Inpatient and outpatient cardiac rehabilitation programmes improve cardiometabolic risk in revascularized coronary patients with type 2 diabetes

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Abstract

The *purpose* of this paper is to evaluate cardiometabolic risk reduction of diabetic patients following coronary revascularization procedures after participation in outpatients or inpatients cardiac rehabilitation programmes. *Materials and methods:* we performed a retrospective analytical study which included a group of 103 revascularized coronary patients with diabetes mellitus. Depending on participation in a cardiac rehabilitation program we have defined the following subgroups of patients: Group O (N=37) - attended the outpatient cardiac rehabilitation program; Group H (N=37) - attended the inpatient cardiac rehabilitation program; Group C (N=34) - did not participate in any cardiac rehabilitation program. Between those two moments of assessment: T0 - revascularization / early post-revascularization and T1 - time of the interview (16±2.3 months after revascularization), patients in groups A and S participated in outpatient cardiac rehabilitation program (12 weeks, 3 sessions/week of exercise training, with clinical and paraclinical evaluation scheduled at 1, 6, 12 months after revascularization), or inpatient cardiac rehabilitation program (3 weeks, intensive sessions, scheduled at 1, 3, 6 and 12 months after revascularization). *Results:* at the end of the study, we found significant differences among the three groups for the following parameters: body mass index (p=0.01), systolic blood pressure (p=0.002), total cholesterol (p<0.001), LDL-cholesterol (p<0.001) and non-HDL cholesterol (p=0.004) in favor of groups A and S, that have participated in comprehensive cardiac rehabilitation programs. *Conclusions:* comprehensive cardiac rehabilitation programmes, performed outpatient or inpatient, are effective methods of reducing the high cardiometabolic risk, specific in revascularized coronary patients with diabetes.

Key words: *cardiac rehabilitation, cardiometabolic risk, diabetes mellitus*

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Rezumat

Scopul lucrarii constă în evaluarea beneficiilor obţinute asupra reducerii riscului cardiometabolic prin participarea la programe comprehensive de recuperare cardiovasculară în spital sau în ambulator a pacienţilor coronarieni revascularizaţi care prezintă asociat diabet zaharat. *Material şi metodă*: In cadrul unui studiu analitic retrospectiv a fost selectat un numar de 103 pacienţi coronarieni revascularizaţi cu diabet zaharat. În funcţie de participarea acestor pacienti la programe de recuperare cardiovasculară s-a constituit grupul de pacienti care a participat la programul de recuperare cardiovasculară din ambulator: Grupul A (N=37); grupul de pacienţi care a participat la programul de recuperare cardiovasculară din spital: Grupul S (N=32) şi grupul de pacienti care nu a participat la programe de recuperare cardiovasculară: Grupul C (N=34). Intre cele doua momente ale evaluarii, T0 – momentul revascularizării/post-revascularizare precoce si T1 - momentul interviului (16±2,3 luni post-revascularizare), pacientii din Grupurile A si S au participat la programul de recuperare cardiovasculară in ambulator (12 săptămâni de antrenamnet fizic supravegheat, 3 şedinţe/săptămână cu evaluare clinică şi paraclinică la 1, 6, 12 luni post-revascularizare); si respectiv in spital (sesiuni intensive, cu durata de 3 săptămâni, programate la un interval de 1, 3, 6 şi 12 luni post revascularizare). *Rezultate*: La finalul studiului am constatat diferenţe semnificative între cele trei grupuri pentru următorii parametrii: indice de masă corporală (p=0,01), tensiune arteriala sistolică (p=0,002), colesterol total (p<0,001), LDL-colesterol (p<0,001) şi Non-HDL colesterol(p=0,004) in favoarea grupurilor A si S care au participat în programe comprehensive de recuperare cardiovasculară. *Concluzii*: Recuperarea cardiovasculară comprehensivă, desfăşurată în spital sau în ambulator, reprezintă o metodă eficientă de reducere a riscului cardiometabolic crescut, specific coronarianului cu diabet zaharat.

Cuvinte-cheie: *recuperare cardiovasculară, risc cardiometabolic, diabet zaharat*

Introduction

High cardiovascular residual risk after revascularization procedures requires a comprehensive approach: proper medication administration, cardiovascular risk factors control and periodic reevaluation, ideally provided by including such patients in cardiac rehabilitation programs.

