The Role of Adherence to Basic Pharmacotherapy of Heart Failure for Prevention of Late Adverse Events in Patients with Coronary Artery Disease and Left Ventricular Dysfunction After Surgical Revascularization of Myocardium

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Aim. To determine the role of adherence to the basic drug treatment of heart failure (HF) in prevention of late major adverse events (MAEs) after isolated coronary artery bypass grafting (CABG) in patients with stable coronary artery disease (CAD) and left ventricular (LV) dysfunction at three-year follow-up.

Material and methods. A prospective non-controlled single-center study included 125 consecutive patients with stable CAD and LVEF<50% (62±8 years; 114 [91.2%] males), after isolated CABG. At three-year follow-up MAEs occurred in 40 (32.0%) patients. The data on pharmacotherapy at follow-up were obtained in 124 patients: 85 (68.6%) patients without MAEs and 39 (31.4%) patients with MAEs.

Results. The enrolled sample of patients was characterized by high discharge prescription rate of renin-angiotensin system (RAS; 86.3%) blockers (angiotensin-converting enzyme inhibitors or angiotensin-II receptors blockers), beta-blockers (BBs; 97.6%) and mineralocorticoid receptors antagonists (MRAs; 79.0%), being comparable in MAEs and non-MAEs groups. The total coverage of basic HF pharmacotherapy (the combination of RAS blockers, BBs and MRAs) at discharge was 66.1%. At follow-up, about one third of patients in both groups withheld previously prescribed triple HF therapy. The MAEs were associated with more frequent withhold of previously prescribed RAS blockers, as opposed to patients without MAEs (20.5% and 7.1%, respectively; p=0.009). The majority of patients in both groups continued BBs therapy at follow-up (95.0% and 92.9%, respectively; p=0.187). Additionally, we observed the decline of MRAs intake frequency at follow-up (to 43.6% and 49.4%, respectively; p=0.547).

Conclusion. During 3-year follow-up after isolated CABG, about one third of patients with stable CAD and baseline LVEF<50% interrupted triple basic HF therapy (including RAS blockers, BBs and MRAs), mainly due to decrease of RAS blockers and MRAs usage. MAEs in patients with stable CAD and baseline LVEF<50% after CABG were associated with suboptimal use and more frequent interruption of RAS blockers.

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Coronary artery bypass grafting (CABG) is the most reliable and effective method of restoring coronary blood flow and a tool to improve the quality of life and increase survival of patients with stable coronary artery disease (CAD) and multi-vessel coronary bed lesions with left ventricular (LV) dysfunction [1]. At the same time, progression of coronary atherosclerosis and the risk of cardiovascular events necessitate strict compliance with the basic pharmacotherapy guidelines [2-4]. In addition to the basic drug treatment of CAD (antiplatelet agents and statins), patients with LV systolic dysfunction and heart failure (HF) necessarily require two or three neurohumoral modulators, namely renin-angiotensin system (RAS) blockers (angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers [ARBs]) [2,3], beta-blockers (BBs) and in many cases mineralocorticoid-receptor antagonists (MRAs) [2,3,5-7]. The proven benefits of using these groups of drugs have not been introduced into clinical practice to full extent primarily due to the poor adherence to drug therapy [8,9]. This, in turn, can potentially limit the beneficial effect of CABG on the course of the disease in the postoperative period and survival of patients with LV dysfunction in the presence of CAD.

Presently it has been found that adherence to drugs for secondary prevention of cardiovascular events after CABG is significantly lower than that in patients after coronary artery stenting (CAS) [10]. Evidence of the long-term survival prognosis for CAD patients with LV dysfunction in the context of the actual use of basic drug treatment of HF (ACEI/ARB, BB and MRA) after CABG is limited [1,4,11-13]. Moreover, patients from the so-called «gray zone» category with LV ejection fraction (EF) of 40-49%, including those with potential LV systolic function improvement in the postoperative period have recently been of interest.

The aim of the study was to determine the role of adherence to the basic drug treatment of heart failure (HF) in prevention of late major adverse events (MAEs) after isolated CABG in patients with stable CAD and LV dysfunction at three-year follow-up.

