Multicenter observational program TARGET

Protocol N° IC4-05153-070-RUS

NCT05764317

DescripTion of the effectiveness, safety, tolerability and adherence to Amlodipine/atoRvastatin/perindopril sinGle pill combination trEatmenT in patients with arterial hypertension and dyslipidemia in the daily clinical practice.

11\08\2022

Non-interventional study name: Descrip**T**ion of the effectiveness, safety, tolerability and adherence to **A**mlodipine/ato**R**vastatin/perindopril sin**G**le pill combination tr**E**atmen**T** in patients with arterial hypertension and dyslipidemia in the daily clinical practice. **(TARGET)**

Protocol №: IC4-05153-070-RUS

INN: amlodipine+atorvastatin+perindopril

Dosage:

Amlodipine 5 mg + atorvastatin 10 mg + perindopril arginine 5 mg

Amlodipine 5 mg + atorvastatin 20 mg + perindopril arginine 5 mg
Amlodipine 5 mg + atorvastatin 20 mg + perindopril arginine 10 mg

Pharmaceutical form: film-coated tablet

National coordinator: acad. Irina E. Chazova.

Confidential

Abbreviations

ACE	Angiotensin-converting enzyme
ADR	Adverse drug reaction
AE	Adverse event
ARB	Angiotensin receptor blocker
BL	Baseline
BP	Blood pressure
CABG	Coronary artery bypass surgery

CHD	Coronary heart disease
CKD	Chronic kidney disease
CHF	Chronic heart failure
CRF	Case report form
CV	Cardiovascular
DAH	Dyslipidemic arterial hypertension
DBP	Diastolic blood pressure
HTN	Arterial hypertension
LDL	Low-density lipids cholesterol
SADR	Serious adverse drug reaction
SBP	Systolic blood pressure
SPC	Single pill combination

Contents

1.1 Introduction

Arterial hypertension (HTN) is one of the most important risk factors for the progression of cardiovascular diseases and plays a crucial role in the clinical course of coronary heart artery disease (CHD), peripheral artery disease, stroke, chronic heart failure (CHF) and chronic kidney disease (CKD). According to the results of Framingham Heart Study, more than 80% of patients with HTN have additional risk factors. Lipid metabolism disorders play a key role in the development of atherosclerosis and are the most important predictors of cardiovascular complications in patients with HTN [1]. Dyslipidemia accompanied by HTN is characterized by an early development of oxidative stress, endothelial dysfunction and leads to atherosclerosis progression [2-8]. The prevalence of co-existing dyslipidemia and HTN is from 15 to 31% [9, 10]. According to M.L. Johnson et al. 30, 47 and 18% of the population have dyslipidemia and HTN , isolated HTN and isolated hypercholerestolemia respectively [11]. According to the results of EUROASPIRE III study that included more than 9 000 of participants with CHD from 22 countries including Russia, hypercholesterolemia (total cholesterol ≥4.5 mmol/l) was identified in 51% of all cases [12]. In Framingham Heart Study about 40% of patients with HTN had hypercholesterolemia. Co-existing significant increase of systolic BP and low density lipoprotein cholesterol (LDL-C) levels was associated with an increased risk of major CV events in a 10 year perspective [1]. It has been clearly demonstrated that for patients with a combination of dyslipidemia and HTN, 10% decrease of total cholesterol level and BP lead to 45% decrease in the risk of cardiovascular complications [13].

Benefits of combined approach to antihypertensive and lipid-lowering treatment was proven in ASCOT LLA trial. According to the design of the study patients receiving antihypertensive treatment were further randomly assigned to atorvastatin 10 mg daily or placebo. The study was stopped prematurely after a median 3.3-year follow-up because of a 36% statisticially significant relative risk reduction (RRR) in non-fatal myocardial infarction and fatal CHD (the primary outcome) in favour of atorvastatin and a statisticially significant RRR in fatal and non-fatal stroke (27%), total CV events (21%) and total coronary events (29%) [17]. Following the addition of atorvastatin to amlodipine-based treatment with or without perindopril, the relative risk of non-fatal MI and of fatal CHD decreased by 53% ($p<0.001$), whereas that of all cardiovascular events and of revascularization procedures by 27% (both $p = 0.001$) after 3.3 years of treatment. By contrast, adding atorvastatin to an alternative antihypertensive combination (atenolol ± bendroflumethiazide) did not achieve any significant reduction of these clinical endpoints [21].

Blood pressure and lipid-lowering effectiveness of a triple fixed combination of atorvastatin, perindopril and amlodipine, administered in various dose combinations, was evaluated in a 3-month , prospective, multicentre, observational, non-interventional study. After 3 months of

therapy mean office blood pressure decreased from 158.5 ± 16.7/ 91.7 ± 9.4 to 132.2 ± 8.3/80.1 ± 6.8 mmHg ($p<0.0001$), whereas mean 24-h blood pressure decreased from 146.0 ± 14.5/82.5 ± 12.1 to 132.1 ± 13.2/75.6 ± 9.9 mmHg. Total cholesterol level decreased from 6.18 ± 1.15 to 5.16 ± 0.88 mmol/l and LDL-C - from 3.41 ± 1.01 to 2.80 ± 0.82 mmol/l and triglyceride level from 2.26 ± 1.17 to 1.82 ± 0.83 mmol/l (all $p<0.0001$) [16].

According to the results of the epidemiological studies in Russia only 20% of patients with HTN achieve target level of BP and only 17.4% achieve target level of LDL-C [14,18]. Non-sufficient adherence to the prescribed antihypertensive treatment is one of the most important reasons for this finding [19]. The use of single pill combinations (SPC) has been shown to increase adherence to treatment by 29% [22]. According to Russian clinical guidelines the majority of patients with HTN require a combination dual treatment from the start. It is clearly stated that SPC should be preferred in all cases [15].

Treatment with the fixed triple combination of atorvastatin, perindopril and amlodipine might take us closer to the optimal therapy for hypertensive patients with hypercholesterolaemia. The expected improvement of patient adherence to treatment may result in an increase of the percentage of patients who achieve both blood pressure control and the LDL-cholesterol targets recommended in guidelines. Moreover, this may translate into the further decline of the risk of major cardiovascular events.

1.2 Objectives

Primary objective is to describe antihypertensive and hypolipidaemic effectiveness of a triple single-pill combination of amlodipine, atorvastatin and perindopril at 12 weeks in patients with arterial hypertension (HTN) and dyslipidemia in the daily clinical practice.

Secondary objectives

- To determine the proportion of patients who reached systolic (SBP) and diastolic blood pressure (DBP) target goals at weeks 4 and 12 of the observation period respectively.
- To determine the proportion of patients who reached LDL-C target goals at week 12 of the observation period.
- To evaluate the quality of life of patients at visit 1 (V1) and visit 2 (V2) as compared to visit 0 (V0) respectively.
- To evaluate the adherence to treatment with the fixed dose combination (FDC) of amlodipine/atorvastatin/perindopril in patients included into the study at V1 and V2 as compared to V0.
- To evaluate predictors of reaching BP and LDL-C target goals in the study population.

1.3 Study variables

Primary variables:

- Mean change from baseline (BL) in SBP and DBP assessed at week 12 of the observational period.
- Mean change from BL in LDL-C assessed at week 12 of the observational period.