Individualized and comprehensive application of cardiac rehabilitation programs in revascularized patients conduct to: improved exercise capacity; decrease in cardiovascular mortality; slower progress or even regression of coronary atherosclerosis through secondary prevention measures; development and improved quality of life; lower long-term medical care costs. (1) These objectives can be achieved by the coronary disease patients after a comprehensive intervention including individual exercise training programs and lifestyle changes interventions, aiming to reducing cardiovascular risk factors and optimizing cardio-protective drug therapy recommendations.

The severity of atherothrombotic damage in diabetes is markedly increased; the risk of post-myocardial revascularization complications is greater than that of non-diabetic coronary patients, indifferent of the type of revascularization procedure applied. EuroAspire trials I (1995-1996), II (1999-2000) and III (2006-2008) have demonstrated an insufficient control of cardiovascular risk factors, especially obesity, diabetes, smoking and hypertension, in patients with known coronary artery disease. (2) Therefore, risk factors control through preventive measures is increasingly becoming a health priority.

In this context, the **purpose** of this paper is to evaluate cardiometabolic risk reduction of diabetic

patients following coronary revascularization procedures after participation in outpatients or inpatients cardiac rehabilitation programmes.

Materials and methods

We performed a retrospective analytical study which included a group of revascularized coronary patients from hospital arm of European multicenter survey *EuroAspire III Romania*, conducted in 2006-2007 at the *Institute of Cardiovascular Diseases from Timisoara*.

The group of patients: were included a total of 103 coronary patients with diabetes mellitus (DM) following a myocardial revascularization procedure (percutaneous transluminal angioplasty with vascular implant placement or aorto-coronary bypass).

Depending on participation in a cardiac rehabilitation program we have defined the following subgroups of patients:

- coronary group who attended the outpatient cardiac rehabilitation program: Group O (N=37);
- coronary group who attended the inpatient cardiac rehabilitation program: Group H (N=37);
- coronary group that did not participate in cardiac rehabilitation program: Group C (N=34).

Evaluation of patients was done at two different times:

- T0 - revascularization time or early post-revascularization;
- T1 - interview time: 16±2.3 month post-revascularization.

Cardiac rehabilitation programme:

- Inpatients rehabilitation: consisted in intensive sessions, lasting for 3 weeks, scheduled at an interval of 1, 3, 6 and 12 months after revascularization, during which the patient was hospitalized. Structure: clinical and paraclinical

assessment, optimize the therapeutic treatment, supervised exercise training, lifestyle changes advice, psychological counseling.

- Outpatients rehabilitation: 12 weeks of supervised exercise training, at least three sessions per week. Structure: clinical and paraclinical evaluation at 1, 6, 12 months post-revascularization, optimize the therapeutic treatment, lifestyle changes advice, psychological counseling.

Statistical analysis:

- parametric variables were expressed as mean ± standard deviation;
- we used Student paired / unpaired t test for comparison of two parametric variables;
- Anova test was used for comparing three or more parametric variables;
- Fisher test was used to compare categorical variables;
- we considered statistically significant p values <0.05.

Results

The results provide an overview of the steps of identifying both cardiovascular risk factors and their management, together with the efficiency and the degree of implementation of current guidelines recommendations for secondary prevention in coronary revascularized patients.

At T0, all patients in the 3 groups were overweight, had overcome recommended target value for blood lipids and they not reached an effective control of fasting plasma glucose (FPG). At this time there were no significant differences among patients in the three study groups in terms of investigated cardiovascular risk factors.

At T1, we obtained significant improvements in cardiovascular risk profile of patients in group O and group H. Diabetic patients in group C had a different pattern of analyzed clinical and metabolic

parameters, statistically significant only for HDL and non-HDL cholesterol (Table I). Although at baseline (T0) there were no significant differences between the 3 groups, at T_1, we found significant differences for the following parameters: BMI (p=0.01), SBP (p=0.002), TC (p<0.001), LDL cholesterol (p<0.001) and Non-HDL cholesterol (p=0.004). Also, differences between the mean PP and FPG at the end of the study, were close to the statistical significance threshold (p=0.052 and p=0.053) (Table II).

