Treatment of stable angina in Ukraine: CLASSICA study

E.G. Nesukay

National Scientific Center «M.D. Strazhesko Institute of Cardiology NAMS of Ukraine», Kyiv, Ukraine

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Cardiovascular diseases are the leading cause of morbidity and mortality of middle-aged and elderly patients in most developed and many developing countries and remain one of important medical issues of the 21st century [12]. Ischemic heart disease (IHD) is the most prevalent of them. It is contributing to the rising cost of healthcare, particularly among aging populations [5]. In 2009 in Ukraine 3,232,026 angina patients (including 1,084,457 of working age) were registered [3].

Despite remarkable advances in the treatment of stable angina over the past 20 years, including preventive therapy, pharmacological agents, and revascularization, symptoms persist in the majority of patients at high and very high risk of complications.

During recent years, a number of well-planned randomized controlled trials have destroyed the widespread belief that intervention in symptomatic stable IHD really treats the patient and saves lives. The large multicenter study COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation) compared a strategy of combining percutaneous coronary intervention (PCI) and optimal medical therapy (OMT) with OMT alone in patients with stable angina with a focus on morbidity and mortality [16]. OMT included acetylsalicylic acid, long-acting metoprolol and amlodipine, as well as simvastatin and ezetimibe when necessary, to achieve target levels of low-density lipoproteins. Anti-ischemic therapy included isosorbide mononitrate, when appropriate. After an average of 4.6 years follow-up, mortality (5.9 % versus 6.5 %) and nonfatal MI (9.4 % versus 10.4 %) did not differ significantly between the groups. The intervention group showed more rapid symptom control, but after 4.6 years of follow up, the groups did not differ in terms of frequency of angina symptoms. Thus, the COURAGE study did not confirm the positive impact of interventional procedures on prognosis in stable IHD.

The results of COURAGE are in good agreement with the results of another study that investigated a primary conservative strategy in patients with stable IHD, i.e. Atorvastatin VErsus Revascularization Treatment (AVERT). In this study optimal medical therapy with high doses of atorvastatin (80 mg/day) resulted in a 36 % reduction in the incidence of new ischemic events (cardiovascular death, nonfatal MI, coronary artery bypass grafting [CABG], angioplasty or hospitalization as a result of angina aggravation), compared to PCI plus concomitant drug therapy [14]. Further, evidence was obtained showing that progression of atherosclerosis is more effectively controlled by OMT.

In several published meta-analyses of clinical studies the strategies of PCI and OMT were compared in patients with stable IHD [7, 15]. In the classic meta-analysis of Katritsis et al., there was no difference in the incidence of cardiac death and nonfatal MI between patients treated with PCI and those treated with OMT [10]. Over the past 20 years cardiovascular mortality reduction in the USA has been attributed to the use of revascularization procedures in only 5 % of cases, with 45–75 % attributed to the prevention measures and impact on risk factors, while the remaining 25–55 % to treatment in general. It turns out that strategy directed towards lifestyle changes and nutrition is twice as efficient as the other more expensive strategies [8, 11]. This implies that future lies in the reduction of risk factors for primary and secondary prevention and individual interventions in high-risk patients [13]. However, there is no doubt regarding

Несукай Олена Геннадіївна, д. мед. н., проф.
03151, м. Київ, вул. Народного Ополчення, 5

the necessity of revascularization after MI in the presence of large areas of myocardium exposed to ischemic risk (patients with severe stenosis, three-vessel damage etc.) [6].

Current recommendations for treatment of stable angina combine lifestyle changes and drug therapy with revascularization strategies [4, 8]. Pharmacological interventions reduce the progression of atherosclerotic plaque, stabilize the plaque by reducing inflammation and preserving normal endothelial function, and finally, prevent the occurrence of thrombosis in cases of endothelial dysfunction or plaque rupture. The mechanisms underlying regression of coronary atherosclerosis include lowering of lipid levels, anti-inflammatory interventions, and increasing shear laminar stress in the vascular endothelium. The contribution of such agents as acetylsalicylic acid, statins, beta-blockers (BB) and angiotensin-converting enzyme (ACE) inhibitors to the pharmacological treatment of atherosclerosis cannot be overestimated [9].