Secondary variables:

- Mean change from BL in SBP and DBP assessed at week 4 of the observation period.
- Proportion of the patients aged 18-64 years who reached SBP <140 mm Hg and DBP <90 mm Hg at week 4 of the observation period.
- Proportion of patients aged 18-64 years who reached target SBP <130 and ≥120-mm Hg and DBP between 70 and79 mm Hg at week 12 of the observation period.
- Proportion of patients older than 65 years who reached SBP < 140 mm Hg and DBP < 90 mm Hg at week 4 of the observation period.
- Proportion of patients older than 65 years who reached SBP ≤139 and ≥ 130 mm Hg and DBP between 70 and79 mm Hg at week 12 of the observation period.
- Proportion of patients at very high CV risk who reached LDL-C decrease ≥ 50% from BL and reached target < 1,4 mmol/l (55 mg/dl) ~~or~~ at week 12 of the observation period.
- Proportion of patients at high CV risk who reached LDL-C decrease ≥ 50% from BL and reached target LDL-C < 1,8 mmol/l (70 mg/dl) at week 12 of the observation period.
- Proportion of patients at moderate CV risk who reached target LDL-C < 2,6 mmol/l (100 mg/dl) at week 12 of the observation period.
- Proportion of patients at different CV risk who reached both BP and LDC-C targets
- Proportion of patients aged 18-64 years at very high CV risk who reached SBP <130 and ≥ 120 mm Hg and DBP between 70 and79 mm Hg at week 12 of the observation period in the subgroups of the patients receiving SPC of amlodipine/atorvastatin/perindopril in the following dosages 5;20;5 mg and 5;20;10 mg and 5;10;5 mg respectively;
- Proportion of patients older than 65 years at very high CV risk who reached SBP ≤139 and ≥ 130 mm Hg and DBP between 70 and79 mm Hg at week 12 of the observation period in the subgroups of patients receiving SPC of amlodipine/atorvastatin/perindopril in the following dosages 5;20;5 mg and 5;20;10 mg and 5;10;5 mg respectively
- Proportion of patients at very high CV risk who reached LDL_C decrease ≥ 50% from BL and reached target <1,4 mmol/l (55 mg/dl) or at week 12 of the observation period in the subgroups of the patients receiving SPC of amlodipine/atorvastatin/perindopril in the following dosages 5;20;5 mg and 5;20;10 mg and 5;10;5 mg respectively;
- Proportion of patients aged 18-64 years at high CV risk who reached SBP <130 and ≥120 mm Hg and DBP between 70 and79 mm Hg at week 12 of the observation period in the subgroups of patients receiving SPC of amlodipine/atorvastatin/perindopril in the following dosages 5;20;5 mg and 5;20;10 mg and 5;10;5 mg respectively;
- Proportion of patients older than 65 years at high CV risk who reached SBP ≤139 and ≥130 mm Hg and DBP between 70 and79 mm Hg at week 12 of the observational period in the subgroups of patients receiving SPC of amlodipine/atorvastatin/perindopril in the following dosages 5;20;5 mg and 5;20;10 mg and 5;10;5 mg respectively;

- Proportion of patients at high CV risk who reached decrease of LDL-C from BL ≥ 50% and reached target <1,8 mmol/l (55 mg/dl) at week 12 of the observation period in the subgroups of patients receiving SPC of amlodipine/atorvastatin/perindopril in the following dosages 5;20;5 mg and 5;20;10 mg and 5;10;5 mg respectively;
- Proportion of patients aged 18-64 years at moderate CV risk who reached SBP <130 and ≥120 mm Hg and DBP between 70 and79 mm Hg at week 12 of observational period in the subgroups of patients receiving SPC of amlodipine/atorvastatin/perindopril in the following dosages 5;20;5 mg and 5;20;10 mg and 5;10;5 mg respectively;
- Proportion of patients older than 65 years at moderate CV risk who reached SBP ≤139 and ≥130 mm Hg and DBP between 70 and 79 mm Hg at week 12 of the observation period in the subgroups of patients receiving SPC of amlodipine/atorvastatin/perindopril in the following dosages 5;20;5 mg and 5;20;10 mg and 5;10;5 mg respectively;
- Proportion of patients at moderate CV risk who reached LDL-C < 2,6 mmol/l (100 mg/dl) at week 12 of the observation period in the subgroups of patients receiving SPC of amlodipine/atorvastatin/perindopril in the following dosages 5;20;5 mg and 5;20;10 mg and 5;10;5 mg respectively;
- Mean change from V0 in scores of the SF-36 questionnaire assessed at V1 and V2;
- Proportion of patients with high, moderate and low adherence to the treatment with SPC of amlodipine/atorvastatin/perindopril at V1 as compared to V0 via medication adherence scale;
- Proportion of patients with high, moderate and low adherence to the treatment with SPC of amlodipine/atorvastatin/perindopril at V2 as compared to V0 via medication adherence scale;
- Association between the fact of achieving target BP levels at week 12 and baseline BP and LDL-C levels;
- Association between the fact of achieving target LDL-C level at week 12 and baseline BP and LDL-C levels as well as CV risk category;
- Association between the fact of achieving target BP and LDL-C levels at week 12 with the categories of CV risk, initial dosage of SPC amlodipine/atorvastatin/perindopril and adherence rate to the administered therapy with FDC.
- Association between patients'adherence to SPC amlodipine/atorvastatin/perindopril therapy at week 4 and week 12 and baseline BP level.
- Predictors for achieving target BP levels (i.e. smoking, sex, baseline SBP and DBP, duration of HTN, level of CV risk, duration of therapy, baseline LDL-C level, CAD diagnosis);
- Predictors for achieving target LDL-C levels (i.e. smoking, sex,baseline SBP and DBP, duration of HTN, level of CV risk, duration of therapy, baseline LDL-C level, CAD diagnosis).

2. Methods and documentation

2.1 Study design with the rationale for its' choice

This is a multi-centre, observational, ambispective study, which will retrospectively and prospectively collect clinical and socio-demographic data from medical records of patients with HTN and dyslipidemia initiated with SPC of amlodipine/atorvastatin/perindopril in real clinical settings.

For parameters of the primary end-point such as BP and LDL-C **a Baseline data** is defined as values of these parameters present in medical records at the nearest date preceding the start of SPC amlodipine/atorvastatin/perindopril. Therefore BP and LDL-C **Baseline data** will be collected retrospectively from medical records of patients with HTN and dyslipidemia. To be included in the study for further prospective observation a patient should have been administered with SPC of amlodipine/atorvastatin/perindopril within one month before the Index Date. The Index date is a date when a decision to include a patient in the study for further 12 week prospective observation made by a treating physician after evaluation of recorded data to confirm patient's eligibility for the study. Once an investigator makes sure that a patient meets all inclusion/non-inclusion critera the investigator will discuss with the patient during his/her next visit and obtain the signed patient's informed consent to participate in the study (V0).

SPC of amlodipine/atorvastatin/perindopril will be administered to the patients in accordance to the instruction for medical use approved in the Russian Federation. Decision on this medicinal product administration will not be dependent on the decision to include a patient into the observational study and according to the study protocol, such decision should precede treating investigator's intention to include a patient in the study.

2.2 Calculation of the sample size

In the clinical study superiority hypothesis over baseline will be assessed.