Table I. Trend of cardiovascular risk factors in the 3 groups

Variables	Group O			Group H			Group C		
	T0	T1	p	T0	T1	p	T0	T1	p
BMI (kg/m²)	27.6±3.6	26.1±3.5	<0.001	28.9±4.6	28.5±4.7	0.051	28.3±4	29.2±4.6	0.006
Hemodynamic Profile									
SBP (mmHg)	133.2±26	125±17.8	<0.001	135.3±24.4	126.1±13.9	0.004	135.6±22.2	138.7±19.7	ns
DBP (mmHg)	77.7±12	76.22±9.6	ns	78.9±13.3	77.1±11.5	0.039	80.4±10.9	81.6±10.2	ns
MBP (mmHg)	96.2±16.1	92.48±11.5	<0.001	97.7±15.7	93.4±11.2	0.002	98.8±12.9	98.7±11	ns
PP (mmHg)	55.54±16.7	48.7±12.2	0.001	56.4±17.6	48.9±10.8	0.012	55.1±18.4	56.2±17	ns
BP (b/min)	67.1±9.8	67.1±7.1	ns	71.1±11.5	72±8.7	ns	69.7±11.7	70.7±10.6	ns
Lipid profile									
TC (mg/dl)	202.2±43.2	179.9±27.8	<0.001	204.8±68.2	178.6±33	0.004	208.8±47.4	215.8±47.5	ns
LDL (mg/dl)	120.5±23.7	103.8±18.7	<0.001	123.8±33.4	101.9±30.3	0.006	133.4±51.2	142.8±48.4	ns
HDL (mg/dl)	37.8±9.2	39.9±7.8	0.001	41.9±12.7	43.8±9.4	ns	42±8.1	40.5±7.8	0.003
TG (mg/dl)	186.9±98.1	169.9±76.7	0.004	217.8±108.7	174.7±77.2	0.002	207.1±93.9	215.5±93.3	ns
Non-HDL (mg/dl)	174.1±47.4	150.2±32.1	<0.001	176.7±71.5	151.8±39.8	0.007	163.6±45.7	180.4±44.8	0.028
Glycemic profile									
FPG (mg/dl)	125.5±37.4	115.1±27	<0.001	116±36.7	106.3±21	0.004	115.5±33.1	122.2±27.3	ns
HbA1c (%)	7.72±1.22	7.12±1.34	ns	7.64±1.29	7.03±1.07	ns	7.59±1.19	7.86±1.35	ns

Table II. Cardiometabolic risk factors comparison in the 3 groups, at the end of the study

Variables	Group O at T1 (n=37)	Group H at T1 (n=32)	Group C at T1 (n=34)	p
BMI (kg/m²)	26.1±3.5	28.5±4.79	29.2±4.6	0.01
Hemodynamic Profile				
SBP (mmHg)	125±17.8	126.1±13.9	138.7±19.7	0.002
DBP (mmHg)	76.2±9.6	77.1±11.5	81.6±10.2	ns
MBP (mmHg)	92.4±11.5	93.4±11.2	98.7±11	ns
PP (mmHg)	48.7±12.27	48.9±10.8	56.2±17	0.052
Lipid profile				
TC (mg/dl)	179.9±27.8	178.6±33	215.8±47.5	<0.001
LDL (mg/dl)	103.8±18.7	101.9±30.3	142.8±48.4	<0.001
HDL (mg/dl)	39.9±7.8	43.8±9.4	40.5±7.8	ns
TG (mg/dl)	169.9±76.7	174.7±77.2	215.5±93.3	ns
Non-HDL(mg/dl)	150.2±32.1	151.8±39.8	180.4±44.8	0.004
Carbohydrate profile				
FPG (mg/dl)	125.5±37.41	116.0±36.76	115.5±33.11	0.053
HbA1c (%)	7.12±1.34	7.03±1.07	7.86±1.35	ns

Notes (for tables I and II): Values are expressed as mean ± standard deviation. Legend: **SBP** - systolic blood pressure; **DBP** - diastolic blood pressure; **MBP** – mean blood pressure; **PP** - pulse pressure; **BP -** heart rate; **TC** – total cholesterol; **LDL** – low-density-lipid cholesterol; **HDL** - high-density-lipid cholesterol; **TG** - triglycerides; **FPG** – fasting plasma glucose.

Mean BMI significantly decreased in Group O after 16 months of ambulatory intervention (-1.5 kg/m²; p<0.001).

BMI reduction of 0.5 kg/m² was noticed in Group H, but the value didn't reach the statistical significance threshold; and patients in Group C had an increased BMI at the end of the study (+0.9 kg/m²; p=0.006) (figure 1).