Materials and methods

A prospective non-controlled single-center study included 576 consecutive patients with stable CAD to perform isolated CABG during 2011-2017. The follow-up median (Me) was 34 months (interquartile range [ICR] 13-60 months). Due to the death of two (0.3%) patients in the early postoperative period, follow-up at discharge was performed for 574 (99.7%) patients. The following MAEs were evaluated in dynamics: 1) death from any cause; 2) myocardial infarction (MI); 3) unstable angina; 4) acute cerebrovascular event (stroke or transient ischemic attack) 5) HF decompensation; 6) sustained ventricular tachycardia; 7) repeated myocardial revascularization; and 8) thromboembolic complications. In general, data on MAEs at follow-up were available for 465 (81.0%) of 574 patients. Taking into account baseline condition of LV systolic function, a sample of 125 individuals with LVEF<50% was formed from the enrolled patients with available data on MAEs at the three-year follow-up (251 [54.0%] out of 465).

The study was carried out in compliance with the main provisions of the Council of Europe Convention on Human Rights and Biomedicine, World Medical Association Declaration of Helsinki on the ethical principles of scientific medical research involving human subjects, as well as current regulations of the Ministry of Health of Ukraine. The study protocol was approved by the local Ethics committee. All patients signed an informed consent to participate in the study.

The study did not include patients during the first month after acute coronary syndromes, those with any conditions that could make CABG impossible, as well as those with a combination of CABG and prosthetic heart valve.

Among the examined patients there were 114 (91.2%) men and 11 (8.8%) women aged 39 to 92 years, the average age (mean±standard deviation) 62±8 years.

123 (98.4%) patients were diagnosed with stable effort angina prior to CABG: 18 (14.6%) patients – functional class (FC) I, 77 (62.6%) – FC III, 28 (22.8%) – FC IV. In 111 (88.8%) patients postinfarction cardiosclerosis was reported. 30 (24.0%) patients had evidence of the recurrent MI, while LV aneurysm was found in 50 (40.0%) individuals. CAS was previously performed in 11 (8.8%) patients.

In 107 (85.6%) patients signs of chronic HF corresponded to stage IIA and in 18 (14.4%) – to stage IIB according to Strazhesko-Vasilenko classification.

120 (96.0%) patients had hypertension, including that with elevated blood pressure (BP): 22 (18.3%) patients – 1st degree; 47 (39.2%) – 2nd degree; 16 (13.3%) – 3rd degree; 35 (29.2%) patients – with normal/corrected BP levels at the time of enrollment. 18 (14.4%) patients had a history of stroke or transient ischemic attack.

Atrial fibrillation was recorded in 20 (16.0%) patients: 12 – paroxysmal type; 8 – permanent type. Moreover, atrial flutter was detected in 2 (1.6%) patients.

Type 2 diabetes mellitus was diagnosed in 38 (30.4%) patients: 6 (16%) – mild, 14 (37%) – moderate, 18 (47%) – severe. Chronic obstructive pulmonary disease was found in 2 (1.6%) patients, whereas bronchial asthma was detected in 2 (1.6%) patients. Signs of chronic kidney disease according to KDIGO criteria (2013) were present in 39 (31.2%) patients.

Echocardiography was performed according to generally adopted techniques [14]. In the overall population of enrolled patients median LVEF values made up 37% (33-43) (minimum – 15%, maximum – 49%). 47 (37.6%) patients were diagnosed with HF and LVEF in the «intermediate» range (40-49%) (HF with "mid-range" LVEF), and 78 (62.4%) were diagnosed with HF with reduced LVEF (<40%).

The types of implanted grafts in the studied sample were distributed as follows: 107 (85.6%) patients – venous; 4 (3.2%) – arterial; 14 patients (11.2%) – mixed arteriovenous. Along with CABG the following interventions were performed: 50 (40.0%) patients – LV repair; 27 (21.6%) – mitral valve repair; 14 (11.2%) – tricuspid valve repair; 3 (2.4%) – papillary muscle approximation; 2 (1.6%) – interventricular septum repair; 1 (0.8%) –interatrial septal repair. In 115 (92.0%) patients surgeries were performed under cardiopulmonary bypass ("on-pump").

