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Pharmacotherapy Evaluation and Utilization in Coronary Artery Bypass Grafting Patients in Kosovo during the Period 2016-2017

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Abstract

BACKGROUND: Coronary Artery Bypass Grafting (CABG) is realized in patients with critical or advanced disease of coronary arteries. There are different pharmacotherapeutic approaches which are used as management, treatment and preventive therapy in cardiovascular disease or related comorbidities. Performing a successful surgery, pharmacotherapy, and increase of bypass patency rate still remains a serious challenge.

AIM: The aim of this study is to analyze the patient characteristics undergoing CABG and eval-uation of their drug utilization rate and daily dosages in the perioperative period.

MATERIAL AND METHODS: Data were collected from 102 patients in the period 2016-2017 and detailed therapeutic prescription and dosages, patient characteristics were analyzed before the operation, after the operation and visit after operation in the Clinic of Cardiac surgery-University Clinical Center of Kosovo.

RESULTS: Our findings have shown that patients provided to have normal biochemical parameters in the clinic before the operation, and were related to cardiovascular diseases and comorbidities and risk factors with mainly elective intervention. However higher utilization of cardiovascular drugs such as beta blockers, diuretics, anticoagulants, statins and lower calcium blockers, ACEi, ARBs, hydrochlorothiazide, amiodarone were founded. ARBs, beta blockers, statins, nitrates and nadroparin utilization decreased after operation and visit after the operation, whereas amiodarone only in the visit after the operation. Diuretics are increased after the operation which decreases in the visit after the operation. Regarding the daily dosage, only metoprolol was increased in the visit after operation ($P < 0.001$) and visit after operation ($P < 0.05$) whereas losartan and furosemide were increased ($P < 0.01$) and ($P < 0.05$) respectively.

CONCLUSION: The study showed that beta blockers, statins, aspirin, nitrates (before the operation), furosemide and spironolactone are the most utilized drugs. However, we found low utilization rate for ACEi, ARBs, clopidogrel, nadroparin, warfarin, xanthines, amiodarone, calcium blockers. Daily dosages were different compared to before CABG only in metoprolol, losartan, and furosemide.

Introduction

Cardiovascular diseases are the biggest cause of mortality and are mostly related to coronary heart being also higher rate cause of morbidity cross-linked with ischemic heart disease and neurologic damages from cerebral hemorrhages [1] [2[[3]. In atherosclerosis, the main mechanism of worsening of the disease remains to inflammatory processes during the atherogenesis [4]. Also, lipid deposits and oxidized phospholipids are involved in many processes such as endothelium dysfunction, activation of adhesive molecules, chemotactic factors which promote interactions between leukocytes and endothelium, tissue factor releases and activation of coagulation cascades up to atherothrombotic formation [5] [6].

Epidemiologic studies provided that diabetes mellitus, hypertension, and lifestyle with high lipid intake, stress, and sedentary life are the main triggers for the appearance of the disease [7]. Due to this pharmacotherapeutic approaches with antithrombotic, antiaggregant, hypolipidemic, anti-inflammatory, vasorelaxant, antihypertensive, percutaneous coronary interventions and cardiovascular surgeries

including coronary artery bypass grafting (CABG) regarding prevention and treatment of cardiovascular diseases, atherosclerosis and endothelial dysfunction and critically advanced stages of coronary artery diseases are improving [8] [9].

Patients with stenosed arteries that undergo CABG are mostly realized with saphenous vein (SV), mammary or radial artery grafts and provides improvement of angina symptoms, better quality of life and survival rates [10], while there is also difference between the type of grafts in terms of susceptibility to atherosclerosis, occlusion, and failure of grafts which mostly included SV as more sensitive to these pathophysiologic processes [11]. Therefore based on these facts among the main problems which are still appeared in patients undergoing CABG are graft failure and occlusion related also with the atherothrombotic formation, increased vasospastic agents which play role in early and late phases of these interventions [12] [13]. The survival rate is higher in left internal mammary artery grafts and radial artery [14] [15].