Systolic blood pressure had a favorable trend in Group O (-8.2 mmHg, p<0.001), respectively in Group H (-9.2 mmHg, p=0.004), but a poor control in Group C (+3.1 mmHg, p=0.034) (figure 2).
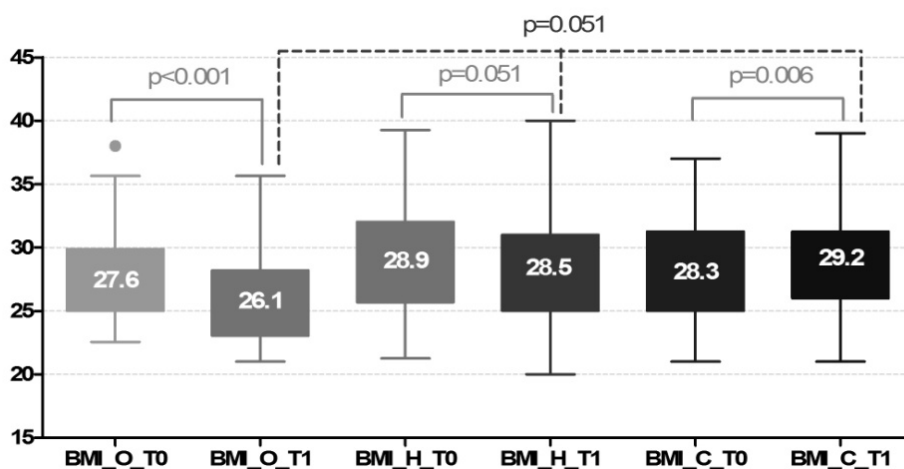

Figure 1. The mean body mass index in the 3 groups when compared to T0-T1.

Legend: **BMI_O_T0** - body mass index in Group O at T0; **BMI_O_T1-** body mass index in Group O at T1; **BMI_H_T0** - body mass index in Group H at T0; **BMI_H_T1-** body mass index in Group H at T1; **BMI_C_T0** - body mass index in Group C at T0; **BMI_C_T1** - body mass index in Group C at T1.
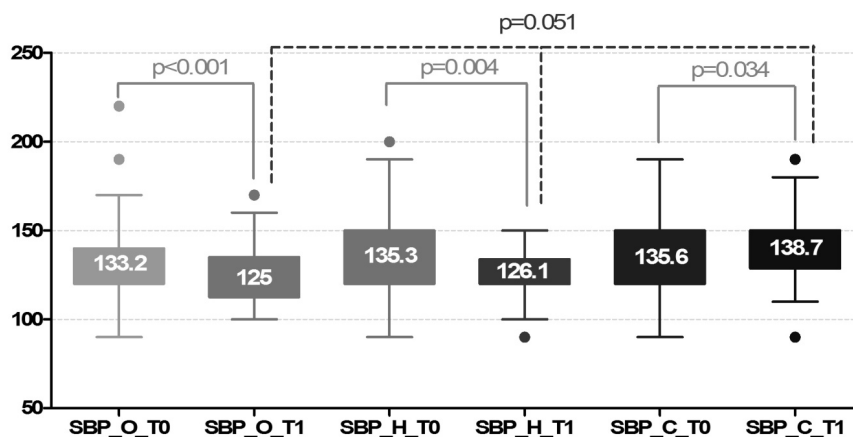

Figure 2. The mean systolic blood pressure in the 3 groups when compared T0-T1

Legend: **SBP_O_T0** - systolic blood pressure in Group O at T0; **SBP_O_T1-** systolic blood pressure in Group O at T1; **SBP_H_T0** - systolic blood pressure in Group H at; **SBP_H_T1-** systolic blood pressure in Group H at T1; **SBP_C_T0** - systolic blood pressure in Group C at T0; **SBP_C_T1-** systolic blood pressure in Group C at T1.

We obtained at the end of the study a significant decrease (p<0.001) of mean total cholesterol in patients from Group O and Group H, while in Group C there was noticed a non significant unfavorable trend (figure 3).