In the perioperative period, all patients received standard drug therapy in accordance with the current guidelines [3,5,15], taking into account concomitant diseases.

The structure of pharmacotherapy at the end of the in-hospital observation was as follows: 103 (82.4%) – ACEIs, 5 (4.0%) – ARBs (ACEI/ARBs in total – 108 [86.4%]), 99 (79.2%) – MRAs, 122 (97.6%) – BBs, 17 (13.6%) – calcium channel blockers, 5 (4.0%) – thiazide/thiazide-like diuretics, 93 (74.4%) – loop diuretics (totally, diuretics were prescribed to 95 (76.0%) patients), 43 (34.4%) – amiodarone, 122 (97.6%) – statins, 32 (25.6%) – nitrates/sydnonimines, 92 (73,6%) – acetylsalicylic acid, 110 (88.0%) – clopidogrel (totally, 123 [98.4%] patients were prescribed antiplatelet therapy, 79 – dual antiplatelet therapy [63.2%]). Besides, oral anticoagulants were prescribed to 49 (19.5%) patients, antihyperglycemic drugs – to 41 (16.3%), and insulin – to 18 (7.2%).

The following MAEs were registered during a three-year follow-up among 125 patients: 8 (6.4%) – deaths (7 of them were associated with cardiovascular causes); 2 (1.6%) – MI; 4 (3.2%) – unstable angina; 4 (3.2%) – stroke; 18 (14.4%) – HF decompensation; 3 (2.4%) – sustained ventricular tachycardia; 4 (3.2%) – repeated myocardial revascularization; 1 (0.8%) – thromboembolism of peripheral arteries. In total, MAEs occurred in 40 (32.0%) patients.

In non-MAEs patients drug intake status was evaluated at a planned follow-up visit 3 years (36 months) after CABG. Data on drug treatment of patients with MAEs were obtained during admission to hospital of the patient due to the event itself, or taken from archival documents (outpatient medical records). Pharmacotherapy which immediately preceded the event was considered in the analysis of archival documentation. Among 40 individuals with MAEs one patient did not have any data on pharmacotherapy at the follow-up. Thus, the overall sample of patients analyzed for the intake frequency of certain classes of cardiovascular drugs at follow-up made up 124 people: 85 (68.6%) non-MAEs-patients, and 39 (31.4%) with MAEs.

To assess compliance with recommendations at follow-up, data on the use of a group of drugs were compared with the information on its prescription at discharge. Basing on such comparisons the studied cohort of patients was divided into 4 categories: 1) "0-0" – the group of drugs not prescribed at discharge, so the patient did not use it during the follow-up; 2) "0-1" – the group of drugs not prescribed at discharge, however the patient used it at the time

of repeated contact during the follow-up; 3) "1-1" — a group of drugs prescribed at discharge, and the patient continued to use it during the follow-up (indicator of «persistence» of administration [16]); 4) "1-0" — a group of drugs prescribed at discharge, but the patient did not use it during the follow-up.

Statistical data analysis was carried out using Statistica v.13.3 and IBM SPSS Statistics v.26.0 software packages. The central tendency and variation of continuous variables were presented as Me [ICR]. Distribution of categorical variables was given in the form of absolute and relative frequency (%). Comparison of continuous variables in two independent samples was performed using the Mann-Whitney U-test. The absolute and relative (%) frequency of categorical variables in unrelated samples were compared using the Pearson χ^2 criterion. If there was a statistically significant difference by χ^2 criterion, the comparison of certain categories (ranks) of categorical variables in the columns of the tables was carried out using z-test. Comparison of the absolute and relative (%) frequency of categorical variables in related samples was performed using the McNemar criterion. Differences at $p<0.05$ were considered statistically significant.

Results and discussion

The analyzed cohort of patients was characterized by a high frequency of ACEI/ARBs administration at the end of the in-hospital observation period, which was comparable in the compared groups (Table 1). However, in the MAEs group the percentage of patients taking RAS blockers for a long time was smaller in comparison with the alternative group.

Analyzing the use of ACEI/ARBs in dynamics, we found that MAEs were more often associated with not taking these drugs as compared to non-MAE patients. Adherence to ACEI/ARB therapy ("1-1") was higher among patients who did not have any MAEs at three-year follow-up (Table 1).