There are different study approaches regarding management of perioperative symptoms and diseases by interfering in graft tissues pathophysiology which increase CABG patency rate and reduce operation complications. These groups of patients are recommended to use multiple pharmacotherapeutic agents to prevent perioperative complications [8]. Main therapies are antithrombotic, antiaggregant and anticoagulant drugs such as aspirin, clopidogrel, tirofiban, eptifibatide, enoxaparin, nadroparin, bivalirudin, fondaparinux and are limited in terms of the different perioperative period due to increased risk of bleeding. Also other antihypertensive groups such as hypolipidemic including statins, beta-blockers, Angiotensin Converting Enzyme Inhibitors (ACEi), Angiotensin Receptor Blockers (ARBs).

The underutilization (lower than 50 %) of these drugs in postoperative discharge have shown an increased risk of myocardial infarction and death [16] [17].

Therefore the strategies for their standardized utilization of these drugs in CABG are essential factors to reduce the risk of coronary diseases and improving the survival rate of the patients [18]. Use of antiaggregant in the early postoperative period have improved the life expectancy of coronary bypass and cardiovascular-related symptoms, reduced graft occlusion [19], while other anticoagulants such as warfarin are shown to play role in patients with atrial fibrillation or with thromboembolism history [20]. Statins are used unless contraindicated in patients before and after operation [21].

Beta-Blockers utilization is found more in postoperative atrial fibrillation prevention, hypertension [22], while ACEi is used more in myocardial infarction, left ventricular dysfunction, diabetes mellitus, chronic renal dysfunction. Also, calcium-blockers and diuretics are used for hypertension control.

Summarizing this number of patients affected by the cardiovascular disease in Kosovo is increasing and in particular, a considered number undergoing CABG exists. Moreover, pharmacotherapeutic evaluation is a necessary approach and intervention in perioperative procedures with the aim to reduce complications and increase the bypass patency and survival rate. Therefore, we aim to evaluate the drug utilization rate in the perioperative state (before, after and after the visit) undergoing CABG and also identify targets for quality improvement with the preparation of guidelines and protocols for prudent use of drugs in cardiovascular surgery.

Material and Methods

This study is prospective observational study realized in 102 selected patients undergoing CABG in the period of hospitalization in the Cardiovascular Surgery Clinic at the University Clinical Center of Kosovo (Prishtina, Kosovo) between the year 2016-2017.

The procedures in this study were conducted according to guidelines in the Declaration of Helsinki and the study design was approved by Ethics Committee in Faculty of Medicine (Nr: 3625), University of Prishtina, Hasan Prishtina and University Clinical Center of Kosovo (Pristina, Kosovo).

Patients were selected from the randomly selected subset of the study cohort to assess medication and participation was voluntary. The sample size also fits calculation of sample size was performed using Raosoft software with a 5% margin of error, a 95% confidence level, and a 50% response distribution. Since the undergoing coronary artery bypass grafting patients in Kosovo was 120-150 in previous years. In this analyzed year, total numbers in this period were 134 patients in this analyzed year (according to the Hospital Statistics), which are in line sample size 102.

Patients with a combination of operations, the absence to visit after the operation and those that did not survive the intervention after surgery were not included in our study.

Data were collected by the clinical pharmacologist, pharmacist and cardiac surgeon with properly designed form sheet. The drug use evaluation involved the therapy prescription and daily dosages in each patient, before the operation in the clinic, in the discharge after the operation and after the first visit in the clinic (≈ 2 months). The characteristics of patients such as age, gender, related comorbidities, metabolic and cardiovascular diseases, risk factors

were collected.

The number of bypass arteries or veins and priority of the intervention and available clinical indicated biochemical parameters in the period previous surgery such as Triglycerides, Cholesterol, Creatinine, AST, ALT, C-Reactive Protein (CRP), Left Ventricular Ejaculation Fraction (LVEF) were registered.

