

Autonomic Cardiac Regulation and Effectiveness of Ambulatory Treatment with Enalapril and Metoprolol among Patients with Chronic Heart Failure

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Topicality of this Issue

Medical and Social Significance

- World prevalence in adult population - 1.5- 10.0%
- Constant increase of number of patients, given the general population aging
- Increase of days in bed and new hospitalizations due to chronic heart failure
- Mortality during the 1st year - 15-25%; at 5 years, up to 50%

Significance of Autonomic Regulation Disorders

- Neurohumoral model of pathophysiology of chronic heart failure.
- Drugs with neuroregulation mechanism, as first line treatment.
- Study methods of autonomic regulation

Unsolved Problems

- Low effectiveness of current management frames (27-64%).
- Absence of studies about initial autonomic regulation influence on chronic HF management
- Absence of studies about the relationship between heart rate variability (HRV) and the results of management in acute pharmacological tests (APT)
- Absence of studies on the relationship between HRV with management and survival of patients

Objective of the Study

To perfect the diagnostic and prognostic approach, and the effectiveness of ambulatory treatment of chronic HF with Enalapril and Metoprolol, based on the study of autonomic regulation with the HRV and its influence on quality of life, demographic, clinical and hemodynamic indicators.

Characteristics of Patients

112 patients with chronic HF, studied in 6 External Offices in Kharkov

- Men - 53 (47%)
- Women - 59 (53%)
- Age range: 52-82 years old
- Average age: 64.9 ± 9.4 years old
- Average time of chronic HF evolution: 3.1 ± 1.9 years old

Distribution of patients according to FC (NYHA, 1964)

- II FC- 62 (56%)
- III FC - 50 (44%)

Etiology:

- Coronary disease: ACE FC I-III and/or
AMI background - 30 (28%)
- HBP: 32 (30%)
- Coronary disease and HBP: 48 (42%)

Control group - 36 patients with coronary disease and/or HBP with no signs of HF in the same age group as the patients of the study group

Study Methods and Indicators

- General clinical evaluation with FC assesment of HF according to the NYHA and Strazhesko-Vasilenko classifications, walk test (6 min)
- BP and HR evaluation
- Evaluation of quality of life with the Minnesota LWHF questionnaire for HF patients
- Conventional ECG
- Echocardiogram with measurement of posterior wall thickness and LVEF
- HRV study: total spectrum power (TP), power in very low frequency areas (VLF), low (LF), high frequency (HF), LF/HF ratio
- Renal echography
- Statistical analysis methods

General Outline of the Study

112 patients with chronic HF
Management with hydrochlorothiazide 25-50 mg daily and nitrites as needed

APT* with Enalapril (Enl), 2.5 mg one time only

Subgroup Enl+

Subgroup Enl-

Stage of treatment with Enl (average dose 16.4 ± 4.3 mg/d)

APT with Metoprolol (MT), 6.25 mg one time only

Subgroup MT -

Subgroup MT +

Subgroup
Enl+MT-

Subgroup
Enl-MT-

Subgroup
Enl+MT+

Subgroup
Enl+MT-

Management with MT addition (average dose 65.3 ± 11.1 mg/d)

*APT – acute pharmacological test, Enl +,-, MT+,- subgroups of patients with positive, negative responses to management with Enl and MT in APT

Distribution of Patients in Subgroups

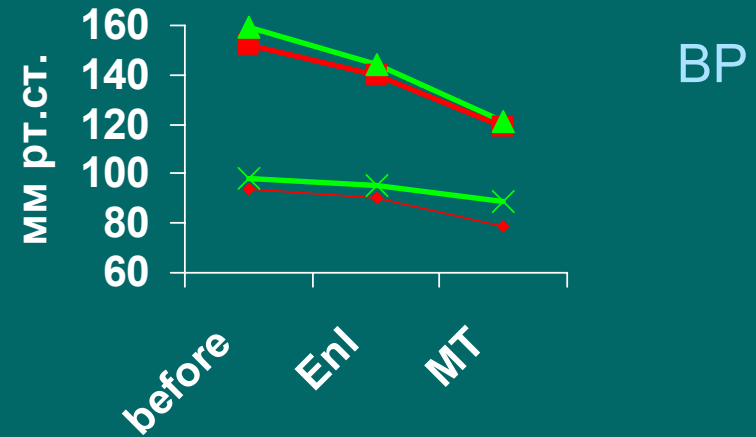
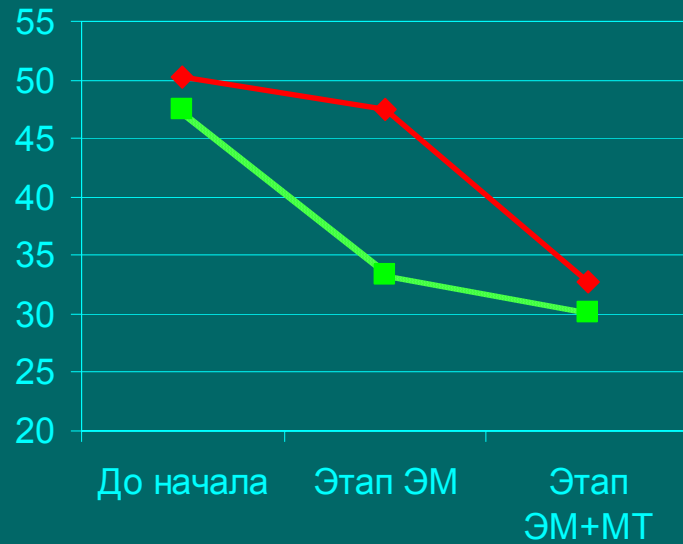
- According to gender:
 - 2 subgroups of patients - 53 men and 59 women
- According to age:
 - subgroup 1 - 32 young adult patients: 36 -60 years,
 - subgroup 2 - 49 elderly patients: 61-74 years,
 - subgroup 3 - 31 patients with advanced age: since 75 years
- According to the initial value of TP of HRV:
 - subgroup 1 - with TP lower than 450 mc², 42 patients,
 - subgroup 2 - with TP from 450 to 750 mc², 37 patients,
 - subgroup 3 - with TP higher than 750 mc², 33 patients
- According to results of TP response of HRV in APT with EnI:
 - subgroup EnI+, 53 patients and EnI-, 59 patients
- According to the results of TP response of HRV in APT with EnI:
 - subgroup MT+ , 60 patients and MT-, 52 patients
- According to the results of LF/HF response of HRV in APT with EnI:
 - subgroup EnI+, 49 patients and EnI- , 63 patients
- According to the results of LF/HF response of HRV in APT with MT
 - subgroup MT+, 50 patients and MT-, 62 patients

Comparison of the State of Autonomic Regulation between Control Group and Study Patients according to Gender

Gender	Group	Study			control		
	Показатели ВСР	Percentiles, %					
		25	50	75	25	50	75
M	TP, мс ²	39	593	731	734	1117	1911
	VLF, мс ²	195	333	507	333	517	856
	LF, мс ²	91	129	152	171	222	562
	HF, мс ²	36	54	76	77	203	363
	LF/HF	2,1	3,1	3,6	1,5	2,5	3,5
F	TP, мс ²	320	625	927	759	1242	1996
	VLF, мс ²	171	360	566	475	710	969
	LF, мс ²	83	139	201	180	209	478
	HF, мс ²	25	55	78	177	246	414
	LF/HF	2,1	2,7	3,9	0,6	1,9	3,0

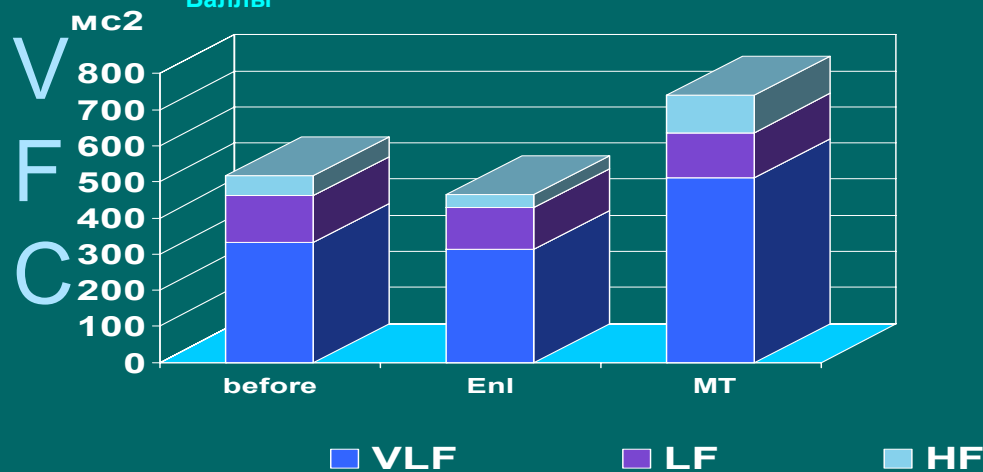
Effectiveness of Management between Men and Women