In patients with IHD the first aim is to eliminate symptoms of angina. According to epidemiological studies, some patients remain symptomatic which dramatically reduces their quality of life despite OMT and sometimes revascularization procedures [9].

During recent years, better understanding of the role of myocardial energy metabolism in the pathogenesis of myocardial ischemia has formed the basis of new approaches to its treatment. The aim of metabolic therapy is to improve energy metabolism of cardiomyocytes through optimization of the formation and transfer of energy without having any direct impact on coronary blood flow, heart rate, or preload and afterload [1, 2]. Today the only antianginal metabolic agent registered in Ukraine that is recommended for use in patients with IHD according to the standards of evidence-based medicine is trimetazidine MR (Preductal MR) [4]. The results of clinical trials of trimetazidine MR have allowed experts of the European Society of Cardiology to recommend it as an agent for treatment of patients with stable angina [8]. Trimetazidine MR selectively inhibits 3-ketoacyl-coenzyme-A-thiolase (3-KAT) in long-chain fatty acids. By reducing fatty acid oxidation and increasing glucose oxidation, trimetazidine MR promotes the use of oxygen by ischemic cells, thus exhibiting a pronounced anti-ischemic effect.

The practicing cardiologist is faced with choosing the optimal drug combination to achieve the best antianginal/antiischemic effect in patients with stable angina. In order to determine the optimal combination of antianginal medications the CLASSICA study (The most Effective Combination of Antianginal Drugs in the Treatment of Patients with Stable Angina) was conducted, in which 144 cardiologists took part in 34 cities all over Ukraine, and cohort of 1423 patients were observed.

Material and methods

In order to examine to what extent the treatment of patients with stable angina in real ambulatory practice corresponds to the requirements of current guidelines and which combination of antianginal medications is most effective in eliminating of angina symptoms doctors completed a questionnaire comprising three questions:

1) which groups of medication should be included in the OMT of patients with stable angina? 95 % of cardiologists included antiplatelet agents, 98 % – statins, 97 % – BB, 54 % – long-acting nitrates (LAN) and 20 % calcium channel blockers (CCB);

2) which tactics eliminates angina symptoms more effectively in patients already receiving an optimal dose of BB? Original trimetazidine MR was prescribed in combination in 92 % of cases. The most popular were the combinations of LAN with original trimetazidine MR (51 %) and LAN with CCB (17 %); 20 % of physicians considered the addition only of original trimetazidine MR to BB to be sufficient;

3) which therapy should be prescribed by cardiologists in the case of intolerance to BB in patients with persistent angina? Original trimetazidine MR in combination was prescribed by 77 % of physicians, more frequently in combination with CCB and LAN (41 %) and rarely with LAN (22 %) or CCB (14 %) alone.

Results and discussion

The CLASSICA study consisted of two sections – the survey section and the clinical one.

To obtain the survey data 1423 ambulatory records of patients with stable angina pectoris were analyzed (67 % male, 33 % female). Most patients were of working age. More than half (54 %) of patients had 3–6 angina attacks/week, more than a third (33 %) had more than six episodes, and 13 % had < 3 angina attacks per week. The most

frequently observed angina functional classes were II and III (38.8 % and 53.9 %, respectively).

The duration of angina was 1 to 5 years in 46 %; 6 to 10 years in 32 %, and more than 10 years in 21 % of patients, among whom 82 % had a history of MI and every fifth patient had had two or more MIs. Coronary angiography was performed in 31 % of men and 12 % of women, in 30 % of patients after MI, and in 13.5 % of patients without MI. Only 10.4 % of patients had revascularization procedures and 9.9 % had CABG surgery. Compared to patients with milder angina, patients with ≥ 3 angina attacks had higher rate of MI (86 % versus 13 %), CABG (88 % versus 20 %) and coronary artery stenting (80 % versus 20.1 %).