Significant differences between groups was obtained regarding LDL cholesterol comparison at the end of the study (p<0.001). We also noticed a significant decrease of LDL cholesterol in Group O (with -16.7 mg/dl, p<0.001) and in Group H (with -11.9 mg/dl, p=0.006); however, mean LDL cholesterol in the two patient groups has not reached the target recommended by the current treatment guidelines (figure 4).
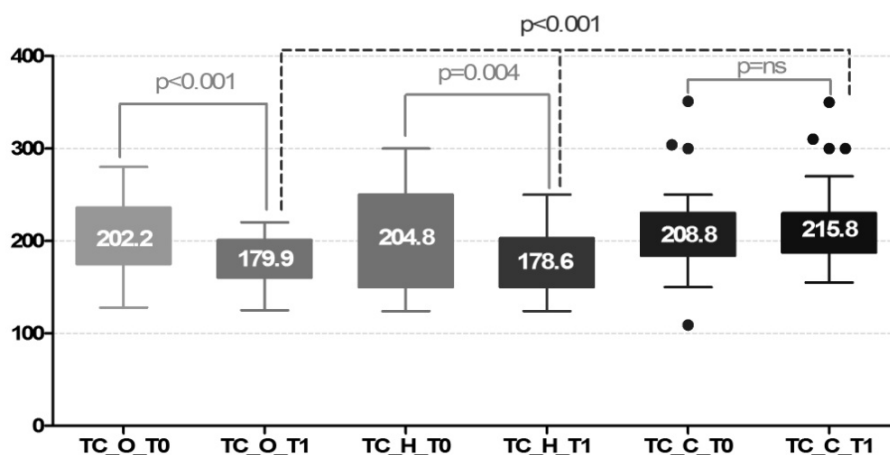
Figure 3. The mean of total cholesterol in the 3 groups when compared T_0-T_1

Legend: **TC_O_T0** - total cholesterol in Group O at T0; **TC_O_T1-** total cholesterol in Group O at T1; **TC_H_T0** - total cholesterol in Group H at T0; **TC_H_T1-** total cholesterol in Group H at T1; **TC_C_T0** - total cholesterol in Group C at T0; **TC_C_T1-** total cholesterol in Group C at T1
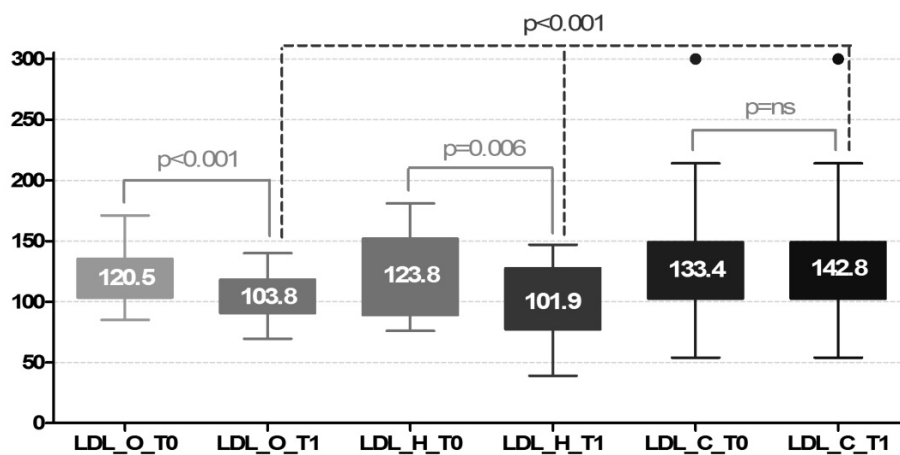

Figure 4. Mean of LDL cholesterol at diabetic patients in the 3 groups when compared T0-T1

Legend: **LDL_O_T0** - LDL cholesterol in Group O at T0; **LDL_O_T1-** LDL cholesterol in Group O at T1; **LDL_H_T0** - LDL cholesterol in Group H at T0; **LDL_H_T1-** LDL cholesterol in Group H at T1; **LDL_C_T0** - LDL cholesterol in Group C at T0; **LDL_C_T1-** LDL cholesterol in Group C at T1.