Quality of life

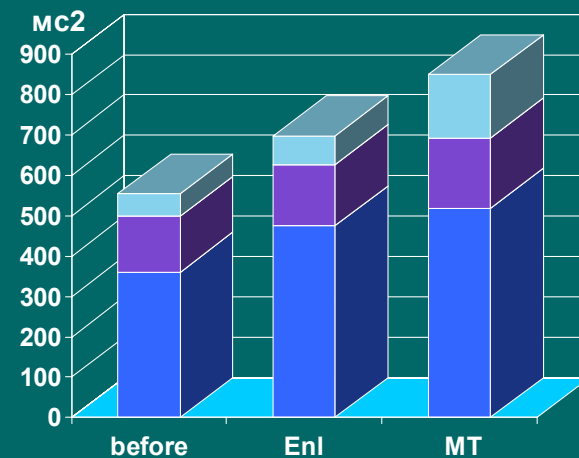


■ SBP, men ◆ DBP, men
▲ SBP, women × DBP, women

◆ мужчины ■ женщины
 Баллы Men

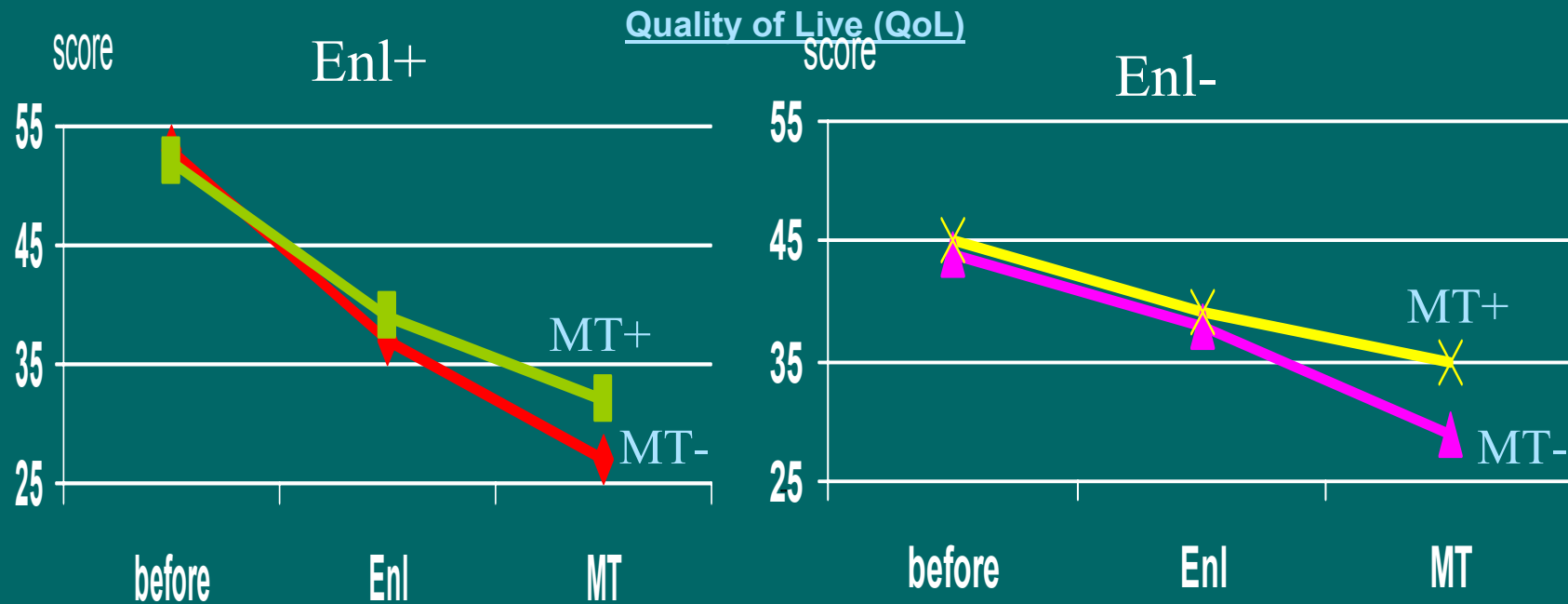


Women



Type of Response of TP of HRV and Effectiveness of CHF

Management

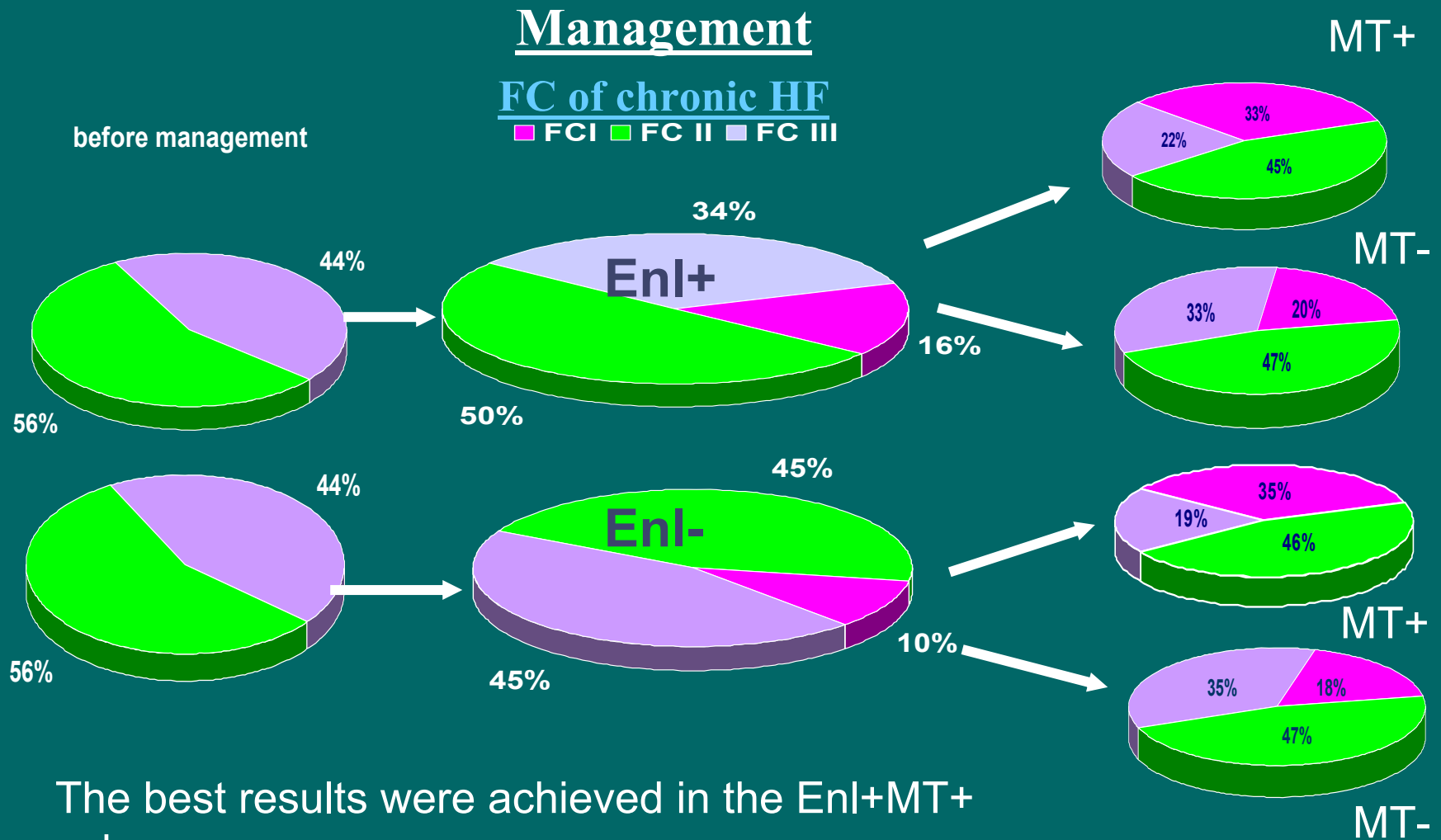


Significant improvement in QoL of patients in the Enl stage in the subgroup with Enl+