The parameters of SBP, DBP and LDL-cholesterol are quantitative and changes between 12 weeks and baseline will be made, therefore, for the sample size calculation was used the following formula:

$$n = \frac{\sigma^2 (Z_{1-\alpha} + Z_{1-\beta})^2}{(\mu_A - \mu_0 - \delta)^2}$$

To calculate the sample size were used the following articles:

- Dézsi, C. A. (2018). Treatment with triple combination of atorvastatin, perindopril, and amlodipine in patients with stable coronary artery disease: A subgroup analysis from the PAPA-CAD study. Journal of International Medical Research, 46(5), 1902-1909.

- Simon, A., & Dézsi, C. A. (2019). Treatment of hypertensive and hypercholesterolaemic patients with the triple fixed combination of atorvastatin, perindopril and amlodipine: the results of the CORAL study. Advances in therapy, 36(8), 2010-2020.

Systolic blood pressure

According to the literature the following assumptions were made:

- Study drug efficacy (μ_A) – mean systolic blood pressure after 3 month of therapy will be 132.2 mmHg.
- Null hypothesis drug efficacy (μ_0) - mean systolic blood pressure will be the same as at baseline – 158.5 mmHg.
- Maximum Standard deviation (σ) – 16.7 mmHg.
- Superiority margin (δ) considered as half of the difference between the drug and baseline – -13.15 mmHg (*D'Agostino Sr R. B., Massaro J. M., Sullivan L. M. Non-inferiority trials: design concepts and issues–the encounters of academic consultants in statistics //Statistics in medicine. – 2003. – Т. 22. – №. 2. – С. 169-186.; Food and Drug Administration et al. Non-inferiority clinical trials to establish effectiveness: guidance for industry //US Department of Health and Human Services. – 2016.; Committee for Proprietary Medicinal Products (CPMP et al. Points to consider on switching between superiority and non-inferiority //British journal of clinical pharmacology. – 2001. – Т. 52. – №. 3. – С. 223.*).
- Type I error (α) – 1%. $Z_{1-\alpha}$ – 2,326.
- Type II error (β) – 10%. $Z_{1-\beta}$ – 1.282.

The null hypothesis is formulated as:

“Change in mean systolic blood pressure after 3 month of therapy comparing to baseline will be not less than -13.15 mmHg”

$$H_0: \mu_A - \mu_0 \geq -13.15$$

The alternative hypothesis is formulated as:

“Change in mean systolic blood pressure after 3 month of therapy comparing to baseline will be less than -13.15 mmHg”

$$H_1: \mu_A - \mu_0 < -13.15$$

As a result of the calculation, it was found that in order to obtain statistically significant results, it is necessary to use data from at least 21 completed cases.

Diastolic blood pressure

According to the literature the following assumptions were made:

- Study drug efficacy (μ_A) – mean diastolic blood pressure after 3 month of therapy will be 80.1 mmHg.
- Null hypothesis drug efficacy (μ_0) - mean diastolic blood pressure will be the same as at baseline – 91.7 mmHg.
- Maximum Standard deviation (σ) – 9.9 mmHg.
- Superiority margin (δ) considered as half of the difference between the drug and baseline – -5.8 mmHg (*D'Agostino Sr R. B., Massaro J. M., Sullivan L. M. Non-inferiority trials:*

design concepts and issues–the encounters of academic consultants in statistics //Statistics in medicine. – 2003. – Т. 22. – №. 2. – С. 169-186.; Food and Drug Administration et al. Non-inferiority clinical trials to establish effectiveness: guidance for industry //US Department of Health and Human Services. – 2016.; Committee for Proprietary Medicinal Products (CPMP et al. Points to consider on switching between superiority and non-inferiority //British journal of clinical pharmacology. – 2001. – Т. 52. – №. 3. – С. 223.).

- Type I error (α) – 1%. $Z_{1-\alpha}$ – 2,326.
- Type II error (β) – 10%. $Z_{1-\beta}$ – 1.282.

The null hypothesis is formulated as:

"Change in mean diastolic blood pressure after 3 month of therapy comparing to baseline will be not less than -5.8 mmHg"

$$H_0: \mu_A - \mu_0 \geq -5.8$$

The alternative hypothesis is formulated as:

"Change in mean diastolic blood pressure after 3 month of therapy comparing to baseline will be less than -5.8 mmHg"

$$H_1: \mu_A - \mu_0 < -5.8$$

As a result of the calculation, it was found that in order to obtain statistically significant results, it is necessary to use data from at least 38 completed cases.

LDL-cholesterol

According to the literature the following assumptions were made:

- Study drug efficacy (μ_A) – mean LDL-cholesterol level after 3 month of therapy will be 2.65 mmol/L.
- Null hypothesis drug efficacy (μ_0) - mean LDL-cholesterol level will be the same as at baseline – 3.09 mmol/L.
- Maximum Standard deviation (σ) – 1.01 mmol/L.
- Superiority margin (δ) considered as half of the difference between the drug and baseline – -0.22 mmol/L (*D'Agostino Sr R. B., Massaro J. M., Sullivan L. M. Non-inferiority trials: design concepts and issues–the encounters of academic consultants in statistics //Statistics in medicine. – 2003. – Т. 22. – №. 2. – С. 169-186.; Food and Drug Administration et al. Non-inferiority clinical trials to establish effectiveness: guidance for industry //US Department of Health and Human Services. – 2016.; Committee for Proprietary Medicinal Products (CPMP et al. Points to consider on switching between superiority and non-inferiority //British journal of clinical pharmacology. – 2001. – Т. 52. – №. 3. – С. 223.*).
- Type I error (α) – 1%. $Z_{1-\alpha}$ – 2,326.
- Type II error (β) – 10%. $Z_{1-\beta}$ – 1.282.

The null hypothesis is formulated as:

"Change in mean LDL-cholesterol level after 3 month of therapy comparing to baseline will be not less than -0.22 mmol/L"

$$H_0: \mu_A - \mu_0 \geq -0.22$$

The alternative hypothesis is formulated as:

"Change in mean LDL-cholesterol level after 3 month of therapy comparing to baseline will be less than -0.22 mmol/L"

$$H_1: \mu_A - \mu_0 < -0.22$$

As a result of the calculation, it was defined that in order to obtain statistically significant results, it is necessary to use data from at least 274 completed cases.

To obtain statistically significant results on all three primary endpoints the greatest value of calculated sample size was chosen – 274 completed cases.

Taking into account the possible drop-out rate of 30% of patients during the study, 400 patients should be included in the study.

2.3 Selection of doctors

A total of 80 general practitioners and outpatient cardiologists will participate in this non-interventional study

2.4 Selection of patients

2.4.1 Inclusion criteria

1. Obtained signed informed consent from the patient
2. Patients of 18 years and older and younger than 80 years.
3. Start of the treatment with SPC of amlodipine/atorvastatin/perindopril within 1 month from the Index date in accordance with the indication in Russian SmPC.
4. Presence of the parameters of interest* in the medical records dated with the nearest to the start of SPC amlodipine/atorvastatin/perindopril treatment date.

* Parameters of interest include measured at rest office BP and LDL-C.