Analysis showed that large proportion of patients had insufficient control of risk factors: a total of 82 % of patients had arterial hypertension, 91 % – heart failure, 22.9 % – diabetes mellitus, 35 % were overweight (body mass index ≥ 30 kg/m^2), and 84 % had total cholesterol level > 4.5 mmol/L. The average heart rate was 74 beats per minute and in 66 % of patients heart rate exceeded 70 beats per minute (in the latter group 63 % had survived MI compared to 37 % in the group with heart rate < 70 beats per minute.)

Thus, the studied cohort of patients with stable angina included patients with high/very high risk, who often had long-term IHD with complications (i.e., MI) and multiple comorbidities, poor control of angina symptoms, risk factors (weight, heart rate, and lipids), and insufficient frequency of coronary angiography and revascularization procedures.

Analysis of prescribed therapy showed that statins were prescribed in 83 % of patients, including 87 % of patients with hypercholesterolemia, 85 % of patients with diabetes mellitus, and 89 % of patients with diabetes mellitus and MI. Antianginal agents were prescribed in 98 % of patients, including BB in 82 %, LAN in 57 %, CCB in 25 %, and trimetazidine MR in 70 % of patients. Interestingly, the average daily dose of beta-blockers did not reach the target level *(Table 1)*. A total of 31 % of patients received a combination of four antianginal medications, 27 % received three antianginal agents, 19 % two antianginal medications, 14 % five medications, and 6.5 % of patients received monotherapy.

The physician has an opportunity not only to correct hemodynamic parameters for control of angina attacks. Myocardial protection achieved through correction of metabolic changes at the cardiomyocyte level provides a pronounced antianginal effect. Thus, in accordance with existing guidelines, the first and only original medication with a mode of action targeting this mechanism is trimetazidine MR (Preductal MR).

Thus, the aim of the clinical part of the CLASSICA study was to confirm the efficacy of combining original trimetazidine MR with traditional hemodynamically active agents for reduction of the number of angina attacks and short nitrate consumption. The clinical part of the study was designed to be as close to real outpatient practice as possible. The inclusion criteria for patients were as follows:

• stable effort angina (functional classes 2–3, ≥ 3 angina attacks per week);

• IHD therapy (administered consistently and unchanged for at least 1 month prior to inclusion): acetylsalicylic acid; statin; treatment of angina with one of the following: BB monotherapy (1st group, n=400); combination of BB + LAN (2nd group, n=691); combination of BB + CCB (3rd group, n=122).

The exclusion criteria were as follows:

• MI (acute MI less than 6 months before inclusion);

• arterial hypertension (office systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg);

• stable angina pectoris 1 and 4 functional classes;

• heart rhythm and conduction disturbances;

• heart failure, systolic dysfunction (ejection fraction < 45 %);

• valvular heart disease (including degenerative aortic stenosis);

• diabetes mellitus;

• chronic obstructive pulmonary disease, bronchial asthma;

• severe renal dysfunction, liver dysfunction (creatinine level 1.5 times higher than normal range;

Table 1
Average daily doses of BB

Medication	Number of patients	%	Average dose, mg/day
Atenolol	17	1	21.1±5.4
Betaxolol	58	5	13.3±1.2
Bisoprolol	698	57	5.9±0.1
Carvedilol	131	11	19.9±1.4
Metoprolol	154	13	57.6±2.3
Nebivolol	155	13	4.8±0.2

Table 2
Changes in evaluated parameters of patients (n=1213)

Parameter	1st visit	2nd visit	3rd visit
Average number of angina attacks per week	6.4±0.1	3.6±0.1*	1.9±0.1*
Average number of doses of short-acting nitrates per week	5.7±0.1	2.8±0.1*	1.2±0.1*
Systolic blood pressure, mm Hg	129.5±0.3	123.7±0.3*	121.4±0.2*
Diastolic blood pressure, mm Hg	80.8±0.2	76.8±0.2*	75.3±0.2*
Heart rate beats/ minute	74.5±0.3	68.5±0.2*	66.1±0.2*
Therapy adjustment (any changes, %)	–	20.8	–

* Differences are significant versus the first visit (P<0.001).