Significant improvement of QoL of patients after adding MT in the Enl+MT+, Enl+MT- and Enl-MT+ subgroups

Best results in the - Enl+MT+ subgroup

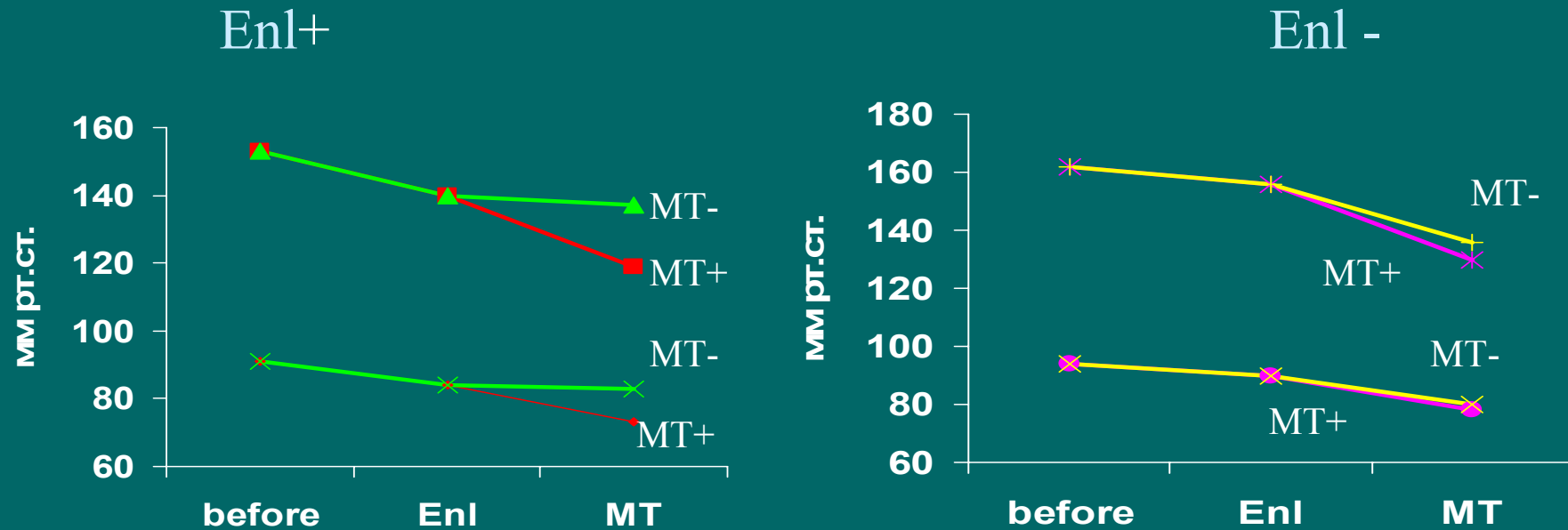
Type of TP Response of HRV and Effectiveness of Chronic HF



The best results were achieved in the EnI+MT+ subgroup

The dynamics of FC improvement in other subgroups did not differentiate

Type of TP Response of HRV and Effectiveness of Chronic HF Management Blood Pressure

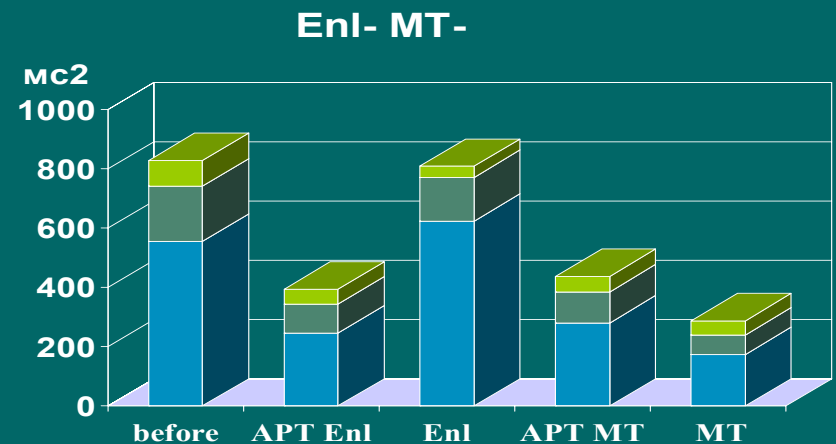
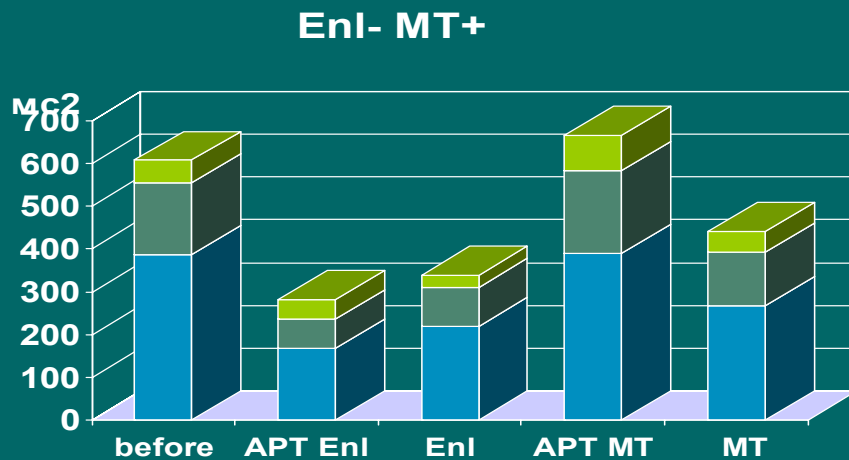
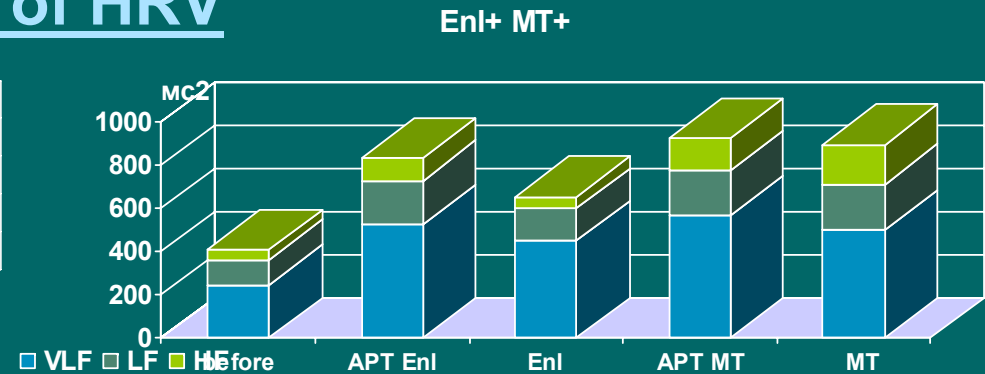
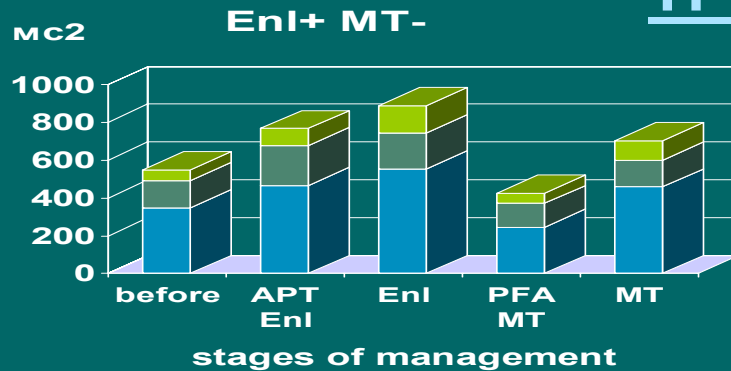


Significant decrease of BP during the whole management, among patients with increase of TP in APT