2.4.2 Non-inclusion criteria

1. Subjects who are unwilling or unable to provide a signed informed consent form;
2. Any contraindication to the treatment with the SPC of amlodipine/atorvastatin/perindopril according to its' approved instruction for medical use in the Russian Federation;
3. Concomitant use of any other ACE inhibitors, CCBs, ARBs and statins.
4. Supposed low treatment adherence to the assigned SPC and the risk for poor collaboration between the patient and the investigator during the study;
5. Any severe, decompensated or unstable somatic diseases or states that according to investigator discretion are life-threatening or worsen the prognosis for the patient: myocardial infarction in the past 3 months, unstable angina, current decompensation of diabetes mellitus, autoimmune or oncological diseases, severe cardiac arrhythmia,

gastrointestinal disorders affecting absorbtion, severe hepatic diseases, pancreatic diseases, severe allergic reactions, connective tissue diseases etc;

6. Secondary arterial hypertension;
7. Alcohol or any drug abuse;
8. Surgical intervention on heart or coronary vessels (i.e., heart valve(s) replacement, stent implantation or CABG), or any non-cardiological serious surgical intervention that are planned within next 3 months and may require withdrawal or changes in current therapy;
9. Glomerular filtration rate less than 60 ml/min/1,72m^2;
10. Participating in any other clinical trial currently or during 30 days period before informed consent was signed.

2.5 Therapeutic strategy during the study

2.5.1 Treatment with the studied drug

Amlodipine 5 mg + atorvastatin 10 mg + perindopril arginine 5 mg

Amlodipine 5 mg + atorvastatin 20 mg + perindopril arginine 5 mg

Amlodipine 5 mg + atorvastatin 20 mg + perindopril arginine 10 mg

This is non-interventional study that is observational by its nature. Therefore there will be no any assignments of subjects to a particular therapeutic strategies defined by this protocol. Decision to treat a patient with SPC of amlodipine/ atorvastatin/ perindopril should be at the descretion of a treating investigator and made in accordance to local standards and protocols.

2.5.2 Concomitant drugs

Due to the non-interventional design of the study, it is allowed to use any concomitant treatments or drugs if it is considered necessary by the treating invstigator. Any changes in the medical treatment are also allowed during the observational period of the study and will be gathered and appropriately reflected in the study documentation at appointed visits to clinics by a treating investigator.

2.6 Duration of non-interventional study

It is planned to complete enrolment of patients in this non-intervention study within 6 months.

Follow-up period for each patient will be 12 weeks.

First patient in is scheduled for Q4 2022

Last patient in is scheduled for Q2 2023

Last patient last visit Q3 2023

Data base lock is scheduled for Q3 2023

Statistical analysis is scheduled for Q4 2023

Clinical study report is scheduled for Q1 2024

2.7 Documentation of the non-interventional clinical study

2.7.1. Documentation folder

Each doctor will be provided with a documentation folder containing a complete set of documents for 5-6 patients + 2 extra sets in case of lost or damage of study documentsincluding:

- One protocol of the observation plan;
- Documents for 5-6 patients (12 *Patient Informed Consent Forms*, with 5-6 *Adverse event/adverse drug reaction/special situation reporting forms*).
- 2 extra sets in case of lost or damage of study documents (*Patient Informed Consent Form„; Adverse event/adverse drug reaction/special situation reporting forms)*

2.7.2 Study schedule and plan

According to the design of this multicentre, non-intervention, observational study in patients with HTN and dyslipidemia treated with SPC of amlodipine/atorvastatin/perindopril, three visits will be appointed to include patients and to gather parameters of interest to describe treatment effectiveness and safety of the FDC.

Following visits will be appointed:

1. Inclusion Visit 0 (V0) – month 0;

2. Follow up Visit 1 (V1) – 4 weeks after V0;

3. Final Visit 2 (V2): 12 weeks after V0;

Table 1 – Planned study visits

Procedure	**Retrospective evaluation of patient's eligibility**	**Inclusion Visit 0 Month 0**	**Follow up visit V1 (4 weeks ± 2 weeks)**	**Final visit V2 (12 weeks ± 2 weeks)**
Written informed consent		×		
Assessment in accordance with inclusion/ non-inclusion critera	×	×		
Demographics		×		
Risk factors and life style		×		
Cardio-vascular disease history		×		
Physical examination with the measurement of BP at rest		×	×	×

LDL-C		×		×
Current treatment with concomitant cardiovascular medications/ changes and reasons		×	×	×
Current treatment with other concomitant medications		×	×	×
Medication adherence scale		×	×	×
Quality of life evaluation (SF-36)		×	×	×
Treatment with the SPC amlodipine/atorvastatin/perindopril status		×	×	×
SPC amlodipine/atorvastatin/perindopril dosage correction (if occured)		×	×	×
Adverse events/drug reactions/ special situations reporting		×	×	×

2.7.4. Data collection:

Data evaluation during the screening period:

HCPs participating in the study will conduct a retrospective analysis of patient's records for the purpose of evaluating patient's eligibility to be enrolled in the study. Patients with HTN and dyslipidemia who had been initiated with SPC amlodipine/atorvastatin/perindopril within one month before the Index Date and who meet other inclusion / non inclusion criteria will be included in the study if they sign a consent form at the inclusion visit.

Data collection at the inclusion visit (V0):

- Obtaining patient informed consent;
- Checking for inclusion/non-inclusion criteria;
- Demographics, CVD history, cardiovascular risk factors (appendix 8)
- Physical examination and vital signs (BP);
- Current status of taking SPC amlodipine/atorvastatin/perindopril and dose regimen;
- SBP, DBP and LDL-C according to the medical records dated with the nearest to the start of treatment with SPC amlodipine/atorvastatin/perindopril;
- Concomitant current use of any other cardiovascular medications (i.e. antihypertensive, anti-ischaemic, anti-platelet, anticoagulant medications) and any other concomitant medications
- Baseline assessment of adherence to SPC amlodipine/atorvastatin/perindopril done by medication adherence scale;

- Quality of life assessment (questionnaire SF-36)
- Adverse events/drug reactions/special situations

Data collection at the Follow up Visit (V1):

- Physical examination and vital signs (BP);
- Current status of taking SPC amlodipine/atorvastatin/perindopril and dose regimen correction if needed;
- Assessment of adherence to SPC amlodipine/atorvastatin/perindopril done by medication adherence scale;
- Quality of life assessment (questionnaire SF-36)
- Concomitant current use of other cardiovascular medications and any other medications
- Adverse events/drug reactions/special situations

Data collection at the Final Visit (V2):

- Physical examination and vital signs (BP);
- Current status of taking SPC amlodipine/atorvastatin/perindopril and a dose regimen correction if needed;
- LDL-C assessment;
- Assessment of adherence to SPC amlodipine/atorvastatin/perindopril done by medication adherence scale;
- Quality of life assessment (questionnaire SF-36)
- Concomitant current use of other cardiovascular medications and any other medications
- Adverse events/drug reactions/special situations