The general data's in the tables are expressed as prevalence or mean values. Drug use and daily dosages were calculated as (%) within each group.

Two sampled t-test were used for the comparison between the data between analyzed groups regarding drug utilization, whereas One-way ANOVA for comparison between the therapeutic daily dosages from each group or unpaired student t-test for differences between the two groups.

P value lower than 0.05 was considered statistically significant and represented the significant differences between the analyzed groups. All analysis was performed using statistical software GraphPad PRISM (version 6.0).

Results

The study included data of 102 patients, aged 62.2±10.3 with woman consulting 24 % of the group analyzed. The comorbidities in our study were Arterial Hypertension 67 %, Angina Pectoris 42 %, Type 2 Diabetes Mellitus 41 %, Hypertriglyceridemia 21 % and Hypercholesterolemia 18 %. In our study, 36 % were not smoking while 0-10 years smokers were 4 %, 10-20 years 11 %, 20-30 years 16 % and 40-50 years 30 %.

Table 1: Patient characteristics

Demographic and Clinical Patient Characteristics	
Gender (M/F)	77/23
Age	62.2 ± 10.3
Angina Pectoris	42 (%)
Hypercholesterolemia	18 (%)
Hypertriglyceridemia	28 (%)
Diabetes Mellitus	41 (%)
Hypertension	67 (%)
Smokers (before/now)	a) 0 years (36%) b) 1-10 years (4%) c) 10-20 years (11%) d) 20-30 years (16%) e) 30-40 years (30%)

Indication for angiography was included in all of our analyzed patients and there was no previous CABG found, Cerebrovascular diseases (ischaemic disease, stroke and carotid stenosis) were widespread in 6 % of patients, whereas peripheral artery diseases (microvascular and macrovascular including varicose veins) 25%, left main coronary artery occlusion was present in 15% and 17% of patients were with post-myocardial infarction status. Chronic renal failure was only 3% patients while 10% were with low degree renal insufficiency. Based on the priority of intervention, only 18% of patients were in urgency for cardiovascular surgery whereas 85% of patients were elective cases. Graft bypass results from the left internal mammary artery and SV. Demographics and clinical characteristics regarding cardiovascular disease, comorbidities, risk factors including smoking, type of intervention, the priority of intervention and type of graft data are featured in (Table 1 and 2).

Table 2: Patient characteristics regarding cardiovascular disorders and CABG intervention

Cardiovascular Characteristics of Patients in CABG	
Indication for coronary angiography	100 (%)
Previous CABG	0 (%)
Cerebrovascular disease	6 (%)
Peripheral artery disease	25 (%)
Left Main Coronary Artery Occlusion	15 (%)
Status post IM	17 (%)
Chronic Obstructive Pulmonary Disease	5 (%)
Chronic Renal Insufficiency/Renal Insufficiency	3/10 (%)
CABG type (CABG Isolated/Combination)	100/0 (%)
Intervention Priority (Urgency/Elective)	18/82 (%)
Arteries (LIMA) Vein (VSM) for CABG (5/4/3/2)	1/29/48/18 (%)

Biochemical parameters and cardiovascular data were within normal range values in all investigated patients as shown in the (Table 3), even though CRP values were in borderline, the specificity also exists for in individual values with higher AST and ALT values in 11 % of patients, CRP higher values in 14 % of patients, Creatinine in 10 % of patients (data not shown).

Table 3: General biochemical - cardiovascular parameters of patients undergoing CABG

Biochemical/Cardiovascular Parameters	
Triglycerides (mmol/L)	1.83 ± 0.9
Cholesterol (mmol/L)	3.64 ± 1.1
Creatinine (μmol/L)	102.9 ± 15.8
AST (U/L)	28.2 ± 12.3
AST (U/L)	31.1 ± 14.5
CRP mg/dL	6.2 ± 4.8
Left Ventricular Ejaculation Fraction (%)	53.7 ± 10.9

The cardiovascular system drug utilization rates in CABG patients in the period before the operation, after operation and visit after the operation are shown in the (Table 4).