Expediency of prescribing ACEI/ARBs to patients with CAD after CABG is primarily determined by the presence of the baseline LVEF<40% [5,6] in most of them. Guidelines regarding the treatment of patients with HF mid-range EF are not that rigorous [17,18]. In this case history of MI, concomitant arterial hypertension, diabetes mellitus, and chronic kidney disease are likely to be the determining factors in favor of prescribing RAS blockers to CAD patients after CABG surgery [2-7,19].

Poor adherence to ACEI/ARBs treatment was previously accounted for both by the lack of convincing evidence regarding the reduction of the risk of adverse cardiovascular events after CABG in patients with preserved LV function [20,21] and concerns regarding the possible renal function deterioration and hyperkalemia in the postoperative period [21,22]. In some patients non-adherence to RAS blockers was also associated with an increased risk of MAEs due to the insufficient control of BP. At the same time, interruption (or "non-prescription") of ACEI/ARBs at follow-up could be associated with hypotension and deterioration of renal function [2,3,5]. Persistent improvement (up to the range of 40-49%) or restoration (LVEF≥50%) of LV systolic function in some patients with baseline LVEF<40% could also potentially affect the use of RAS blockers at follow-up [6,23,24]. In the mentioned ranges of LV systolic function the available body of evidence regarding the expediency of the long-term routine use of RAS blockers is rather ambiguous [25,26].

Table 1. The administration of ACEI/ARB at discharge and follow-up

Variable		All patients (n=124)	Patients with MAEs (n=39)	Non-MAEs patients (n=85)	p_1
Prescription frequency at discharge, n (%)		107 (86.3)	31 (79.5)	76 (89.4)	0.136
Intake frequency at follow-up, n (%)		101 (81.5)	25 (64.1)	76 (89.4)	0.001
p_2		0.286	0.109	1.000	–
Administration at follow-up, n (%)	"0-0"^{z}	9 (7.2)	6 (15.4)	3 (3.5)	0,009*
	"0-1"	8 (6.5)	2 (5.1)	6 (7.1)	
	"1-1"^{z}	93 (75.0)	23 (59.0)	70 (82.3)	
	"1-0"^{z}	14 (11.3)	8 (20.5)	6 (7.1)	

p_1 – significance of difference between MAEs and non-MAE groups, p_2 – significance of difference in the frequency of use of a class of drugs at follow-up, ^{z} significance of difference in z-test, *unstable result
ACEI – angiotensin converting enzyme inhibitors, ARB – angiotensin-II receptors blockers, MAEs – major adverse events

The analyzed sample of patients was characterized by high frequency of BBs prescriptions in the postoperative period (Table 2). Cases of continued administration of previously prescribed BBs prevailed in the overall sample design of enrolled patients at follow-up, as well as in non-MAEs and MAEs groups.

High adherence to BBs, including patients from the MAEs group, can be accounted for by some baseline and postoperative clinical features. Thus, non-MAEs and MAEs groups were comparable by the severity of HF (HF IIA and IIB stages in the group with MAEs: 32 [80%] and 8 [20%] patients, respectively; in the non-MAEs group: 75 [88%] and 10 [12%] patients, respectively [p=0.221]), as well as by the frequency of previous MI (35 [(88%) and 76 (89%) patients in non-MAEs and MAEs groups, respectively; p=0.752). Moreover, in comparison with the non-MAEs group, MAEs group of patients was characterized by a slightly worse LV systolic function both before the surgery (LVEF 34% [27-38%] and 39% [34-45%], respectively; p<0.001) and at the end of the hospital observation (LVEF 39% (34-45%) and 43% (39-48%), respectively; p <0.001). Besides, high adherence rate to the use of BBs in both compared groups could be associated with their use as a component of antihypertensive therapy, drugs for heart rate control in case of permanent AF, as well as those to prevent recurrent ventricular arrhythmias (recorded previously and at further follow up).

The compared groups were also comparable by the number of patients advised to take MRAs at discharge (Table 3). Decreased intake frequency of these drugs at follow-up in both the overall sample and in MAEs and non-MAEs groups drew special attention. Whereas MRAs intake status did not significantly differ in the compared groups.