The best results were achieved in the EnI+MT+ subgroup

Type of TP Response of HRV and Effectiveness of Chronic HF Management

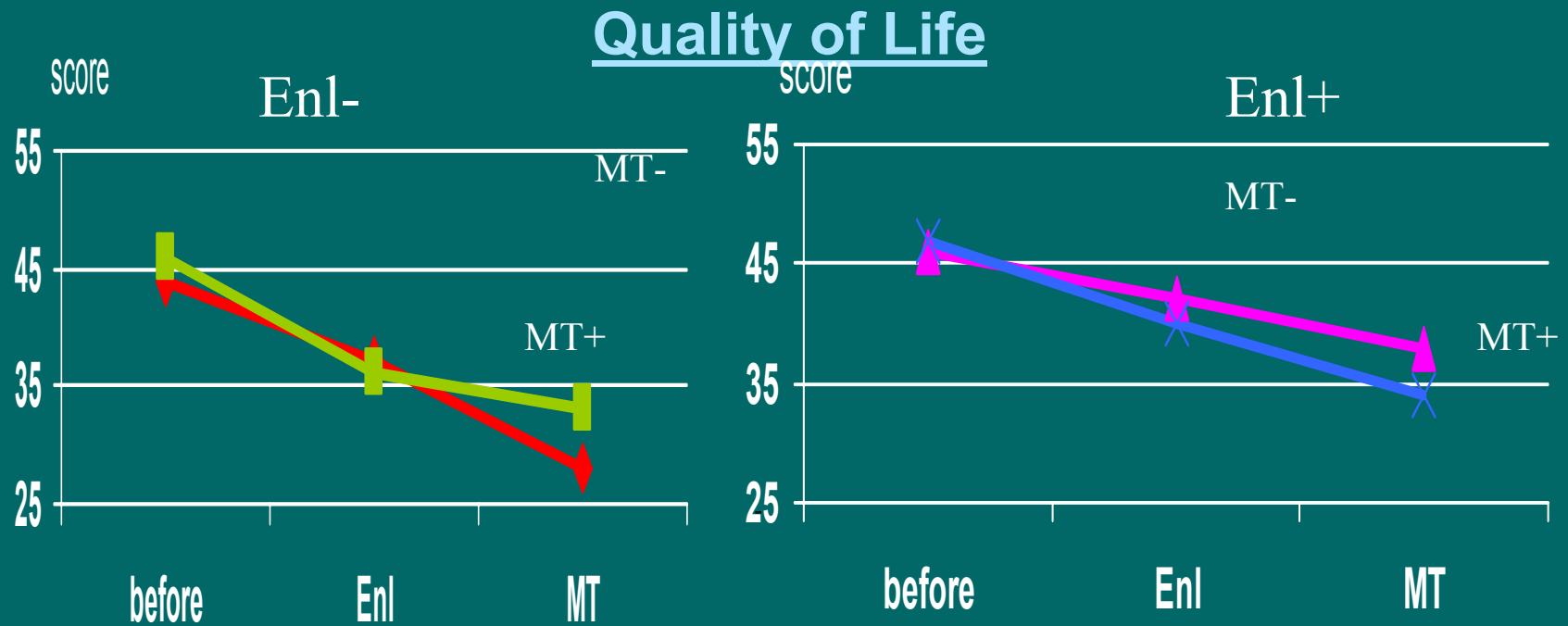
TP of HRV



The tendency of TP change of HRV in APT with EnI and MT defines the results of management

The best results were in the EnI+MT+ subgroup

Type of LF/HF Response of HRV and Effectiveness of Chronic HF Management



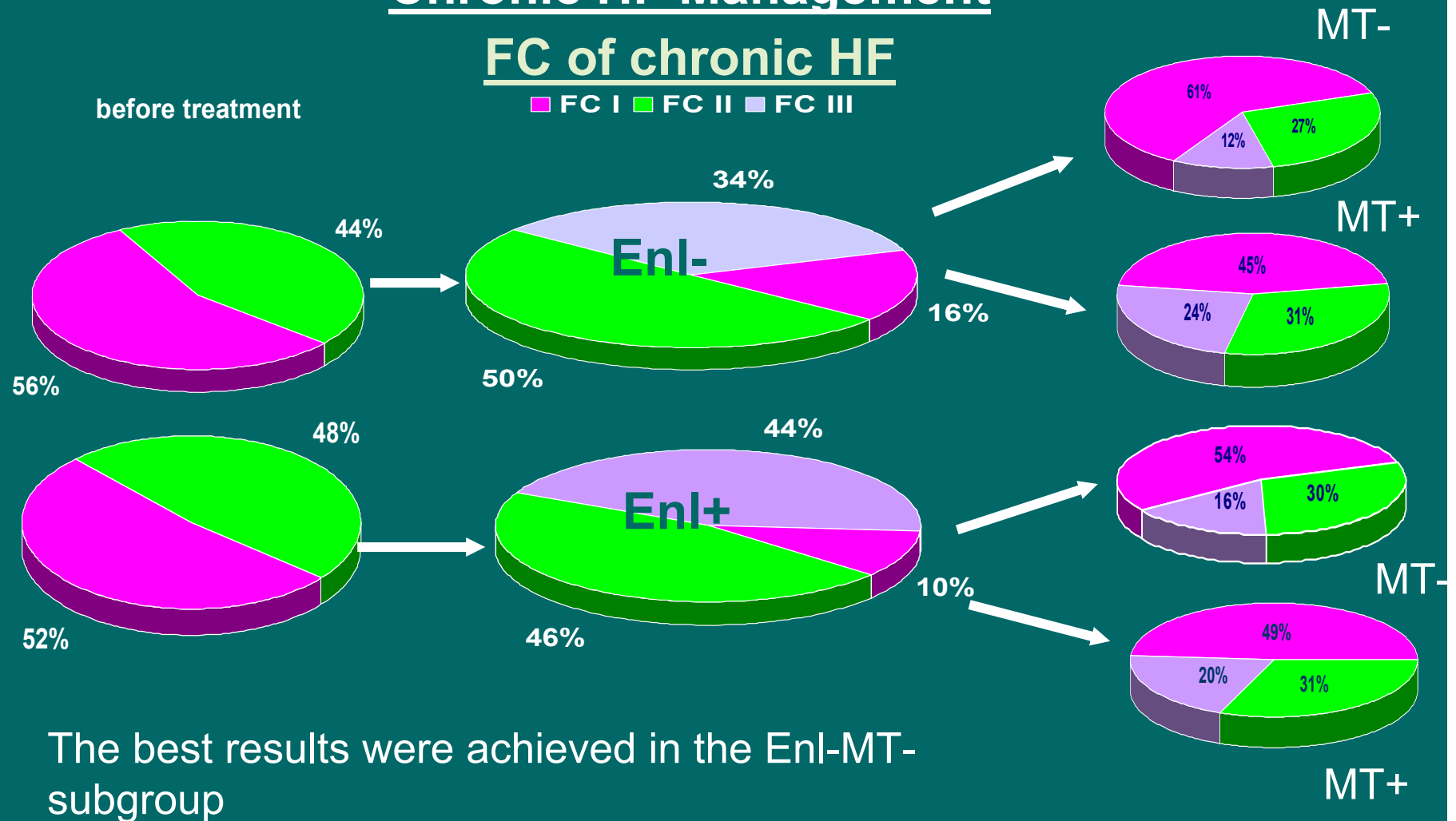
Significant improvement of QoL in patients in the Enl - stage in the Enl+ subgroup

Significant improvement in QoL of patients after addition of MT in the MT- subgroup