Table 4: Cardiovascular pharmacological treatment administered in CABG Patients

Drug Utilization Rates in CABG Patients			
Type of Drugs	Before Operation (%)	After Operation (%)	Visit after Operation (%)
Beta Blockers	77.1	48.2	59.1
Calcium Blockers	4.9	9.6	8.1
ACEi	31.3	30.1	23.5
ARBs	22.9	3.6	8.5
Hydrochlorothiazide	25.2	1.6	15.6
Furosemide	15.7	97.6	52.8
Spironolactone	12.2	91.6	70.1
Nitrates	77.1	1.6	10.2
Xanthines	7.3	19.3	7.3
Statins	86.7	62.7	64.5
Amiodarone	1	21.8	8.8
Digitoxin	4.9	6.1	8.9

Moreover, the other drug utilization administered for the treatment and management of

CABG patients are shown in (Table 5).

Table 5: Other pharmacological treatment administered in CABG Patients

Type of Drugs	Drug Utilization Rates in CABG Patients Before Operation (%)	After Operation (%)	Visit after Operation (%)
Warfarin	0.5	4.8	0.5
Nadroparin	100	0.5	9.8
Clopidrogrel	0.5	33.8	21.9
Aspirin	0.5	97.6	76.5
IPP	49.4	65.1	51.8
H2 Blockers	37.4	35.5	38.5
Acetaminophen	4.8	35.5	12.2
76.5Indomethacin	0	14.5	7.3
Acetilcystine	2.4	72.3	11.8
Anxiolytics	6.5	4.9	4.9
Ceftriaxone	14.5	100	21.1
Insulins	32.5	42.2	27.9
Supplements	1	33.7	17.7

The daily dosage rates from the widely prescribed groups such as beta-blockers, ACEi, and ARBs, Diuretics are shown in (Figure 1-3).

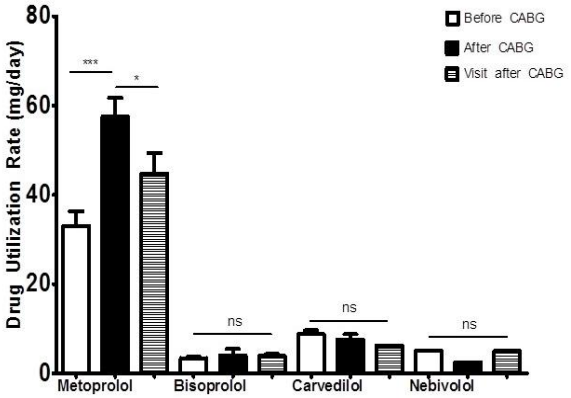

*Figure 1: Drug Utilization Rates expressed as daily dosage (mg/day) of beta blockers: Before CABG; After CABG and Visit after CABG. * P < 0.05, ** P < 0.01, *** P < 0.001*

In beta blockers only metoprolol dosages are increased after the operation (P<0.001), and de-creased in the visit after operation (P<0.05) (Figure 1).

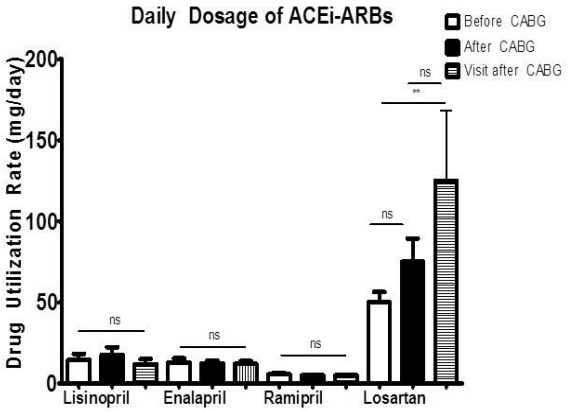

*Figure 2: Drug Utilization Rates expressed as daily dosage (mg/day) of ACEi/ARBs: Before CABG; After CABG and Visit after CABG. * P < 0.05, ** P < 0.01, *** P < 0.001*