A uniform decrease in the use of MRAs at follow-up and the absence of significant differences in the frequency of their intake in both MAEs and non-MAEs groups reflect the actual practice of their predominant prescription as the "third" neurohumoral blocker in addition to RAS blockers and BBs. MRAs are known as an important component in the treatment of patients with HF with reduced EF, while non-adherence to their use can increase the risk of further HF decompensation and life-threatening ventricular arrhythmias [2,5-7]. Similar to ACEI/ARBs, functional renal impairment should be noted among the factors potentially influencing MRAs interruption (or "non-prescription") at follow-up [5-7], as well as improvement or restoration of LV systolic function after surgical myocardial revascularization in some patients with the baseline LVEF<40%. Although ACC/AHA/HFSA experts [7] recommend considering the use of MRAs in certain categories of patients with LVEF⩾45% to reduce the risk of hospitalization, this recommendation does not have such a high level of evidence as in patients with EF⩽35% (40%) [6].

Coverage by prescription of basic HF therapy, including the coadministration of RAS blockers, BBs and MRAs in the overall sample of included patients was about 70% and was comparable with that in the comparison groups (Table 4).

We clearly observed the decrease of administration frequency of the triple basic HF therapy at follow-up. Both in total and in each group about a third of

Table 2. The administration of BB at discharge and follow-up

Variable		All patients (n=124)	Patients with MAEs (n=39)	Non-MAEs patients (n=85)	p_1
Prescription frequency at discharge, n (%)		121 (97.6)	37 (94.9)	84 (98.8)	0.184
Intake frequency at follow-up, n (%)		117 (94.4)	38 (97.4)	79 (92.9)	0.314
p_2		0.219	1.000	0.063	–
Administration at follow-up, n (%)	"0-0"	2 (1.6)	1 (2.5)	1 (1.2)	0.187
	"0-1"	1 (0.8)	1 (2.5)	0	
	"1-1"	116 (93.6)	37 (95.0)	79 (92.9)	
	"1-0"	5 (4.0)	0	5 (5.9)	

p_1 – significance of difference between MAEs and non-MAEs groups, p_2 – significance of difference in the frequency of use of a class of drugs at follow-up

BB – beta-blockers, MAEs – major adverse events

Table 3. The administration of MRA at discharge and follow-up

Variable		All patients (n=124)	Patients with MAEs (n=39)	Non-MAEs patients (n=85)	p_1
Prescription frequency at discharge, n (%)		98 (79.0)	32 (82.1)	66 (77.6)	0.576
Intake frequency at follow-up, n (%)		59 (47.6)	17 (43.6)	42 (49.4)	0.547
p_2		<0.001	<0.001	<0.001	–
Administration at follow-up, n (%)	"0-0"	23 (18.5)	6 (15.4)	17 (20.0)	0.709
	"0-1"	3 (2.4)	1 (2.6)	2 (2.3)	
	"1-1"	56 (45.2)	16 (41.0)	40 (47.1)	
	"1-0"	42 (33.9)	16 (41.0)	26 (30.6)	

p_1 – significance of difference between MAEs and non-MAEs groups, p_2 – significance of difference in the frequency of use of a class of drugs at follow-up

MRA – mineralocorticoid receptors antagonists, MAEs – major adverse events

patients interrupted the previously prescribed therapy with a combination of three neurohumoral modulators (Table 4). To explain these data, it is important to take into account the predominant use of two (rather than three) neurohumoral modulators in the absence of a pronounced decrease in LV systolic function, as well as improvement or even restoration of LV systolic function in some patients with baseline LVEF <40% [6]. At the same time, taking into account the preservation of neurohumoral activation and the risk of further deterioration of LVEF (including the post-CABG one) [23,24], basic pharmacotherapy is potentially capable of modifying the course of the disease and slowing down the progression of HF in patients with LVEF in the «intermediate» range and among individuals who switched to the category of "restored" LV systolic function [17,25,27]. On the other hand, early interruption of the use of neurohumoral modulators may lead to the further decrease in LVEF and HF decompensation [28].

