hypertension is one of the major modifiable risk factors associated with CAD, together with hyperlipidemia, diabetes, obesity and smoking. It is a well known fact that prevalence of these risk factors in CAD population is very high, and despite of a high level of medical treatment, their management is very poor (3). The incidence of HTA in CAD patients who undergo CABG ranges from 40–60 %, 29 % of whom are patients with isolated systolic hypertension (4).

In our study similar results were found. HTA was found to be the most frequent risk factor in CAD patients who underwent CABG, followed by smoking and hyperlipidemia.

Data refers to different incidences of hypertension after CABG (ranging from 15 to 80 %) (5). In our study, postoperative incidence of hypertension was low –30 %, with significant reduction for almost 20 % in comparison with pre-operative period. In our opinion this is a result of medical treatment of post-CABG patients. Our results are in conflict with the data from literature. Belcher for example, refers poor medical management for secondary prevention, with less widespread and less effective medical therapy in post-CABG patients, which results in unfavourable post-operative outcome (6).

Prognostic implications of HTA

HTA is associated with increased in-hospital morbidity. Several studies refer that hypertension (including isolated systolic hypertension) is associated with 40 % increase of likelihood of peri-operative morbidity (4). Not like other major risk factors, such diabetes and non-modifiable (age and gender) which are independent predictors of early in-hospital mortality, hyperten-

sive disease is indirectly associated with mortality through PVD, CVD and renal dysfunction-conditions that are highly predictable for cardiac death. Hypertension is responsible especially for neurological complications during the first 30 days after the operation, equally for type 1 and type 2 neurological derangements (1, 2).

In our study, HTA was identified as predictor of in-hospital morbidity, especially associated with neurological (Type 1) deficits, but wasn't identified as independent risk factor (as referred in other studies). No correlation for HTA and in-hospital mortality was found, comparable to the literature data.

HTA is one of the determinants of aggressiveness of atherosclerotic process, and associated with other modifiable risk factors (especially diabetes, obesity and hyperlipidemia-today recognised as metabolic syndrome or "Deadly quartet") (7), is an important prognostic factor of long life prognosis, clinical outcome late after CABG and graft potency and disease progression in native coronary arteries (1, 2). Small series of studies pointed on hypertension as a better predictor of vein graft potency, than of arterial ones (8). Aggressive risk factor reduction, results in angina reduction, improvement of cardiovascular capacity, and decrease of the average degree of coronary artery stenosis (8). This can be accomplished by lifestyle modification and pharmacotherapy (9). *Van Brussel* found that presence of major risk factors (HTA, diabetes, smoking) before, and its continuation after the operation (in patients with vein grafts), is predictable for overall and cardiac mortality, myocardial infarction, recoronarography and PCI (10). *Herlitz* identified several factors that were independent predictors of impaired quality of life late after CABG, and hypertension, diabetes, advanced age, gender, HOPD, impaired quality of life before CABG, and early post-operative complications were among them (11, 12).

In our study HTA was found to be a predictor of long life prognosis in CABG patients, but linear regression analysis of non-modifiable and modifiable risk factors (age, gender, obesity, HTA, HLP, DM and smoking) that were found to be significantly associated with adverse cardiac events, as independent predictors identified only diabetes and smoking ($F=2.201$; $p=0.027$). Surprisingly, we found no significant correlation between graft disease/native coronary artery disease progression and pre/post-operative persistence of risk factors including HTA.

Medical treatment of hypertension after CABG

Patients with arterial hypertension after CABG in our country were most frequently treated with ACE-inhibitors, Ca-antagonists, and B-blockers. Choice of antihypertensive medication depended on coexisting risk factors and co-morbidities, left ventricular function after the operation and performed additional cardiac procedure together with CABG (aneurysmectomy, ventriculoplasty etc). The most widely used were ACE-inhibitors (especially in diabetic and hyperlipidemic patients, but also in patients with reduced LV function, and those who underwent aneurysmectomy and ventriculoplasty). We unwillingly registered that B-blockers were underused in the whole post-CABG population in our country, because of different reasons. In diabetic patients, because of a

still persisting opinion that they will worsen the disease and that they will increase lipid levels in hyperlipidemic patients. They were also underused in patients with left ventricular dysfunction and those who underwent aneurysmectomy or ventriculoplasty, in whom they are absolutely indicated according to the recommended guidelines. Ca-antagonists were widely used in the last few years, after the introduction of radial artery as conduit, not only for regulation of hypertension, but also with the aim to reduce the incidence of arterial spasms, and early graft closure.