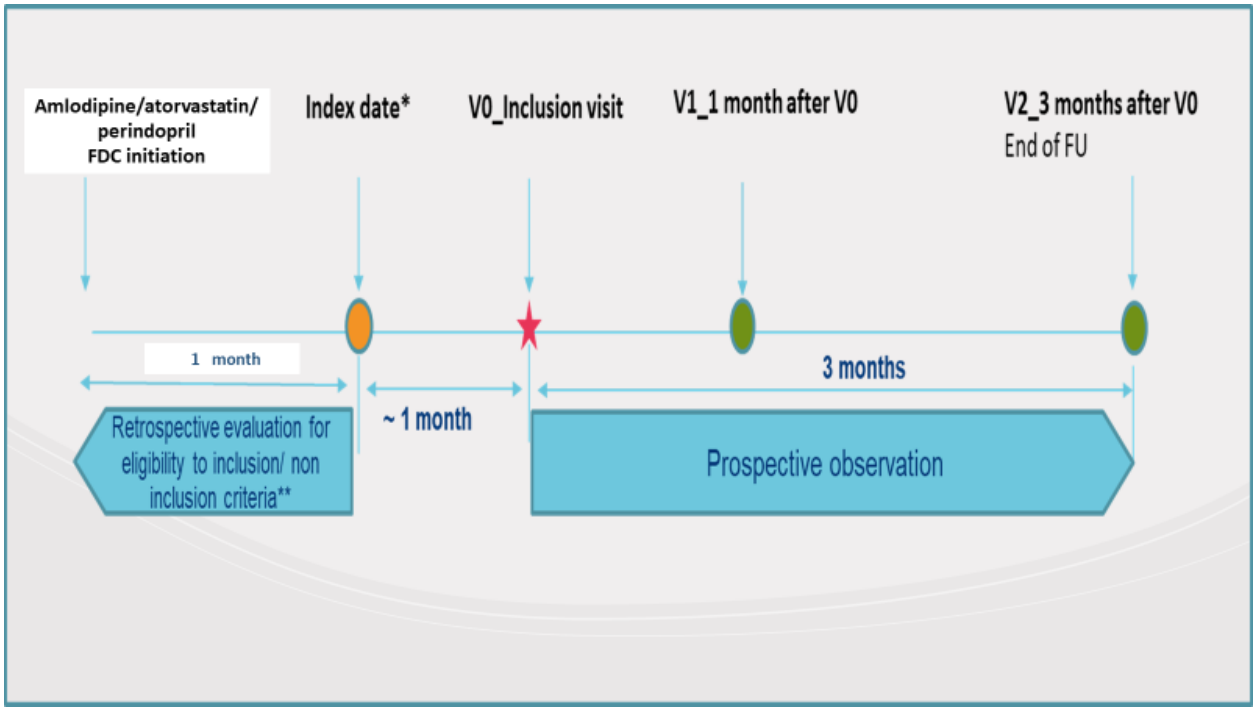


Figure 1. The scheme of TARGET study

2.7.5 Implementation of non-intervention study

The treating investigator will receive a documentation folder and instructions from the Servier staff. The patient should be informed of his/her participation in this study and the transfer of his/her clinical data from the site to the responsible professional subcontractor for statistical analyses. Written informed consent must be obtained from the patient at the inclusion visit.. In case of occurrence of adverse events (AEs), adverse drug reactions (ARDs), or special situations, it is necessary to follow the requirements listed in the section «*Responsibilities of the investigator*». Please hand over the folder with the complete documentation to your Servier local executive.

Patients will undergo clinical assessment and receive the standard medical care as usual determined by the treating doctors based on their clinical judgement and national guidelines. Patients will not receive experimental treatment as a consequence of their participation in the observational study

3 Pharmacovigilance

3.1 Definitions

3.1.1 Pharmacovigilance information

Pharmacovigilance data include any unintended or adverse event associated with the use of a medicinal product in humans, whether or not considered drug related, including the following special situations (situations where no adverse event occurred but information needs to be collected):

- exposure during pregnancy or breastfeeding;
- overdose, abuse, misuse, off-label uses, medication error, or occupational exposure (including professional one);
- lack of treatment effectiveness of a medicinal product;
- any suspected transmission via medicinal product of an infection agent;
- unintended therapeutic benefit.

3.1.2 Adverse Event (AE)

Adverse event is any untoward medical occurrence in a patient or a clinical-trial subject who received the medicinal product, which does not necessarily have a causal relationship with the use of this medicinal product.

An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

3.1.3 Adverse (drug) reaction (ADR)

Adverse reaction (synonyms: Adverse drug reaction, Suspected adverse (drug) reaction, Adverse effect, Undesirable effect) is a response to a medicinal product which is noxious and unintended.

"Response" in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

3.1.4 Serious adverse (drug) reaction (SADR)

Serious adverse reaction is an adverse reaction, which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

"Life threatening" in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

3.2 Responsibilities

3.2.1 Events to be reported

All available information about the following reported events occurring during the study will be recorded. All reported AEs/ADRs will be described in the statistical analysis report.

- All serious adverse drug reactions related to the use of amlodipine/atorvastatin/perindopril FDC;
- All non-serious adverse drug reactions related to the use of SPC amlodipine/atorvastatin/perindopril);
- All reports about special situations (see 3.1.1);

- All adverse events

3.2.2 Responsibilities of the investigator

At the visits during the study,the treating physician will ask the participating patient to indicate whether or not an adverse event (serious or not) has occurred.

The treating physician should determine the presence/absence of a causal relationship between the use of the study drug and the adverse event, the presence/absence of criteria for seriousness, and then the outcome of the event.

In case of detection of any adverse event/adverse drug reaction or occurrence of a special situation during the study (both serious or not serious), the treating physician must fill out the «*Adverse event/adverse drug reaction/special situation reporting form»* (Appendix No.4) without waiting for the clinical outcome or the results of additional investigations.

If the event is serious, the form should be sent immediately (same or next working day at the latest) to Servier company in Russia via e-mail to address pvmail.rus@servier.com or by fax to number (495) 937-47-66. The anonymized copies of all the available and relevant laboratory findings, hospitalisation reports or other investigation results performed in relation to the adverse event should be attached to the form. All other events should be transmitted by the treating physician within 2 working days.

The same obligations will apply for follow-up reports. The treating physician must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution. She/he will continue to notify follow up data according to timeframes defined above.

If the follow-up of the participant is not done by the treating physician him/herself (hospitalisation, followed by a specialist or the participant's general practitioner,…), the treating physician will do every effort to establish/maintain contact with the person/department in charge of follow-up of the participant, so as to have additional information and report it.

3.2.3 Responsibilities of the Sponsor/Marketing Authorisation Holder

Independently of the regulatory obligations of investigator, the sponsor/marketing authorisation holder (MAH) must report the pharmacovigilance data to the appropriate authorities in accordance with the Good PharmacoVigilance Practice and local regulations.

Cases of adverse event are considered to be closed when the patient has recovered or his/her condition was stabilised, providing that the available data are sufficiently detailed for adequate medical analysis of the case.

4 Data management, quality management, statistics and reporting

4.1 Data management

Data collection in this study is carried out using documentation forms. Centralized data entry will be carried out by a responsible professional subcontractor for statistical analyses after receiving documentation forms. Statistical analysis of the data and the creation of the final statistical report on the study will also be carried out by the responsible professional subcontractor for statistical analyses.

4.2 Statistical analysis

Due to the non-interventional nature of this study, statistical analysis will be carried out in descriptive and exploratory forms. All parameters will be analysed using descriptive statistics. For each parameter, the following will be specified: number of patients, mean value, standard error, minimum and maximum values, or proportion of each category. All composite endpoints will be listed and presented in visual form as graphs and in tables of parameters and their frequencies. For categorical variables, absolute values and rates in per cents be calculated. The calculations of relative rates will include only patients in whom values of the corresponding variables will be available.

Accepted level of significance

In all tests, a significance level of 0.05 will be used, and 2-sided statistical tests will be carried out.

Search statistical analysis will be performed in the following subgroups of patients:

- patients with stable CAD
- patients with diabetes mellitus type 1 or type 2
- patients with chronic kidney disease

All reports of adverse drug reactions (ARDs), adverse events (AEs), serious ADR/AE, and special situations will be encoded using MedDRA by the subcontractor , and the results will be listed and classified according to the System-Organ-Classes (SOCs). Descriptive statistics will be used.