From the standpoint of current guidelines on pharmacotherapy of HF [5-7], "triple" neurohumoral blockade (ACEI/ARBs, BBs and MRAs) is an integral component of the management of CAD patients with reduced LVEF. At the same time, data from real clinical practice testify to poor adherence to basic drug treatment of HF, including post-CABG one [4,10,19].

Recently an analysis of pharmacotherapy in seven randomized trials of myocardial revascularization – CAS (total n=3542) and CABG (total n=11397) was published [4]. Significant differences were noted in the frequency of prescription and intake at follow-up after the CABG of the studied groups of drugs, in particular RAS blockers (18-62% at discharge, and 21.7-72.2% at follow-up) and BBs (35,3-92.5% at discharge, and 37-94.1% — at follow-up) [4]. Patients after CABG showed worse adherence to the recommended pharmacotherapy than after CAS, while after 5-year follow-up, the association of clinical outcomes with adherence to pharmacotherapy was determined. In particular, the advantages of CABG over CAS in long-term outcomes were set off due to the insufficient ad-

Table 4. The administration of triple basic HF therapy (ACEI/ARB+BB+MRA) at discharge and follow-up

Variable		All patients (n=124)	Patients with MAEs (n=39)	Non-MAEs patients (n=85)	p_1
Prescription frequency at discharge, n (%)		82 (66.1)	25 (64.1)	57 (67.1)	0.747
Intake frequency at follow-up, n (%)		48 (38.7)	13 (33.3)	35 (41.2)	0.405
p_2		<0.001	0.002	<0.001	–
Administration at follow-up, n (%)	"0-0"	38 (31.0)	13 (33.3)	25 (29.4)	0.873
	"0-1"	4 (3.0)	1 (2.6)	3 (3.5)	
	"1-1"	44 (35.0)	12 (30.8)	32 (37.7)	
	"1-0"	38 (31.0)	13 (33.3)	25 (29.4)	

p_1 – significance of difference between MAEs and non-MAEs groups, p_2 – significance of difference in the frequency of use of a class of drugs at follow-up

HF – heart failure, ACEI – angiotensin converting enzyme inhibitors, ARB – angiotensin-II receptors blockers, BB – beta-blockers, MRA – mineralocorticoid receptors antagonists, MAEs – major adverse events

herence to the prescribed treatment. Populations selected for the analysis of studies were characterized by a small number of patients with systolic LV dysfunction [4].

Data on the dynamics of the intake frequency of RAS blockers after isolated CABG, as well as on the association of more poor adherence to ACEI/ARBs treatment with the prognosis are consistent with the results of a recently published study [10], performed in a clinical practice setting. The authors revealed a decrease in the intake frequency of RAS blockers from 72.9% (baseline) to 65.9% (at 8-year follow-up) and the associative relationship of long-term use of these drugs with survival. This study also showed a high baseline frequency of BBs prescription (91.0%), as well as a decrease in this indicator at follow-up (up to 76.4%); at the same time, the indicated specifics of BBs use did not affect the long-term prognosis. However, it should be taken into account that the studied sample included patients with both chronic and acute forms of CAD and the rate of patients with LVEF<50% was only 30.0%. It should be noted that no data were available on the use of MRAs in these studies [4,10].

Clinical characteristics of our sample of patients most closely resembled those in the STICH study [29] involving CAD patients with LVEF≤35% and multi-vessel coronary bed lesions. The authors demonstrated a high frequency in the number of RAS blockers prescriptions (91%) and BBs (83%) after CABG, maintenance of the proper adherence rate to the use of these groups of drugs at the 5-year follow-up stage (89% and 90%, respectively); a slight decrease in the frequency of use ACEI/ARBs at the 10-year follow-up stage (83%), in contrast to BBs (87%). The frequency of the baseline MRAs prescription rate was significantly lower (46%), however, it increased and remained uniform throughout follow-up (54% at 5- and 10-year follow-up). At the same time, it should be noted that STICH study did not enroll patients with baseline LVEF in the range of 36% to 49%, which limits the possibility of extrapolating the results to the entire spectrum of patients with LVEF <50%, including the so-called "gray" zone (40-49%). Furthermore, when studying adherence to basic pharmacotherapy in patients with systolic LV dysfunction, changes in the dynamics of

LVEF after surgical myocardial revascularization should be taken into account.