The best results were observed in the Enl- MT- and Enl+MT- subgroups

Type of LF/HF Response of HRV and Effectiveness of Chronic HF Management

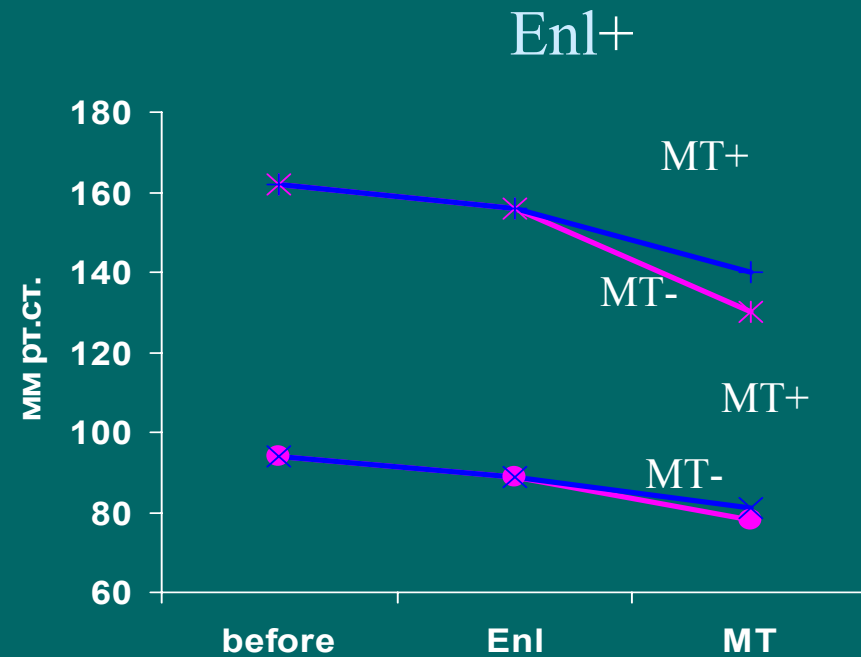
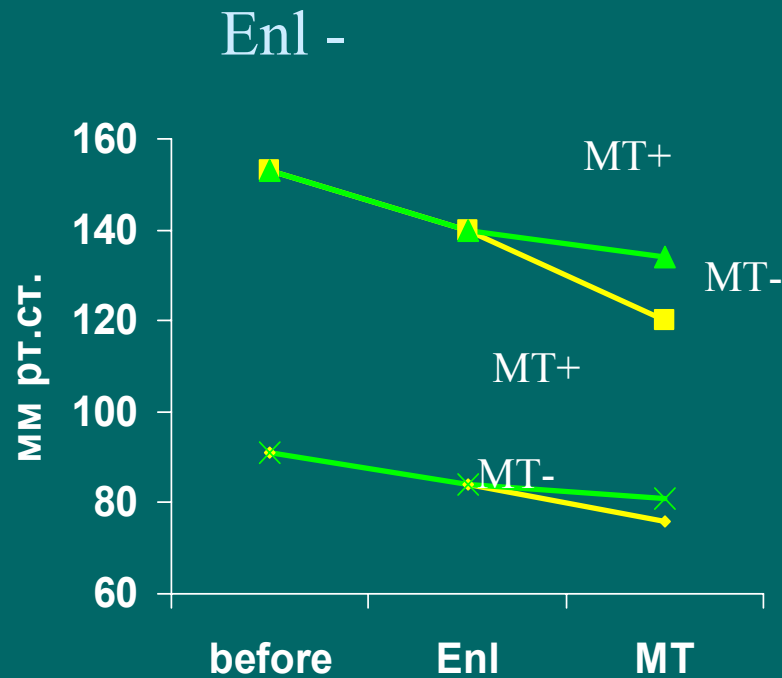
FC of chronic HF



The best results were achieved in the Enl-MT- subgroup

The dynamics of FC improvement in other subgroups did not differentiate between them

Type of LF/HF Response of HRV and Effectiveness of Chronic HF Management Blood Pressure

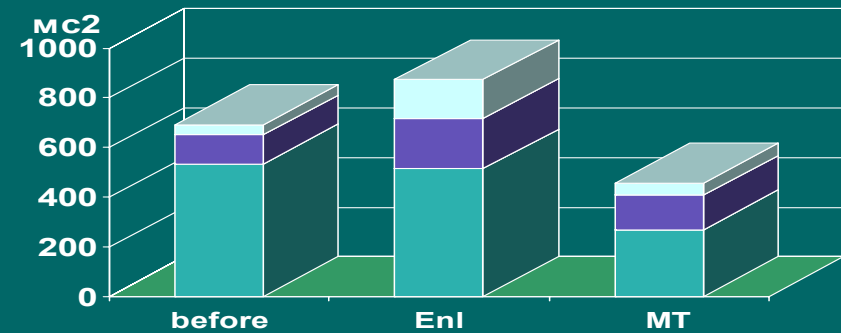
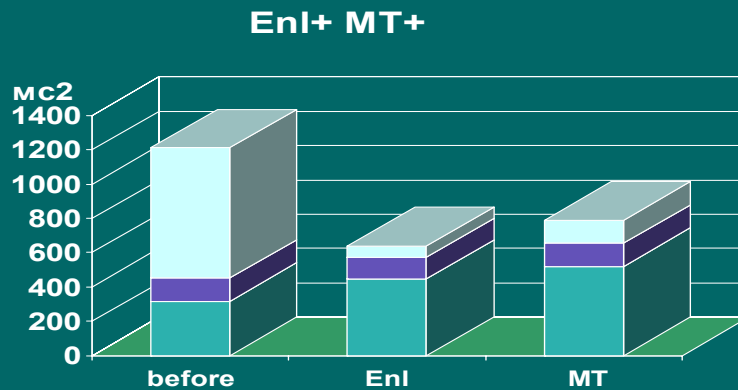
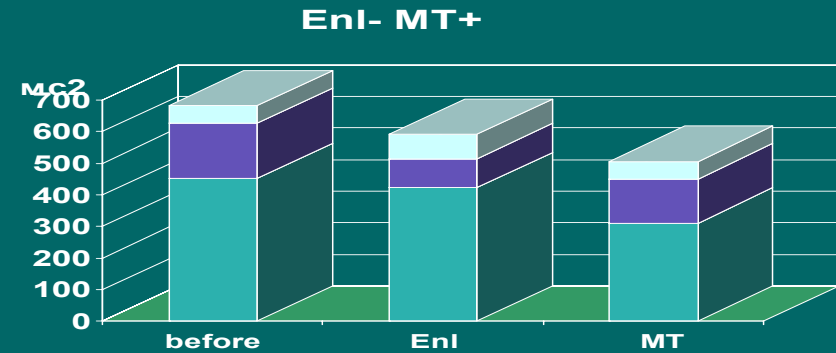
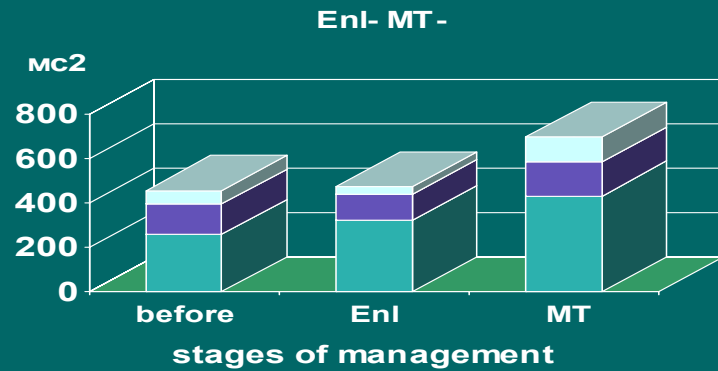


Non significant decrease of BP was evident in the two stages, among patients with low LF/HF ratio during APT

Type of LF/HF Response of HRV and Effectiveness of Chronic HF Treatment

TP of HRV

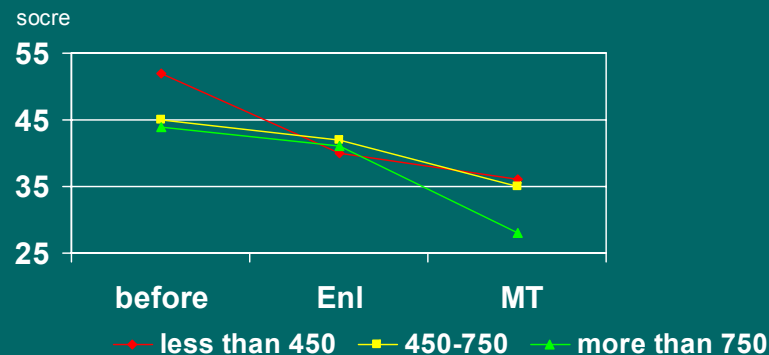
■ VLF ■ LF ■ HF



TP changes of HRV with management, did not depend on the LH/HF ratio response of HRV in APT with EnI and MT