4.3 Report preparation

The preparation of the final report on the study will begin after the completion of the statistical analysis. The publication of the main results is planned within 12 months after the end of the study.

5. Ethical considerations

The study will be carried out in accordance with the principles of the Helsinki Declaration, according to the version revised in Brazil in 2013. The protocol must be reviewed and approved by an independent ethics committee after it is submitted by the coordinator or sponsor in accordance with local regulatory requirements, especially on the matters relating to data protection. Patients will be informed about the conditions for participation in the study, and they will have to provide written consent to participate in the study. The doctor must confirm in the Case report form (CRF) that the informed consent has been obtained, and he/she must keep one

original of the signed informed consent form in the patient's file. "Informed consent" also means an individual discussion of procedures, that will be conducted as a part of the study, with the patient.

5.1 Patient data privacy

Investigators should maintain confidentiality of information about patients included in this study. Confidential data should contain enough information to contact the patient in case of emergency, or if further monitoring is required. Patient's right to privacy is of utmost importance. To protect the data confidentiality and preserve patient anonymity, patient's identity will be encoded in the study documentation. Patients can be identified using a unique number, age and gender, which will be recorded in the CRF. To reveal the patient's identity, all investigators will keep a confidential list for patient identification containing the names and addresses of the patients, as well as their assigned numbers. Thus, only investigator will be able to decode the identity of a patient.

6. Appendices

Appendix 1. Classification of blood pressure and definition of hypertension grade [15].

BP categories	**SBP, mm Hg**		**DBP, mm Hg**
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1	140–159	and/or	90–99
Grade 2	160–179	and/or	100–109
Grade 3	≥180	and/or	≥110
Isolated systolic hypertension[1]	≥140	and	<90

[1] Isolated systolic hypertension (ISH) should be classified into grades 1, 2, and 3 according to the SBP level.

Appendix 2.

Medication Adherence Scale [20].

1. Sometimes I can make a break in my daily medication therapy for:
   a) One day
   b) Two days
   c) Three days
   d) I don't make breaks at all
2. I take my medications:
   a) Every day
   b) Only when I feel unwell
   c) I take courses of medication treatment
   d) In exceptional cases
3. I change dosage/frequency of medication administered by the doctor:
   a) I start taking medications as administered and then I change as I feel appropriate
   b) I make the dosage lower when I feel better
   c) I change the dosage (make it higher or lower) depending on the way I feel
   d) I take the dosage administered by the doctor independently of how I feel
4. I stop taking medication when:
   a) I feel that I am not sick anymore
   b) I don't feel pain or discomfort anymore
   c) Medication is withdrawn by the doctor
   d) Medication doesn't help me

Appendix 3.

The SF-36 health survey questionnaire

(The survey was developed by RAND Health on the basis of Medical Outcomes Study; the Russian version was developed and recommended by the Multinational Center for Quality of Live Research)

Name of patient _____

Date of completion _____

Please circle one number for each statement.

1. In general, would you say your health is?

Excellent 1

Very good 2

Good 3

Fair..... 4

Poor 5

2. *Compared to one year ago*, how would you rate your health in general *now*?

Much better now than one year ago..... 1

Somewhat better now than one year ago …… 2

About the same 3

Somewhat worse now than one year ago……..... 4

Much worse now than one year ago …….5

3. The following items are about activities you might do during a typical day. Does *your health now limit you* in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
A. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports.	1	2	3
B. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	1	2	3
C. Lifting or carrying groceries.	1	2	3
D. Climbing **several** flights of stairs.	1	2	3
E. Climbing **one** flight of stairs.	1	2	3
F. Bending, kneeling, or stooping.	1	2	3
G. Walking **more than a mile**.	1	2	3

H. Walking **several blocks**.	1	2	3
I. Walking **one block**.	1	2	3
J. Bathing or dressing yourself.	1	2	3

4. During the *past 4 weeks*, have you had any of the following problems with your work or other regular daily activities *as a result of your physical health*:

	Yes	No
A. Cut down the **amount of time** you spent on work or other activities.	1	2
B. **Accomplished less** than you would like.	1	2
C. Were limited in the **kind** of work or other activities.	1	2
D. Had **difficulty** performing the work or other activities (for example, it took extra effort).	1	2

5. During the *past 4 weeks*, have you had any of the following problems with your work or other regular daily activities *as a result of any emotional problems* (such as feeling depressed or anxious)?

	Yes	No
A. Cut down the **amount of time** you spent on work or other activities.	1	2
B. **Accomplished less** than you would like.	1	2
C. Didn't do work or other activities as **carefully** as usual.	1	2

6. During the *past 4 weeks*, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all 1

Slightly 2

Moderately..... 3

Quite a bit 4

Extremely 5

7. How much *bodily* pain have you had during the *past 4 weeks*?

None 1

Very mild..... 2

Mild 3

Moderate..... 4

Severe 5

Very severe ……..……6

8. During the *past 4 weeks*, how much did *pain* interfere with your normal work (including both work outside the home and housework)?

Not at all 1

A little bit..... 2

Moderately..... 3

Quite a bit 4

Extremely 5

9. These questions are about how you feel and how things have been with you *during the past 4 weeks*. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the *past 4 weeks*...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
A. Did you feel full of pep?	1	2	3	4	5	6
B. Have you been a very nervous person?	1	2	3	4	5	6

C. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
D. Have you felt calm and peaceful?	1	2	3	4	5	6
E. Did you have a lot of energy?	1	2	3	4	5	6
F. Have you felt downhearted and blue?	1	2	3	4	5	6
G. Did you feel worn out?	1	2	3	4	5	6
H. Have you been a happy person?	1	2	3	4	5	6
I. Did you feel tired?	1	2	3	4	5	6

10. During the *past 4 weeks*, how much of the time has *your physical health or emotional problems* interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time..... 1

Most of the time..... 2

Some of the time..... 3

A little of the time ……..…… 4

None of the time 5

11. How TRUE or FALSE is *each* of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
A. I seem to get sick a little easier than other people	1	2	3	4	5
B. I am as healthy as anybody I know	1	2	3	4	5
C. I expect my health to get worse	1	2	3	4	5
D. My health is excellent	1	2	3	4	5

The survey has the following scales:

1. Physical functioning (PF).
2. Role physical (RP).
3. Bodily pain (BP).
4. General health (GH).
5. Vitality (VT).
6. Social functioning (SF).
7. Role emotional (RE).
8. Mental health (MH).

All the scales of survey constitute two composite measurements: Physical Component Summary (PCS) (scales 1 to 4) and Mental Component Summary (MCS) (scales 5 to 8).

The method for calculating the main parameters of the SF-36 questionnaire

Scale	Questions	Minimal and maximal values	Possible range of values
1. Physical functioning (PF)	3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, and 3J	10 – 30	20
2. Role physical (RP)	4A, 4B, 4C, and 4D	3 – 8	4
3. Bodily pain (BP)	7 and 8	2 – 12	10

4. General health (GH)	1, 11A, 11B, 11C, and 11D	5 – 25	20
5. Vitality (VT)	9A, 9E, 9G, and 9I	4 – 24	20
6. Social functioning (SF)	6 and 10	2 – 10	8
7. Role emotional (RE)	5A, 5B, and 5C.	3 - 6	3
8. Mental health (MH)	9B, 9C, 9D, 9F, 9H.	5 – 30	25

For items 6, 9A, 9E, 9D, 9H, 10, and 11, the count-down is applied.