Limitations

Limitations of the clinical interpretation of the results include the uncontrolled design of the study; the need to adjust for other factors that potentially affect the risk of MAEs, including the use of survival analysis; relatively low response after 3 years of follow-up; use of the frequency of drug administration at follow-up as a surrogate indicator of adherence; lack of information on possible subjective and objective reasons for interrupting the intake of certain drugs; the fact that improvement or restoration of LV systolic function in patients with baseline LVEF<40% at follow-up after CABG potentially impacts the appropriateness of prescribing certain groups of drugs. Moreover, the results obtained in real clinical practice setting reflect the problem of insufficient adherence to basic pharmacotherapy, which can offset the beneficial effect of CABG on the course of the disease. At a long-term follow-up of patients after CABG one should take into account the established associative relationship between the development of adverse events and the decreased intake frequency of RAS blockers.

Conclusions

During 3-year follow-up after isolated CABG, about one third of patients with stable CAD and baseline LVEF<50% interrupted triple basic HF therapy (including ACEI/ARBs, BBs and MRAs), mainly due to the decrease in the frequency of use of RAS and MRA blockers. MAEs at three-year follow-up in patients after isolated CABG were associated with suboptimal use and more frequent interruption of RAS blockers (ACEI/ARBs) therapy. Compliance with the current guidelines on basic pharmacotherapy of patients with stable CAD and LV dysfunction, as well as adherence to the prescribed treatment are crucial in reducing the risk of cardiovascular complications at the later stages after surgical myocardial revascularization.

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References

1. Yanagawa B., Lee J., Puskas J.D., Verma S. Revascularization in left ventricular dysfunction: an update. Curr Opin Cardiol. 2019;34(5):536-42. DOI:10.1097/HCO.0000000000000662.

2. Kulik A., Ruel M., Jneid H., et al. Secondary prevention after coronary artery bypass graft surgery. Circulation. 2015;131(10):927-64. DOI:10.1161/CIR.0000000000000182.

3. Sousa-Uva M., Head S., Milojevic M., et al. 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg. 2017;53(1):5-33. DOI:10.1093/ejcts/ezx314.

4. Pinho-Gomes A., Azevedo L., Ahn J., et al. Compliance with guideline-directed medical therapy in contemporary coronary revascularization trials. JACC. 2018;71(6):591-602. DOI:10.1016/j.jacc.2017.11.068.

5. Ponikowski P., Voors A., Anker S., et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37(27):2129-200. DOI:10.1093/eurheartj/ehw128.

6. Yancy C.W., Jessup M., Bozkurt B., et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-239. DOI:10.1016/j.jacc.2013.05.019.

7. Yancy C.W., Jessup M., Bozkurt B., et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. Circulation. 2017;136:e137-61. DOI:10.1161/CIR.0000000000000509.

8. Ali M., Yasir J., Sherwani R., et al. Frequency and predictors of non-adherence to lifestyle modifications and medications after coronary artery bypass grafting: A cross-sectional study. Indian Heart J. 2017;69(4):469-73. DOI:10.1016/j.ihj.2017.05.017.

9. Sengstock D., Vaitkevicius P., Salama A., Mentzer R.M. Under-prescribing and non-adherence to medications after coronary bypass surgery in older adults. Drugs & Aging. 2012;29(2):93-103. DOI:10.2165/11598500-000000000-00000.

10. Björklund E., Nielsen S.J., Hansson E.C., et al. Secondary prevention medications after coronary artery bypass grafting and long-term survival: a population-based longitudinal study from the SWEDEHEART registry. Eur Heart J. 2019. pii: ehz714. DOI:10.1093/eurheartj/ehz714. [Epub ahead of print].

11. Drenger B., Fontes M., Miao Y., et al. Patterns of use of perioperative angiotensin-converting enzyme inhibitors in coronary artery bypass graft surgery with cardiopulmonary bypass. Circulation. 2012;126(3):261-9. DOI:10.1161/CIRCULATIONAHA.111.059527.