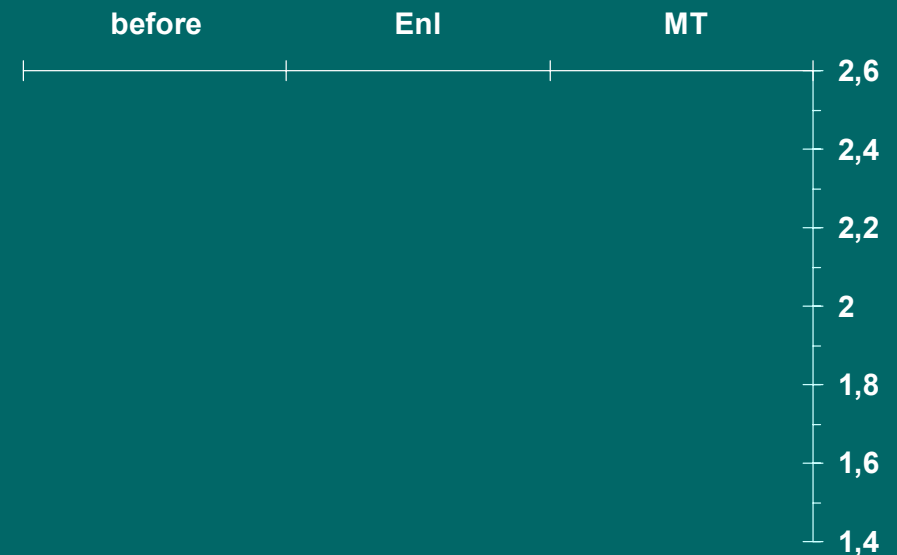
Initial TP Level of HRV and Effectiveness of Chronic HF Management

Quality of Life (QoL)



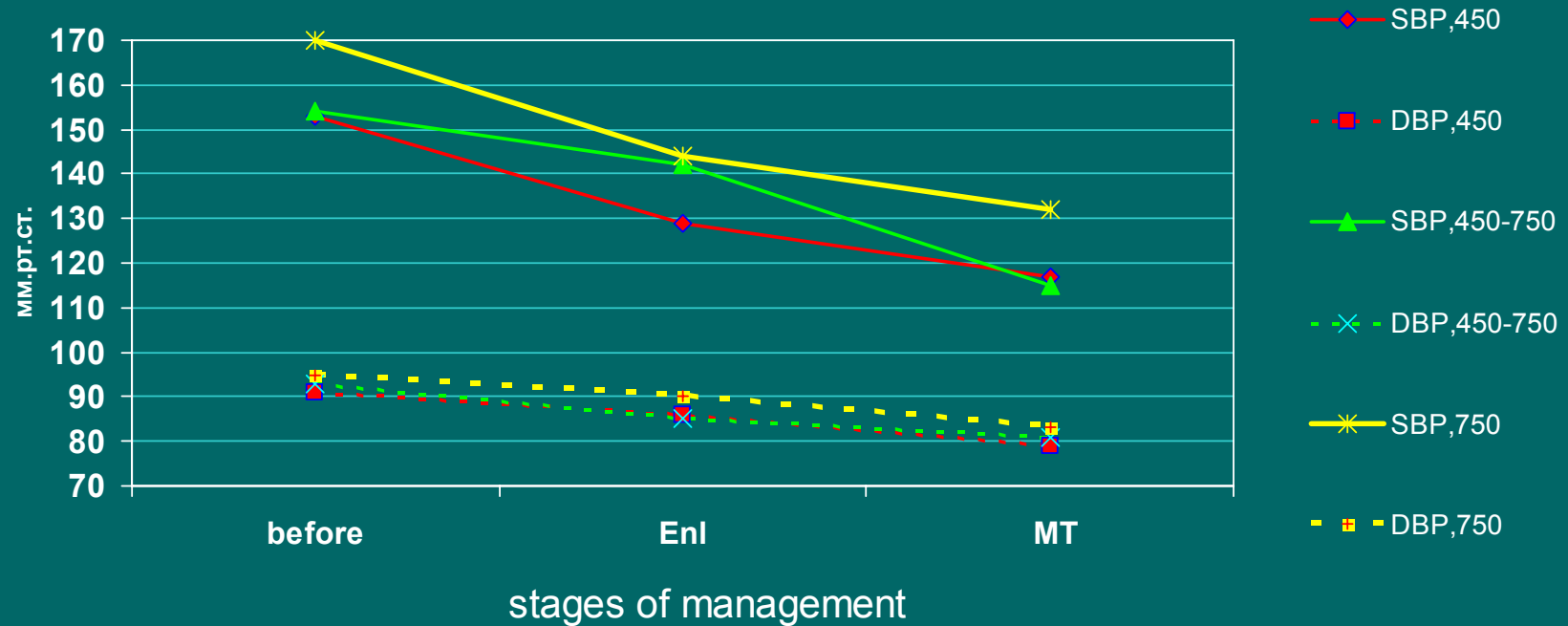
Initial QoL and in the stages of treatment was significantly better in patients with a greater TP value of initial HRV

FC of HF



FC of HF before the treatment was lower in patients with a higher initial TP value of HRV, and viceversa. During the stages of treatment, such value gradually decreased in comparison to the initial values

Initial TP Level of HRV and Effectiveness of Chronic HF Treatment Blood Pressure

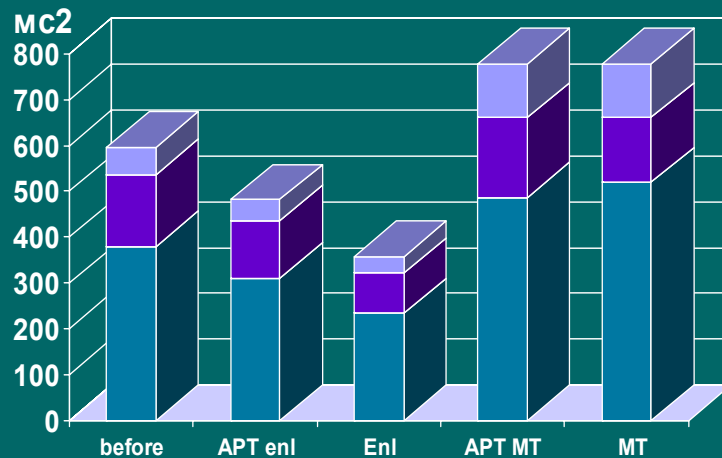
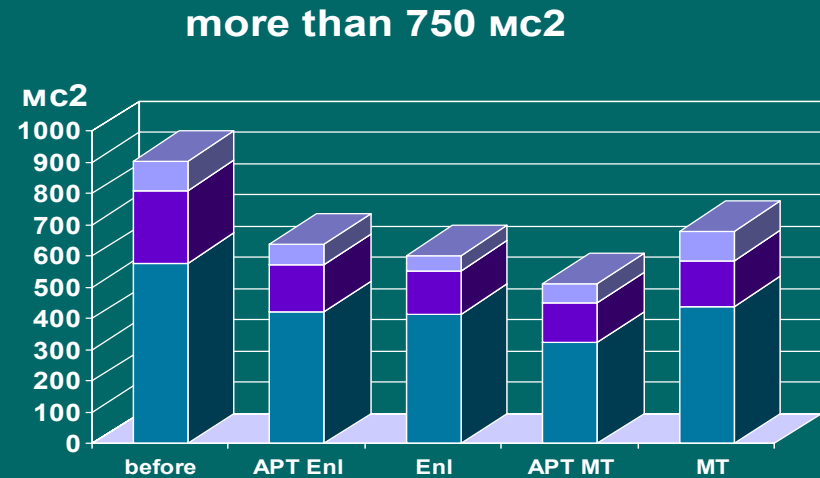
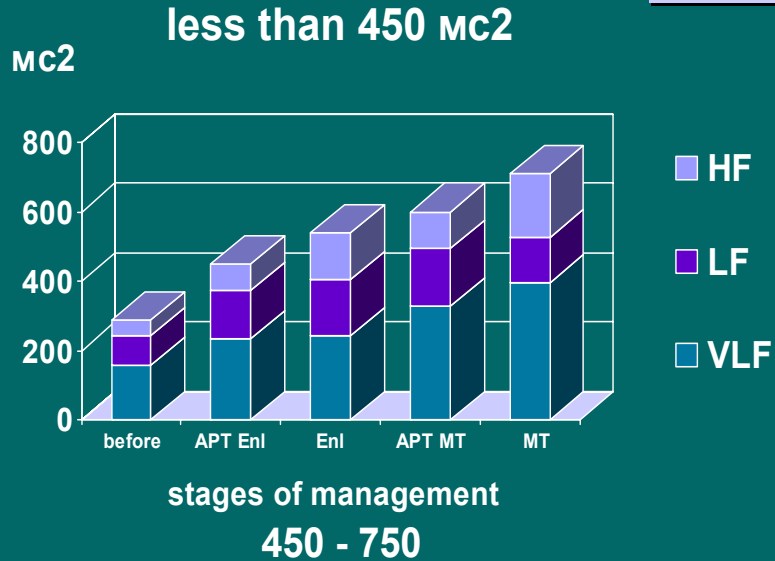


The results of management were better in the stage of EnI in the subgroups with greatest and lowest initial TP value of HRV.