The formula for calculating the values:
[(actual value of the scale) – (minimal possible value on the scale] : (possible range of values) □ 100.

Requirements for presenting the results:

1. Number of cases per each parameter should be indicated;
2. Descriptive statistics: M ± SD, Me (LQ; UQ), % (n/N);
3. Accuracy of results (estimates, P value); Confidence interval (for main results of the study) and P value;
4. Statistical methods (parametric and non-parametric) and statistical packages should be mentioned.

The recommended statistical packages for the data processing are StatSoft Statistica v.6.0, and SPSS 9.0.

Appendix 4. Adverse event / Adverse drug reaction / Special Situation Reporting Form

TARGET

Protocol № IC4-05351-070-RUS

Please send this form immediately by fax (495) 937-47-66 or by email to pvmail.rus@servier.com, or pass it to the associate of the company.

Year of birth	**or**	**Age**	**Gender**	**Height**	**Weight**	**Patient number**
____	or	___	M / F	___	___	_____

Observed adverse event:	**Date of onset**	**Until (if recovered)**
	__ __ ____	__ __ ____

Serious:	**Outcome:**
☐ No	
☐ Yes, because: (please choose below)	☐ Recovered
☐ Fatal	☐ Recovered with sequelae
☐ Life-threatening	☐ Recovering
☐ Hospitalisation or prolongation of hospitalisation	☐ Not recovered
☐ Persistent or significant disability or incapacity	☐ Fatal
☐ Congenital anomaly/birth defect	☐ Unknown
☐ Medically significant	

General disease(s) / Concomitant disease(s) (please indicate year of first diagnoses):

Course (please enclose relevant findings e.g. laboratory, hospital reports, histology, etc.):

Causal relationship with the <u>studied</u> Servier drug:

☐☐ ☐ No ☐ Yes ☐ Not applicable

***If yes**, please specify dates of treatment with the studied drug in the table below <u>on the first line</u>:*

***If no or not applicable,** please indicate whether the adverse event /special situation is related to a Servier medicinal product (as mentioned in the following table)*:

☐ No ☐ Yes *please specify which Servier medicinal product: …….*

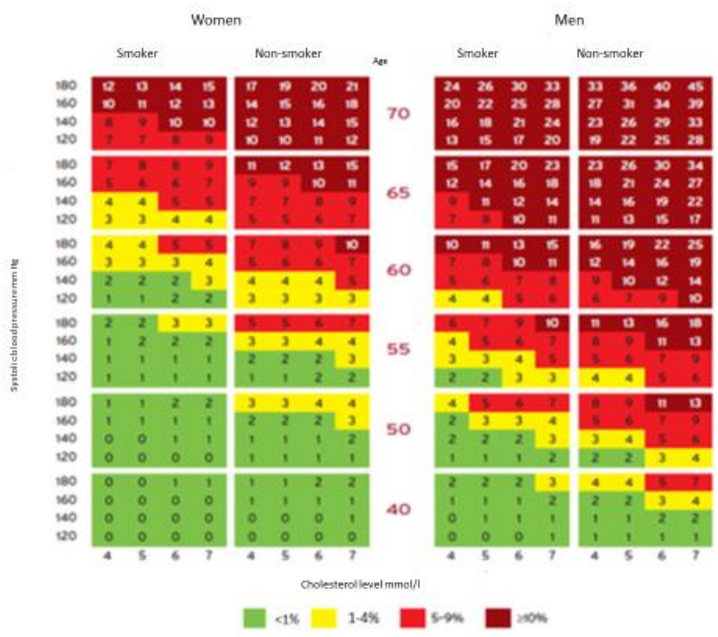
Medication list	Daily dosage / application	Administered	Indication
		-	
		-	
		-	

Name: Speciality: Address: Phone:	Date: Signature:

Special situations: situations where no adverse events occurred but information needs to be collected: exposure during pregnancy or breastfeeding, abuse, misuse, medication error, overdose, off label use, occupational exposure, lack of efficacy, suspected transmission of infectious agent via a medicinal product, unintended therapeutic benefit …*

Appendix 5. Score Scale

Name: SCORE scale (Systematic Coronary Risk Evaluate)
Source: http://www.heartscore.org/ru_RU
Purpose: clinical tool for the assessment of the fatal CV event risk in the next 10 years. The scale has been developed for the countries with high CV mortality rate (including Russia) based on the following factors: age, smoking, SBP and total cholesterol levels. Level od HDL-C is not taken into consideration in this scale. It is recommended to use SCORE scale to assess risk in asymptomatic patients older than 40 years, without CVD, diabetes mellitus, chronic kidney disease or familial hypercholesterolemia



Interpretation:

Total CV risk according to SCORE scale:

Less than 1% — low.

1 - 4% — moderate.

5% - 9% — high.

> 10% - very high

Appendix 6. Categories of CV risk and target levels of LDL-C [15]

Risk	Definition	Target level ofLDL-C, mmol/l (mg/dl)
Extreme	Combination of ACVD[1] with DM 2 and/or FH or two cardiovascular complications within 2 year[2] in a patient with ACVD regardless of optimal hypolipidemic therapy and/or achieved level of LDL-C ≤ 1,4 mmol/l	< 1,4 (55), optimal < 1,0 (40)
Very high	- Documented CVD with clinical or based on instrumental findings (history of ACS, stable angina, PCI, CAPG or other interventions on the arteries,	< 1,4 (55) or decrease from baseline ≥ 50%

	Stroke/TIA, atherosclerosis of peripheric arteries) – Clinically significant athersclerothic plaque based on CAG/CT (stenosis ≥ 50% in 2 coronary arteries) or duplex scan of carotid arteries (stenisos > 50%) – DM + target organs damage + ≥ 3 RF and early start of DM 1 with the duration > 20 years – CKD with eGFR < 30 ml/min/1,73 m2 – SCORE risk ≥ 10% – FH + CVD or RF	
High	Important RF Total cholesterol > 8 mmol/l, and/or LDL-C > 4,9 mmol/l and/or BP ≥ 180/110 mm Hg – FH without RF – DM without target organ damage, DM ≥ 10 years or with the RF –Moderate CKD with eGFR 30–59 ml/min/1,73 m2 – SCORE risk 5–10% – Hemodynamically non-significant atherosclerosis of non-coronar y arteries (stenosis 25–49%)	< 1,8 (70) or decrease from baseline и ≥ 50%
Moderate	Young patients (DM 1 – younger than 35years, DM 2 – younger than 50 years) with the duration of DM < 10 years without target organ damage and RF – SCORE risk 1–5%	< 2,6 (100)
Low	SCORE risk < 1%	< 3,0 (116)

Notes: LDL-C – Low-density lipoprotein cholesterol; DM – diabetes mellitus; FH – familial hypercholesterolemia; ACVD – atherosclerothic cardiovascular disease; CVD – cardiovascular diseases; ACS – acute coronary syndrome; PCI – percutaneous coronary intervention; CAPG – coronary artery bypass grafting; TIA – transient ischaemic attack; АСБ – атеросклеротическая бляшка; CAG – coronary angiography; CT – computer tomography; RF – risk factor; eGFR – glomerular filtration rate; SCORE Systematic Coronary Risk Evaluation. 1 CAD: angina 3-4 FC, non-stable angina, history of MI, ischaemi stroke, PCI, CAPG, angioplastics of carotid arteriesor low extremities arteries, carotid endarterectomy, ilio-femoral, femoral-popliteal bypass grafting. 2 Miocardial infarction, non-stable angina, intermittent

claudication, transient ischaemic attack/ischaemic stroke. 3 Administration of statins in max tolerated dosage in comination with ezetimibe.