Our data are very similar to that reported from other authors. Bradshaw, in a population based study in 2500 patients, 6–20 years after CABG registered reduction in medications usage, with increasing time after the operation. Among antihypertensive medications, ACE inhibitors were the most widely used (in 59% of post-CABG hypertensive patients), and also the most often applied medications in the total post-CABG population (in 42%), and B-blockers were underused (in 36% of the total population) (13).

Conclusion

Hypertension is the most powerful risk factor in CAD patients who underwent CABG surgery in Republic of Macedonia. Hypertension is a powerful prognostic factor of in-hospital morbidity and late clinical outcome in CABG patients. Today, decreasing incidence of hypertension in post-CABG population is observed as a result of the improvement of medical treatment after CABG.

References

- Eagle KA, Guyton RA, Davidoff R et al.** ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery: A report of the American College of Cardiology/American Heart Association task force on Practice Guidelines (Committee to update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *J Amer Coll Cardiol* 2004; 34: 1262–1347.
- Georgievska-Ismail L, Borozanov V.** Clinical evaluation, following, prognosis and quality of life after successful revascularization with aorto-coronary bypass surgery in patients with coronary artery disease. A report from the scientific project Nr. 40079798/0, Ministry of education and science of Republic of Macedonia, Skopje 2002.
- Baskett RJ, Buth KJ, Collicott C, Ross DB, Hirsch GM.** Preoperative cardiovascular risk factor control in elective coronary artery bypass graft patients: a failure of present management. *Canad J Cardiol* 2002; 18 (4): 397–402.
- Aronson S, Boisvert D, Lapp W.** Isolated systolic hypertension is associated with adverse outcomes from coronary artery bypass grafting surgery. *Anesth Analg* 2002; 94 (5): 1079–1084.
- Weinstein GS, Zabetakis PM, Clavel A, Franzone A, Agrawal M, Gleim G et al.** The renin-angiotensin system is not responsible for hypertension following coronary artery bypass grafting. *The Annal Thorac Surg* 1987; 43: 74–77.
- Belcher PR, Gaw A, Cooper M, Brown M, Wheatley DJ, Lindsay GM.** Are we negating the benefits of CABG by forgetting secondary prevention? *J Hum Hypertens* 2002; 16 (10): 691–697.

- 7. Sprecher D, Pearce G.** How Deadly is the „Deadly Quarter“? *J Amer Cardiol Coll* 2000; 36 (4): 1159–1165.
- 8. Hayat N, Shafie M, Al-Ghoui S, Abraham T, Endrus J.** Follow-up of 122 Symptomatic Patients after CABG: Coronary Arteriographic Definition of Disease Progression and Choise of Therapeutic Options. *Med Principles Practice* 1999; 8: 58–63.
- 9. Cundiff D.** Review Article. Coronary Artery Bypass Grafting (CABG): Reassessing Efficacy, Safety, and Cost.(serial online), 2002 (cited June 19, 2002). Available from: <http://www.medscape.com/viewarticle/434471>.
- 10. Herlitz J, Brandrup-Wognsen G, Caidahl K, Haglid M, Karison BW, Hartford M et al.** Improvement and factors associated with improvement in quality of life during 10 years after coronary artery bypass grafting. *Coron Artery Dis* 2003; 14 (7): 509–517.
- 11. Herlitz J, Brandrup-Wognsen G, Caidahl K, HartfordM, Haglid M, Karison B et al.** Determinants for an impaired quality of life 10 years after coronary artery bypasssurgery. *Int J Cardiol* 2005; 98 (3): 447–452.
- 12. Van Brussel BL, Plokker HW, Voors AA, Ernst JM, Ernst NM, Knaepen PJ et al.** Multivariate risk factor analysis of clinical outcome 15 years after venous coronary artery bypass grafting. *Europ Heart J* 1995; 16 (9): 1200–1206.
- 13. Bradshaw PJ, Jamrozik K, Gilfillan I, Thompson PL.** Preventing recurrent events long term after coronary artery bypass graft:suboptimal use of medications in a population study. *Amer Heart J* 2004; 147 (6): 1047–1053.

Received February 6, 2007.

Accepted June 9, 2007.