After the addition of MT, the results improved in the group with a median TP value of HRV

Initial TP Level of HRV and Effectiveness of Chronic HF Management

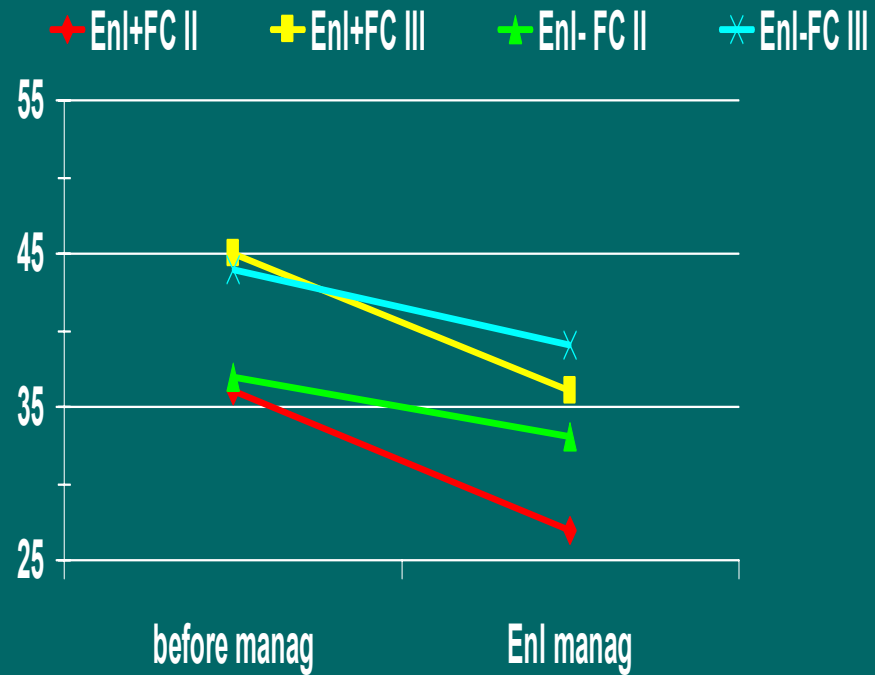
TP of HRV



TP changes of HRV in the stages of treatment depend more on APT results with Enl and MT, than the initial TP level of HRV

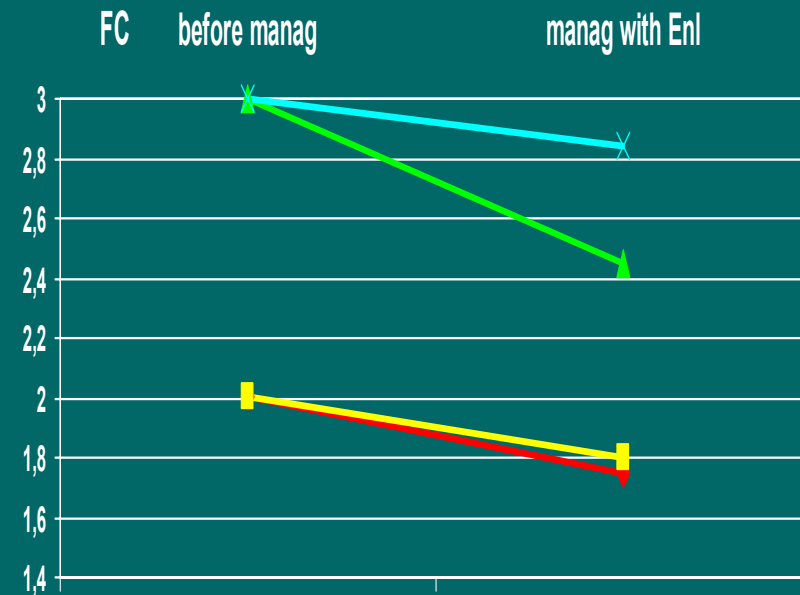
FC of Chronic HF and TP Response of HRV in APT with EnI