12. Griffo R., Ambrosetti M., Tramarin R., et al. Effective secondary prevention through cardiac rehabilitation after coronary revascularization and predictors of poor adherence to lifestyle modification and medication. Results of the ICAROS Survey. Int J Cardiol. 2013;167(4):1390-5. DOI:10.1016/j.ijcard.2012.04.069.

13. Szychta W., Majstrak F., Opolski G., Filipiak K.J. Trends in pharmacological therapy of patients referred for coronary artery bypass grafting between 2004 and 2008: a single-centre study. Kardiol Pol. 2015;73(12):1317-26. DOI:10.5603/KP.a2015.0094.

14. Lang R.M., Badano L.P., Mor-Avi V., et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14. DOI:10.1016/j.echo.2014.10.003.

15. Montalescot G., Sechtem U., Achenbach S., et al. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J. 2013;34(38):2949-3003. DOI:10.1093/eurheartj/eht296.

16. Khanderia U., Townsend K., Erickson S., et al. Medication adherence following coronary artery bypass graft surgery: assessment of beliefs and attitudes. Ann Pharmacother. 2008;42(2):192-9. DOI:10.1345/aph.1K497.

17. Webb J., Draper J., Fovargue L., et al. Is heart failure with mid-range ejection fraction (HFmrEF) a distinct clinical entity or an overlap group? Int J Cardiol Heart Vasc. 2018;21:1-6. DOI:10.1016/j.ijcha.2018.06.001.

18. Koh A.S., Tay W.T., Teng T.H.K., et al. A comprehensive population based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail. 2017;19:1624-34. DOI:10.1002/ ejhf.945.

19. Ruel M., Kulik A. Suboptimal Medical Therapy After Coronary Revascularization: A Missed Opportunity. J Am Coll Cardiol. 2018;71(6):603-5. DOI:10.1016/j.jacc.2017.12.007.

20. Kalavrouziotis D., Buth K.J., Cox J.L., Baskett R.J. Should all patients be treated with an angiotensin-converting enzyme inhibitor after coronary artery bypass graft surgery? The impact of angiotensin-converting enzyme inhibitors, statins, and β-blockers after coronary artery bypass graft surgery. Am Heart J. 2011;162(5):836-43. DOI:10.1016/j.ahj.2011.07.004.

21. Rouleau J.L., Warnica W.J., Baillot R., et al. Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. Circulation. 2008;117(1):24-31. DOI:10.1161/CIRCULATIONAHA.106.685073.

22. Drenger B., Fontes M.L., Miao Y., et al. Patterns of use of perioperative angiotensin-converting enzyme inhibitors in coronary artery bypass graft surgery with cardiopulmonary bypass: effects on in-hospital morbidity and mortality. Circulation. 2012;126(3):261-9. DOI:10.1161/CIRCULATIONAHA.111.059527.

23. Ngu J.M.C., Ruel M., Sun L.Y., et al. Left ventricular function recovery after revascularization: comparative effects of percutaneous coronary intervention and coronary artery bypass grafting. Curr Opin Cardiol. 2018;33(6):633-7. DOI:10.1097/HCO.0000000000000566.

24. Unkovic P, Basuray A. Heart Failure with Recovered EF and Heart Failure with Mid-Range EF: Current Recommendations and Controversies. Curr Treat Options Cardiovasc Med. 2018;20(4):35. DOI:10.1007/s11936-018-0628-9.

25. Tsuji K., Sakata Y., Nochioka K., et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. Eur J Heart Fail. 2017 Oct;19(10):1258-69. DOI:10.1002/ejhf.807.

26. Lund L.H., Claggett B., Liu J., et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail. 2018;20(8):1230-9. DOI:10.1002/ejhf.1149.

27. Lupón J., Gavidia-Bovadilla G., Ferrer E., et al. Dynamic Trajectories of Left Ventricular Ejection Fraction in Heart Failure. J Am Coll Cardiol. 2018;72(6):591-601. DOI:10.1016/j.jacc.2018.05.042.

28. Halliday B.P., Wassall R., Lota A.S., et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet. 2019;393(10166):61-73. DOI:10.1016/ S0140-6736(18)32484-X.

29. Velazquez E.J., Lee K.L., Jones R.H., et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. N Engl J Med. 2016;374(16):1511-20. DOI:10.1016/j.jacc.2019.08.001.

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