At T0 there were no significant differences between the proportions of patients in the 3 groups who achieved the targets recommended by the current therapeuitc guidelines. The best controlled risk factor at the beginning of the study was hypertension, although optimal blood pressure control was achieved in approximately one quarter of the 3 groups of patients (figure 5). At T1, in Group O there was a significantly increase in the number of patients who obtained the optimal control of risk factors analyzed: 29% more patients had a good blood pressure control (p<0.001), 43% more patients had mean total cholesterol less than 175mg/dl (p<0.001) and 31% more patients had optimal control of LDL cholesterol (p<0.001). The number of patients who achieved an optimal glycemic control at the end of the study increased by only 12%, but this trend was statistically significant p=0.008 (figure 6).
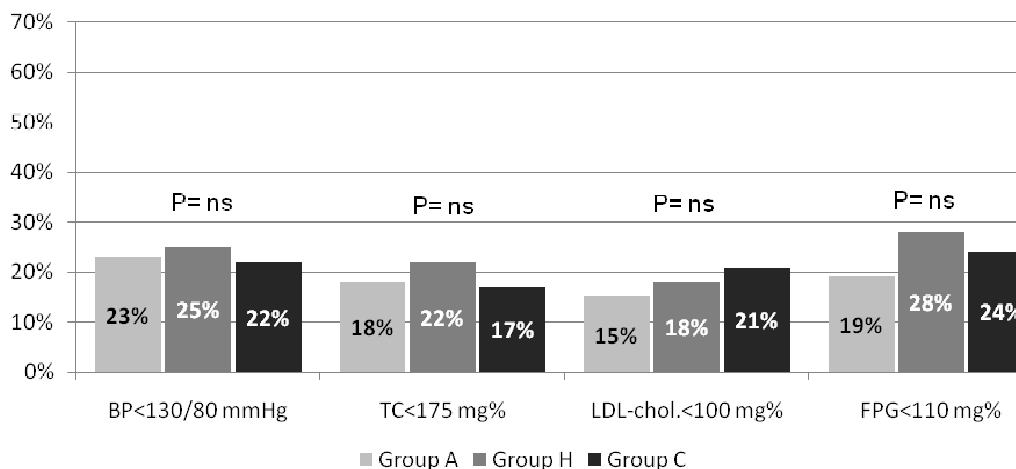

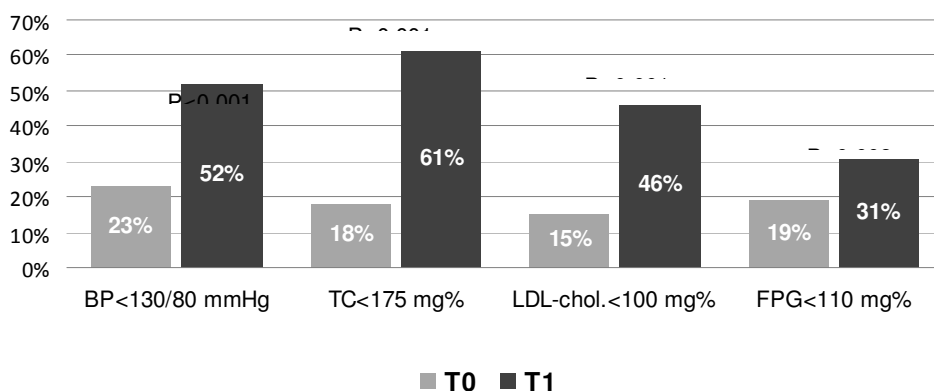**Figure 5.** Reaching therapeutic targets for major cardiometabolic risk factors in the 3 groups at baseline

Figure 6. Reaching therapeutic targets for major cardiometabolic risk factors in patients from Group O when compared T0-T1
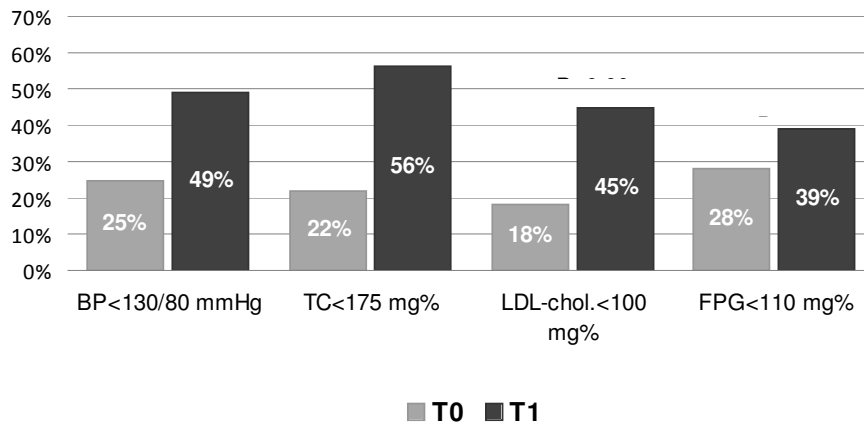
Figure 7. Reaching therapeutic targets for major cardiometabolic risk factors in patients from Group H when compared T0-T1
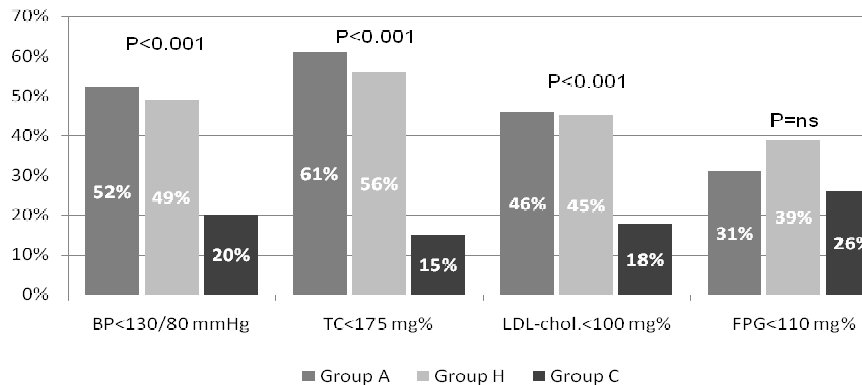