Quality of Life



Improvement of QoL depend more on TP response of HRV in APT with EnI, than on FC

FC of HF

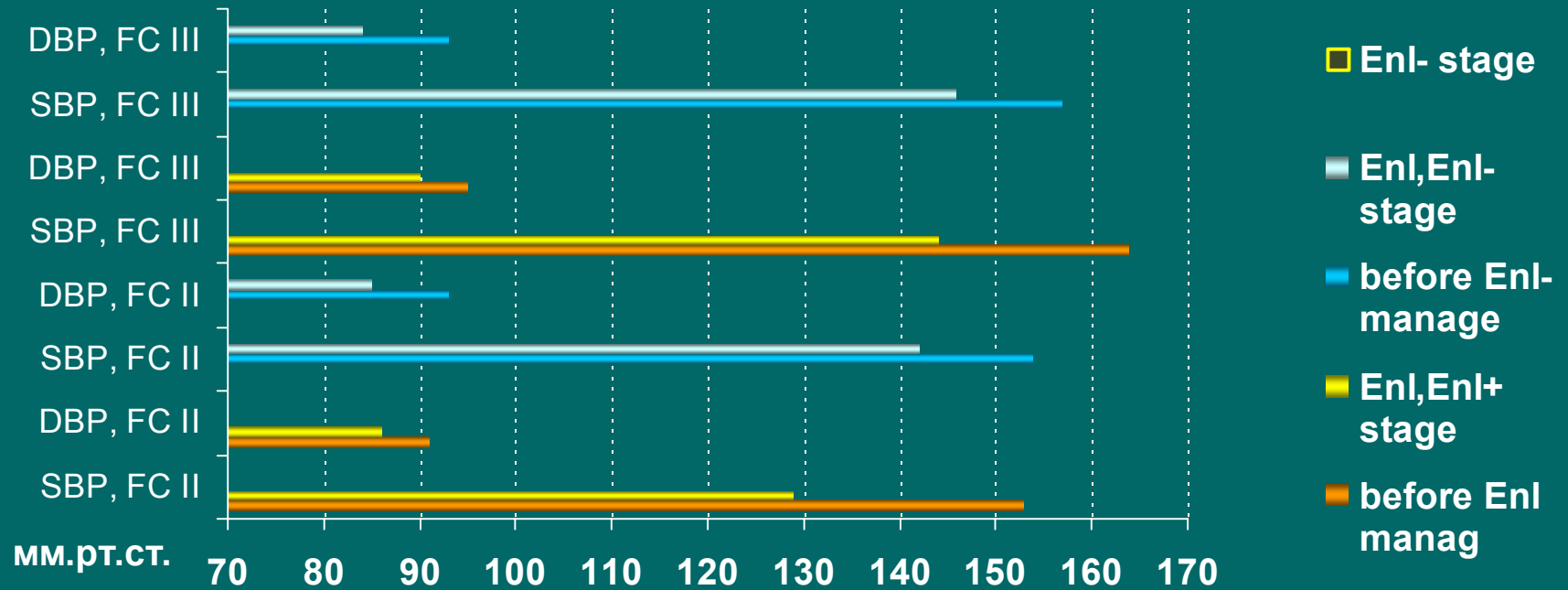


FC significantly decreased in patients of the EnI+ subgroup vs. EnI- subgroup

FC of Chronic HF and TP Response of HRV in APT with

EnI

Blood Pressure



BP changed independently from FC and TP response of HRV

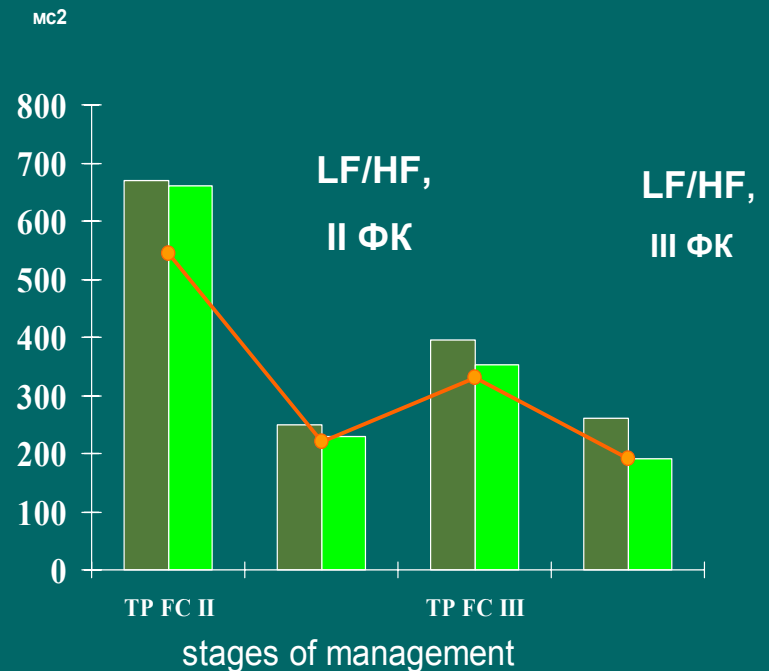
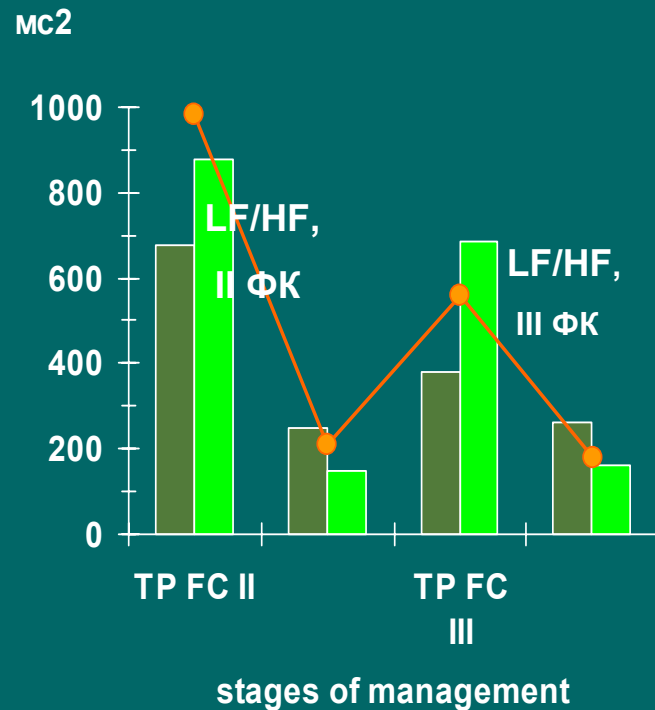
FC of Chronic HF and TP Response of HRV in APT with

Enl

TP of HRV

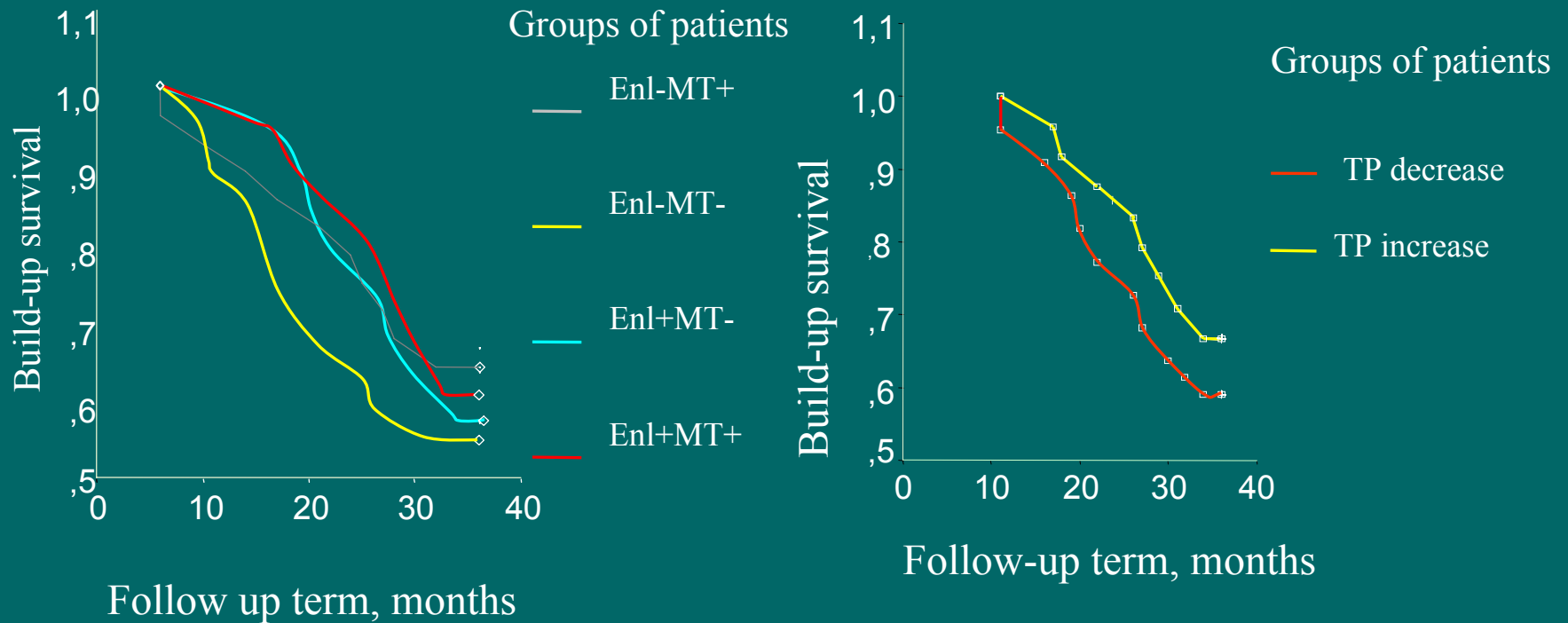
TP+

TP-



TP and LF/HF values of HRV changed during Enl treatment, and depended on APT results and did not relate to FC

Build-up Survival of Patients with Chronic HF and TP of HRV



According to the results of management with Enl and MT, the patients achieved a better prognosis at 3 years (statistically significant) with TP increase of HRV in APT with Enl and/or with MT and with TP increase of HRV

Conclusion 1

Between the patients with HF, during management with Enl and MT, 2 types of responses of autonomic regulation of HR were observed: TP increase or decrease of HRV.

Such responses were observed after the first administration of the drug (2.5 mg Enl or 6.25 mg MT in APT) and continued during the whole period of treatment.

Conclusion 2

A significant improvement of quality of life, FC, decrease of BP with TP increase of HRV and LF/HF decrease during the treatment with Enl, was observed more between women than men.

The addition of MT for the treatment improves the mentioned indicators, most of all, among men, a fact that leads to the disappearance of intersexual differences regarding quality of life, hemodynamic parameters and HRV.

Conclusion 3

Autonomic cardiac regulation disorders, which are exacerbated with age, worsen even more with chronic HF.

The management with EnI leads to better hemodynamics, quality of life and HRV, more between young adults than in the elderly.

The addition of MT strengthens the improvement of quality of life, FC, BP and HR decrease among all age groups. A significant TP increase of HRV and normalization of LF/HF ratio in this stage of the treatment is seen in all age groups, but more in elderly patients.

Conclusion 3

Between patients with FC III, in comparison to FC II, quality of life is significantly worse ($p=0.032$), TP of HRV is lower ($p=0.036$) and LF/HF ratio is greater ($p=0.041$)

A greater effectiveness of treatment with EnI and MT is observed in patients with TP increase of HRV in APT

Conclusion 4

Among patients with chronic HF, 2 types of LF/HF response are observed: increase or decrease.

The treatment with EnI is more effective in the case of increase of LF/HF ratio, a significant decrease of FC ($p=0.036$), BP ($p<0.03$) and HR ($p=0.048$) is observed, improvement of quality of life ($p=0.031$) and TP of HRV ($p=0.029$).

The addition of MT influences even more the FC, BP, HR and quality of life of patients with the decrease of LF/HF ratio in APT. HRV indicators, after the addition of MT, improve independently from LF/HF response.

Conclusion 5

The prognosis of survival at 3 years does not depend on initial TP of HRV; however, such prognosis presents a significant improvement ($p < 0.05$) in patients with TP increase of HRV and with the positive results of management with EnI and/or MT