From the ACEi or ARBs, only daily dosages of losartan were increased in the visit after the oper-ation (P<0.01) (Figure 2), whereas in diuretics furosemide dosage was increased only in the peri-od after the operation (P<0.05) (Figure 3).

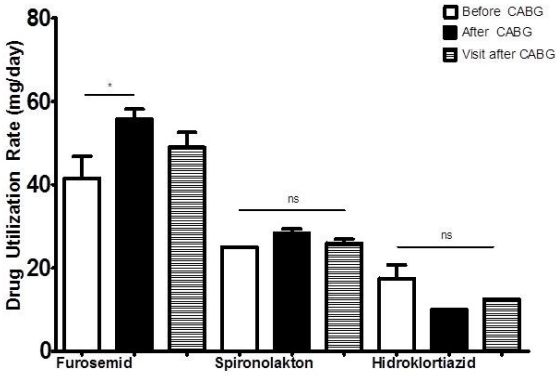

*Figure 3: Drug Utilization Rates expressed as daily dosage (mg/day) of Diuretics: Before CABG; After CABG and Visit after CABG. * P < 0.05, ** P < 0.01, *** P < 0.001*

The daily dosages regarding statins, antiacids (IPP and H2 Blockers), amiodarone are within the therapeutic values but when compared from our analyzed study groups they remain to be un-changed (P>0.05) (data not shown).

Discussion

In the present study, most of the patients were affected by cardiovascular diseases and comorbidities such as angina pectoris, hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, hypertension and risk factors including smoking as observed in other studies [23].

Moreover, arterial diseases were also present including status post myocardial infarction, left main coronary artery occlusion, rare cases of cerebrovascular disease such as ischaemic stroke and carotid stenosis and renal failure and insufficiency. Elective patients have dominated and SV was used more compared to a left internal mammary artery for the bypass grafting. Biochemical parameters previous intervention were within the normal ranges however there was a low number of patients which were presented with abnormal measured values. Left ventricular ejaculation fraction was standard in all analyzed patients at a similar level to other reports [24] [25].

Pharmacotherapeutic evaluation has shown an increasing number of drugs in all groups corre-sponding three monitoring phases. The beta blockers were utilized with 77% before the opera-tion, 48% after the operation and 59% visit after the operation. Metoprolol is the most pre-scribed medication with a higher dosage in the postoperative period. This data

are in line with other previous findings [18]. Also, the higher utilization in the preoperative period was shown to improve clinical outcomes by reducing the number of complications and total mortality [26]. However, there are contradictory reports in beta blockers users which showed the no beneficial effect of beta-blockers in the clinical outcomes and mortality, even though the underutilization of beta blockers (30%) were lower when compared with our data [27]. Another study performed in the larger number of patients from the national database analysis in the including no emergent and without previous MI patients showed not to be favorable in the reduction of perioperative complications. However, the preoperative utilization rates of beta-blockers were pretty similar to our findings [28].

Additional studies with the use of the beta blockers in the secondary prevention after CABG showed lower death and myocardial infarction rate and are found to be suboptimal with reduc-tion rate from 89 after discharge and 77% after one year [17]. In addition, the higher rates of uti-lization of beta-blockers have been shown in other related studies (94 %) [29] [30], which are not in agreement with our data.