[> 170 mmol/L], total bilirubin level 1.5 times higher than normal range [> 35 mmol/L].

After the selection at 1st (inclusion) visit all patients received trimetazidine MR 35 mg twice daily for two months. During the 2nd visit (1 month after inclusion) clinical examination was carried out with measurement of blood pressure and heart rate, assessment of the number of angina attacks and doses of short-acting nitrates. The therapeutic dose was adjusted in one in five patients. During the 3rd visit (2 months after inclusion) repeat clinical examination was carried out.

Analysis of baseline data showed that patients included in the study were mostly receiving OMT, however, daily doses of BB were under the target levels *(Table 1)*.
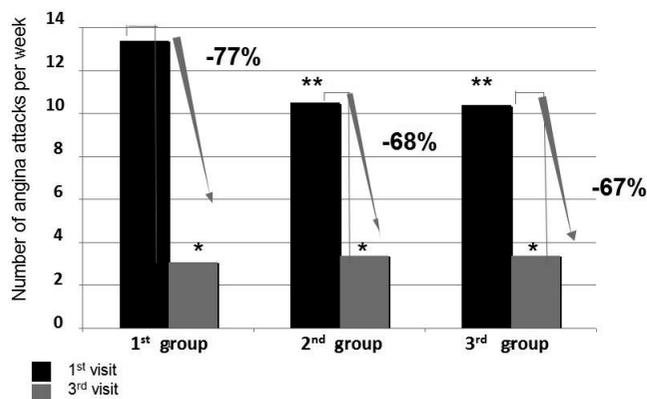

Figure. Change in number of weekly angina attacks in patients with more severe IHD (baseline ≥ 7 angina attacks per week). * P<0,001 vs 1st visit; ** P<0,001 vs 1st group.

Data analysis on at the 2nd visit showed 44 % decrease of angina attacks per week and further significant decline after 2 months of treatment from 6.4±0.1 to 1.9±0.1 attacks per week (P<0.001) *(Table 2)*. Similarly, the average weekly number of short-acting nitrate doses showed 51 % decrease and further decline after 2 months of treatment to 1.2±0.1 (P<0.001) (see *Table 2*).

To address the issue of the optimal combination of antianginal medications to treat angina, the treatment effectiveness was assessed separately in all three treatment groups. The analysis of results for patients with different frequencies of weekly angina attacks showed maximal treatment efficiency in the 1st group (BB + trimetazidine) with no benefits of additional prescription of LAN (2nd group) or CCB (3rd group) to BB and trimetazidine MR *(Figure)*.

Conclusions

1. The studied cohort of patients with stable angina included those with high/very high risk, often with long standing IHD and complications (MI), with multiple comorbidities, poor control of angina symptoms, risk factors (body weight, heart rate, level of lipids), and insufficient frequency of coronary angiography and use of revascularization procedures.

2. Additional usage of original trimetazidine MR significantly reduces the weekly number of angina attacks and consumption of short-acting nitrates in patients with persistent angina attacks who are treated with beta-blockers or their combination with long-acting nitrates or calcium channel blockers.

3. The combined usage of long-acting nitrates or calcium channel blockers with beta-blockers doesn't provide additional reduction of the weekly number of angina attacks compared with patients receiving beta-blocker and original trimetazidine MR.

4. As it has no effect on hemodynamics, original trimetazidine MR can be used in combination for the treatment of stable angina, providing antianginal and anti-ischemic efficacy in symptomatic patients.