Appendix 7 Target office BP levels depenfing on age and concomitant diseases [15]

Age	Target office SBP mm Hg					Target office DBP mm Hg
	HTN	+ DM	+ CKD	+ CAD	+ Stroke[a]/TIA	
18 – 64 years	< 130 if tolerated but not <120	< 130 if tolerated but not <120	<140 to 130 if tolerated	< 130 if tolerated but not <120	< 130 if tolerated but not <120	70-79
65-79 years[a]	130-139 if tolerated	130-139 if tolerated	130-139 if tolerated	130-139 if tolerated	130-139 if tolerated	70-79
≥ 80 [b]	130-139 if tolerated	130-139 if tolerated	130-139 if tolerated	130-139 if tolerated	130-139 if tolerated	70-79

a Refers to the patients with the history of stroke and not to the BP measure in acute stroke.
b Target levels can be modified in elderly fragile patients**.**

Appendix 8 Cardiovascular risk factors [14]
Male sex

Age ≥55 years in men, ≥65 years in women

Smoking (currently or in the past)

Dyslipidemia (any of the named below parameters)
o Total cholesterol >4,9 mmol/l and/or
o LDL-C >3,0 mmol/l and/or
o HDL-C in men — <1,0 mmol/l (40 mg/dl), in women — <1,2 mmol/l (46 mg/dl)
o Triglycerides >1,7 ммоль/л

 Fasting hyperglycemia 5,6–6,9 mmol/l (102–25 mg/dl)
o Impaired glucose tolerance

 Increased body mass index (BMI 25-29,9 kg/m2) or obesity (BMI ≥ 30 kg/m2)

 Family history of CHD development at young age (< 55 years in men and <65 years in women)

- Uric acid (≥360 mcmol/l in women, ≥420 mcmol/l in men)
- Development of HTN at young age in parents or in the family
- Early menopause
- Sedentary lifestyle
- Psychological or social economic factors
- Heart rate (>80 Beats per min at rest)

7. References

1. Kannel W.B. (2000) Risk stratification in hypertension: new insights from the Framingham Study. Am. J. Hypertens., 13(1 Pt. 2): 3S–10S.

2. Mason R.P. (2003) Atheroprotective effects of long-acting dihydropyridine-type calcium channel blockers: evidence from clinical trials and basic scientific research. Cerebrovasc. Dis., 16 Suppl. 3: 11–17.

3. Anderson K.M., Castelli W.P., Levy D. (1987) Cholesterol and mortality. 30 years of follow-up from the Framingham study. JAMA, 257(16): 2176–2180;

4. Kaplan M., Aviram M. (1999) Oxidized low density lipoprotein: atherogenic and proinflammatory characteristics during macrophage foam cell formation. An inhibitory role for nutritional antioxidants and serum paraoxonase. Clin. Chem. Lab. Med., 37(8): 777–787.

5. Nickenig G. (2002) Central role of the AT(1)-receptor in atherosclerosis. J. Hum. Hypertens., 16 Suppl 3: S26–S33.

6. Nickenig G., Harrison D.G. (2002) The AT(1)-type angiotensin receptor in oxidative stress and atherogenesis: part I: oxidative stress and atherogenesis. Circulation, 105(3): 393–396.

7. O'Donnell V.B. (2003) Free radicals and lipid signaling in endothelial cells. Antioxid. Redox. Signal., 5(2): 195–203.

8. Wong N.D., Pio J.R., Franklin S.S. et al. (2003) Preventing coronary events by optimal control of blood pressure and lipids in patients with the metabolic syndrome. Am. J. Cardiol., 91(12): 1421–1426.

9. Eaton C.B., Feldman H.A., Assaf A.R. et al. (1994) Prevalence of hypertension, dyslipidemia, and dyslipidemic hypertension. J. Fam. Pract., 38(1): 17–23.

10. Chobanian A.V., Bakris G.L., Black H.R. et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee (2003). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA, 289(19): 2560–2572.

11. Johnson M.L., Pietz K., Battleman D.S., Beyth R.J. (2004) Prevalence of comorbid hypertension and dyslipidemia and associated cardiovascular disease. Am. J. Manag. Care, 10(12): 926–932.

12. Kotseva K., Wood D., De Backer G. et al.; EUROASPIRE Study Group (2009) EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. Eur. J. Cardiovasc. Prev. Rehabil., 16(2): 121–137.

13. Emberson J., Whincup P., Morris R. et al. (2004) Evaluating the impact of population and high-risk strategies for the primary prevention of cardiovascular disease. Eur. Heart J., 25(6): 484–491.

14. Rotar et al. Adherence to treatment and arterial hypertension control assessed in Russian arm of the screening program MMM19. Russian cardiology journal, 25(3):3745 [Ротарь и соавт. Приверженность к лечению и контроль артериальной гипертензии в рамках российской акции скрининга МММ19. РКЖ, 25(3):3745].

15. Arterial hypertension in adults. Clinical guidelines 2020. Russian cardiological journal. 2020;25(3):3786. doi:10.15829/1560-4071-2020-3-3786 [Артериальная гипертензия у взрослых. Клинические рекомендации 2020. Российский кардиологический журнал. 2020;25(3):3786. doi:10.15829/1560-4071-2020-3-3786]

16. Simon et al. Treatment of hypertensive and hypercholesterolaemic patients with the triple fixed combination of atorvastatin, perindopril and amlodipine: The results of the CORAL Study. Adv Ther (2019) 36:2010–2020.

17. Sever PS, Dahlof B, Poulter N et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicenter randomised controlled trial *Lancet* 2003; 361: 1149–58.

18. Boytsov et al. Suboptimal control of lipid levels: results from the non-interventional Centralized Pan-Russian Survey of the Undertreatment of Hypercholesterolemia II (CEPHEUS II). Cardiovasc Diabetol. 2017; 16:*158* https://doi.org/10.1186/s12933-017-0641-4

19. Ionov et al. Patient-oriented approach to the assessment of telemonitoring and remote consulting effectivenss in patients with arterial hypertension: pilot project. Arterial hypertension. 2018; 24(1):15-28 doi:10.18705/1607-419X-2018-24-1-15-28 [Ионов М. В., Юдина Ю. С., Авдонина Н. Г. и др. Пациент-ориентированный подход к оценке эффективности телемониторирования артериального давления и дистанционного консультирования при артериальной гипертензии: пилотный проект. Артериальная гипертензия. 2018;24(1):15-28. doi:10.18705/1607-419X-2018-24-1-15-28].

20. Fofanova TV, Ageev FT, Smirnova MD. Domestic questionnaire of adherence to therapy: testing and application in outpatient practice. Systemic hypertension. 2014;2:13-6.

21. Sever et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre

randomised controlled trial*Lancet* 2003; 361: 1149–58. Published online April 2, 2003

http://image.thelancet.com/extras/03art3046web.pdf

22. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension. 2010;55(2):399-407. doi:10.1161/HYPERTENSIONAHA.109.139816