Figure 8. Reaching therapeutic targets for major cardiometabolic risk factors in the 3 groups at the end of the study.

In Group H there was a significant improvement in the number of patients who reached an optimal control of risk factors at the end of the study; it effectively doubled the number of those that controled blood pressure (p=0.003); the number of those who had improved lipid profile increased with 34% for total cholesterol (p<0.001), respectively 27% for LDL-cholesterol (p<0.001) and 11% for fasting plasma glucose (p=0.002) (figure 7). In Group C we observed no significant differences regarding therapeutic targets at T1 when compared with T0. The number of patients who controled blood pressure and blood lipids decreased by 2%, and of those who attained the recommended lipid targets,

but p=ns. At T1 there were significant differences between the 3 groups on the number of patients who attained recommended guidelines goals for blood pressure (p<0.001), total cholesterol (p<0.001) and LDL-cholesterol (p<0.001) (figure 8).

Discussions

The severity of atherothrombotic process in diabetic patients is markedly increased; risk of complications post-myocardial revascularization is higher than in patients without diabetes, regardless of the revascularization procedure applied. Lesional substrate of the coronary artery is complex, diabetic

patient usually presenting multiple lesions, disseminated throughout the coronary, which increases the difficulty of revascularization procedures. [3] The cardiovascular morbidity and mortality risk in patients with diabetes is 2 to 6 times higher when compared with subjects without diabetes, which causes shortening life expectancy by 5 to 10 years. [4]

Clinical trials over the past 10 years have demonstrated the benefit of comprehensive interventions in the management of coronary patients with diabetes. *Steno-2* study showed the effectiveness of comprehensive intervention, based on lifestyle changes and medication, to achieve the optimization of therapeutic targets, and reducing by 50% the incidence of major cardiovascular events. [5] *Steno-2 Study Follow-up* reconsidered after an interval of 13.3 years the evaluation of patients undergoing multi-factorial intervention in the Steno-2 study. It was observed that patients who received optimal medication, in the recommended dosage, showed a 20% reduction (p<0.001) of the absolute risk of cardiovascular events. Intensive treatment was also associated with a lower risk of cardiovascular death (p<0.04) and cardiovascular events (p<0.001). [6]

Laurent and colleagues published in 2010 a study that analized the benefit of cardiac rehabilitation programmes in coronary patients with diabetes. The study compared diabetic patients with coronary heart disease (n=413) with coronary artery disease without diabetes (n=614) at baseline and at the end of a comprehensive cardiac rehabilitation program. At the end of the study, both groups of patients improved their cardiovascular risk profile. In the coronary diabetics group, the improvement was significant for the following parameters: systolic blood pressure (133.8±20.3mmHg vs 127.6±16.4, p=0.01), diastolic blood pressure (83.7±11.3 mmHg

vs 28.6±9.3 mmHg, p=0.039), LDL-cholesterol (115.8±20.3 mg/dl vs 101±10.9, p=0.01), triglycerides (175.3±32.5 mg/dl vs 143.5±14.3 mg/dl) and glycosylated hemoglobin (7.7% vs 6.8%, p=0.004). [7]

In our study we noticed a similar trend of cardiovascular risk factors in patients who participated in both inpatient and outpatient cardiac rehabilitation programmes. Patients in Group O, who attended the outpatient rehabilitation program, had a significant decrease in the mean values of the following parameters: systolic blood pressure (from 133.2±26 mmHg to 125±17.8 mmHg, p<0.001) LDL-cholesterol (from 120.5±23.7 mg/dl to 103.8±18.7 mg/dl, p<0.001), fasting plasma glucose (from 125.5±37.4 mg/dl to 115.1±27 mg/dl, p<0.001); they also increased HDL cholesterol (from 37.8±9.2 mg/dl to 39.9±7.8 mg/dl, p=0.001) as well as decrease of the body mass index (from 27.6±3.6 kg/m² to 26.1±3.5 kg/m², p<0.001). Patients in Group H, included in the inpatient cardiac rehabilitation programme, showed a significant decrease in mean values for the following parameters: systolic blood pressure (from 135.3±24.4 mmHg to 126.1±13.9 mmHg, p=0.004), diastolic blood pressure (from 78.9±13.3 mmHg to 77.1±11.5 mmHg, p=0.039), LDL-cholesterol (from 123.8±33.4 mg/dl to 101.9±30.3 mg/dl, p=0.006) and fasting plasma glucose (from 116±36.7 mg/dl to 106.3±21 mg/dl, p=0.004).