In continuity ACEi drug utilization rates were (31%, 30%, and 24%) and for ARBs (23%, 4%, and 9%), hydrochlorothiazide (23%, 2%, and 16%), which show a decreasing trend in postop-erative and after the first visit. Only losartan daily dosage was increased in the visit after the op-eration. Our data are not in accordance with previous findings which showed increased utiliza-tion rates of the ACEi/ARBs in postoperative CABG period, even though no effect were ob-served in terms of death and re-hospitalization for cardiovascular events [17] [30]. Also, the pre-operative utilization of ACEi is shown to be higher compared to our data (30% vs. 50%) which still did not reflect the in the improvement of clinical outcomes or adverse events (with the only increased risk of readmission for heart failure) [31]. Moreover, in another related study, the pre-operative utilization of ACEi was 45 % with an increased number of the major adverse events (in particular renal dysfunction and atrial fibrillation) without an impact in mortality, stroke and my-ocardial infarction [32].

Diuretics such as furosemide and spironolactone utilization were increased in the period after the operation, with slowly decreasing in the visit after operation (16%, 98%, and 53%) and (12%, 92%, and 70%). The daily dosage of furosemide was increased only after the operation. Also, the diuretic use was found to be in line with our data and increased reports of major adverse events suggest their utilization reduction prior to surgery (excluding to higher clinical evidence) [33].

Moreover antiaggregant drugs such as aspirin and clopidogrel were interrupted a week before operation in all patients, hence the utilization of them were continued after operation and in the visit after operation with (98% and 77%) for aspirin, (34 and 22%) for clopidogrel which under-lies that the combination of dual antiplatelet therapy was not as reported studies [27]. Whereas the anticoagulant therapy with nadroparin has dominated only in the period before the operation. The daily dosages were similar in all groups.

Our data are in accordance with other findings in the antiaggregant drug utilization in related studies by showing an increased utilization in the postoperative operative period suggesting their preventive role and lower long-term cardiovascular events [17] [34].

Utilization of hypolipidemic drugs including statins were reduced after operation (87%, 63%, and 65%) however proportional daily dosages were found, which are in line with other recommendation which emphasizes their continuity in the period after operation [35].

The increased utilization rates of statins are recommended for the further improvement of cardiovascular clinical outcomes, perioperative and postoperative complications, inflammation [36]. Their postoperative use is also shown to be higher utilized and was associated with reducing recurrent ischaemic events and mortality [17] [29] [30], which were not in accordance with our findings due to their underutilization in the period after CABG. Moreover, according to the recent study, the loading dose of statins in the period after CABG is shown to be superior to regular dose in the terms of cardiovascular events and without proof of serious adverse events which might reflect their strategy in the dosing guidelines and prescribing in the future [21].

Based on our findings the utilization of aspirin, beta-blockers, statins are comparable also with other related studies while ACEi/ARBs are underutilized in our study [18]. However, our findings are in line also in the utilization of beta blockers, aspirin, ACE, higher in statin and underutilization nitrates [37]. In another study, the secondary prevention in patients undergoing coronary bypass, the utilization of beta blockers, aspirin, a statin was in agreement with our findings, excluding the lower rate of ACEi or ARBs [38]. Other reports after operation have shown similar trends in beta blockers, statin, with lower ACEi/ARBs which potentiate also the necessity for the optimization of the drug use in the postoperative period [39]. A possible explanation regarding lower rates of ACEi/ARBs utilization may be the normal values of left ventricular ejaculation fraction, even though these values were not higher as previous studies [40].

Moreover, one retrospective study was observed by providing the recorded clinical data in the period when patients were admitted and also in the discharge. In this study, the use beta blockers, aspirin, and statin were in similar range but with higher ACEi, lower ARBs (only before the operation) compared to

our findings. It is worth mentioning the fact that utilization of beta blockers, ACEi, statins were decreasing in the analyzed years, and ARBs were increasing in the period before operation whereas after operation beta blockers and statins were decreasing [41].

The antiaggregants such as aspirin was used regularly and in a standard dosage and not all patients were combined with clopidogrel as dual antiplatelet.