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Лечение стабильной стенокардии в Украине: исследование КЛАССИКА

Е.Г. Несукай

ГУ «Национальный научный центр "Институт кардиологии им. акад. Н.Д. Стражеско" НАМН Украины», Киев

В исследование КЛАССИКА (Наиболее эффективная комбинация антиангинальных препаратов в лечении пациентов со стабильной стенокардией), в котором приняли участие 144 врача-кардиолога из 34 городов Украины, было включено 1423 пациента со стабильной стенокардией напряжения. Изученная когорта состояла из пациентов с высоким/очень высоким сердечно-сосудистым риском, нередко – с длительной ишемической болезнью сердца и осложнениями (инфаркт миокарда), с множественной сопутствующей патологией, неудовлетворительным контролем симптомов стенокардии, факторов риска (масса тела, частота сокращений сердца, уровень липидов), недостаточной частотой проведения коронаровентрикулографии и процедур реваскуляризации.

Для решения вопроса об оптимальной комбинации антиангинальных препаратов в лечении стенокардии был проведен анализ эффективности в группах лечения: оригинальный триметазидин MR и β-адреноблокатор (β-АБ) (1-я группа, n=400); триметазидин MR, β-АБ и нитрат длительного действия (2-я группа, n=691); триметазидин MR, β-АБ и блокатор кальциевых каналов (3-я группа, n=122).

Анализ результатов показал, что применение триметазидина MR существенно уменьшает количество приступов стенокардии и потребление нитратов короткого действия у симптомных пациентов во всех группах лечения. Максимальная эффективность дополнительного назначения триметазидина MR была продемонстрирована у пациентов с тяжелой стенокардией напряжения (≥ 7 приступов в неделю). Комбинированное назначение нитратов длительного действия или блокаторов кальциевых каналов с β-АБ не приводило к дополнительному уменьшению частоты приступов стенокардии по сравнению с больными, получающими β-АБ и триметазидин MR.

Ключевые слова: стабильная стенокардия, факторы риска, лечение.

Treatment of stable angina in Ukraine: CLASSICA study

E.G. Nesukay

National Scientific Center «M.D. Strazhesko Institute of Cardiology NAMS of Ukraine», Kyiv, Ukraine

144 cardiologists from 34 regions of Ukraine participated in prospective CLASSICA (The most Effective Combination of Antianginal Drugs in the Treatment of Patients with Stable Angina) study. The CLASSICA study consisted of two parts: the epidemiological section and the clinical section. The analysis of 1423 ambulatory records of patients with stable angina pectoris showed that the studied group of patients with stable angina included patients with high/very high risk, who often had long-term IHD with complications (ie, MI) and multiple concomitant pathologies, with poor control of angina symptoms, risk factors (weight, heart rate, and lipids), and insufficient frequency of coronary angiography and revascularization procedures.

The clinical part of the study was designed to be as close to real outpatient practice as possible. The aim of the clinical part of the CLASSICA study was to confirm the efficacy of combining original trimetazidine MR (TMZ MR) with traditional hemodynamic active agents for reduction of the number of angina attacks and nitrate consumption in 1213 patients with stable effort angina, functional class II–III (≥ 3 episodes of angina attacks per week) in the following treatment groups: beta-blocker (BB) + TMZ MR (1st group, n=400); BB + long-acting nitrate (LAN) + TMZ MR (2nd group, n=691); BB + calcium channel blocker CCB + TMZ MR (3rd group, n=122) after two months of therapy. Data analysis showed that after adding TMZ MR the number of angina attacks was substantially diminished on background treatment with BBs or their combination with LANs or CCBs. Maximal efficacy was among patients with more severe effort angina (≥ 7 heart attacks per week). The combined use of LANs or CCBs with BBs did not result in additional decrease in frequency of angina attacks per week compared with patients receiving only BBs and TMZ MR.

Key words: stable angina pectoris, treatment.