Patients who did not attend a cardiac rehabilitation programme, significantly increased weight and failed to achieve an improvement in the cardiovascular risk profile, at the end of the study.

Studies have shown that therapeutic targets are difficult to achieve. In the *Steno-2* study, for example, glycemic control was the most difficult to obtain: approximately 20% of diabetic patients had glycosylated hemoglobin of less than 6.5%.

Approximately half of the subjects had optimal blood pressure, and 75% of subjects reached the recommended targets for total cholesterol and LDL-cholesterol. [5]

Comparable data were identified in an *observational study* which included 1612 diabetic patients diagnosed with coronary heart disease, divided into two groups according to time of diagnosis, consecutively identified from the Swedish National Diabetes Register. An optimal glycemic control was achieved in half of the patients (p<0.01); 31% of the first group of patients vs. 60% of the the second group (p<0.001); only 49% from patients in the first group vs. 65% in the second group had an LDL cholesterol <2.5 mmol/l (p <0.001). [7] Analysis carried out at the end of our study showed comparable data to those presented above. Approximately half of coronary patients with diabetes obtained at the end of the study an optimal control of blood pressure in the groups who participated in rehabilitation programmes (52% in Group O vs 49% in Group H, p<0.001) comparing with only 20% of patients in Group C. At the end of the study, total cholesterol was the best controlled modifiable risk factor by the patients who participated in cardiac rehabilitation progra-mmes (61% in Group O vs 56% in Group H vs 15% in Group C, p<0.001). The optimal level of LDL-cholesterol was achieved in 46% patients from Group O vs 45% of patients from Group H vs 18% of patients from Group C, p <0.001. In our study, optimal glycemic control was the most difficult to obtain (31% patients in Group O vs 39% patients in Group H vs 26% patients in Group C, p=ns).

Conclusions

Both inpatient and outpatient cardiac rehabilitation programmes are efficient in reducing cardiovascular

risc in revascularized coronary patients with diabetes.

The number of patients reaching guidelines recommendations for cardiovascular risk factors, increased significantly at the end of the study in both groups who attend cardiac rehabilitation programmes. Total cholesterol was the risk factor most tightly controlled; about half of the patients obtained the guideline recommendation for blood pressure; and glycemic control was most difficult to obtain.

Comprehensive cardiac rehabilitation programmes, performed outpatient or inpatient, are effective methods of reducing the high cardiometabolic risk, specific in coronary patients with diabetes mellitus.

References

1. Piepoli M., Corra U., Benzer W. et al. (2009) *Secondary prevention through cardiac rehabilitation from knowledge to implementation: a position paper from the cardiac rehabilitation section of the European association of cardiovascular prevention and rehabilitation*, Eur J Cardio Prev Rehab;

2. Kotseva K., Wood D., De Backer G., et al for the EUROASPIRE Study Group (2009) *Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries.* Lancet; 373: 929–40;

3. Marcheix B., Vanden E.F., Demers P., Bouchard D., Cartier R., (2008) *Influence of diabetes mellitus on long-term survival in systematic off-pump coronary artery bypass surgery,* Ann Thorac Surg, 86:1181–1188;

4. Rydén L., Standl E., Bartnik F. et al (2007) *Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary*, EurHeart J; 28, 88–136;

5. Gaede P., Vedel P., Larsen N. et al. (2003) *Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes*, N Engl J Med;348:383–393;

6. Gaede P., Lund-Andersen H., Parving H.H., Pedersen O.(2008) *Effect of a multifactorial intervention on mortality in type 2 diabetes,* N Engl J Med; 358: 580-591;

7. Laurent M., Boussuges A., Maunier S., et al. (2010) *Cardiovascular Rehabilitation in Patients With Diabetes,* Journal of Cardiopulmonary Rehabilitation and Prevention 09, 30(3):157-164.