Beta-blocker usage is in line with our data as recommended with previously reported guidelines for the pharmacotherapy after CABG [42]. However, ACEi or ARBs are not used properly in all patients due to normal LVEF in our study. Moreover, aldosterone antagonists need to be reevaluated due to their limited use in LVEF < 35% or cardiac insufficiency II-IV patients. Statin utilization was not monitored properly and titrated in our study.

Approximate data regarding existing protocol and evidence for the management of patients after CABG are found also in other guidelines from American heart association which relies also on the type of evidence and relevant treatment [8].

Other utilized drugs in our study were: vasodilators including nitrates with (77%, 2% and 10%) and xanthines with (7%, 19% and 7%). Even though amiodarone utilization were (1%, 18%, 7%) more should be done to replace it with beta blockers and also the use of statins with the magnesium in the same period [39]. Also, the use of amiodarone in the prevention of atrial fibrillation only 24 hours after operation intravenously and in lower dosages is another promising strategy [43].

Cardiovascular pharmacotherapeutic approaches in diabetes mellitus consisted usage of insulin which was accompanied with a reduction in the period after the operation, probably due to the increased risk of clinical features in patients with CABG [44].

Also, the antiacids such as IPP or H2 blockers are mainly used as prophylaxis regarding the surgical intervention which is a common indication [45] and decrease in the visit after the operation. Other drugs such as analgesics including acetaminophen are indicated as needed mostly in postoperative period with nonsteroidal anti-inflammatory drugs indomethacin, acetylcysteine dominated in the period after the operation and reduced in the visit after operation with also cephalosporin antibiotics. The frequency of NSAID administration after CABG has declined since the FDA recommendations and advice due to safety concerns and from 2004 (39%) to 2010 (29%) which may impact also the lower utilization in our group of patients (15%) [46], also the higher utilization of acetylcysteine need to be considered also to its scientific evidence in the prevention of atrial fibrillation to undergoing CABG patients [47].

Rare cases of digoxin, trimetazidine, tamsulosin, doxazosin, levotiroksin, fluoxetine, metformin, and ipratropium-budesonide were also founded.

In the meantime with our study regarding utilization and daily dosages, we have performed also experimental studies for the alternative in compounds (arctigenin) for vasorelaxation and decreasing inflammation level in SV tissues [23].

In addition to this omega 3 polyunsaturated fatty acids were shown to be beneficial in inflammation and contractility in SV tissues [48].

There are undergoing similar approaches by other groups by investigating endothelin-1 antagonists [49], levosimendan [50], anti-ischaemic agents including ranolazine were shown to improve postoperative fibrillation in patients after CABG [40], and additional pharmacologic agents which inhibit the vasospasm of coronary grafts [51].

The drug utilization after CABG have shown to be an important factor in terms of long-term management of the clinical outcomes, the adherence of this drugs were not satisfactory after the first year after the revascularization period [29], which suggests different strategies and interventions increase the improvements of clinical outcomes and bypass patency rates.

Despite the clinical relevance of this study, the absence of official protocols which are in the procedure of establishment to maintain effective use of drugs may affect drug prescription and utilization, long-term monitoring (more than three months) after CABG, short period of study (for 1-5 years after CABG) and the adherence monitoring after discharge including also clinical outcomes and adverse events could be considered as a limitations of our study. Taking this into consideration our work may set the stage for larger investigational studies aimed at evaluating the utilization and also drug adherence, long-term monitoring including also the long period after the discharge and clinical outcomes and adverse events.

In summary in our study, we have found that therapeutic groups such as beta blockers, statins, aspirin, thiazides, nitrates (before the operation), furosemide and spironolactone are the most utilized drugs. However, we found low utilization rate for ACEi, ARBs, clopidogrel, nadroparin, warfarin, xanthines, amiodarone, calcium blockers. Daily dosages were different compared to before CABG only in metoprolol, losartan, and furosemide.

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