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INTERNATIONAL CLINICAL TRIALS IN CARDIOLOGY

2010-2022 years

This book includes the results of the most important international clinical trials presented in 2010-2022. The authors systematized studies in 20 sections, which include risk factors, antiplatelet and anticoagulant therapy, laboratory and instrumental diagnostics, rhythm disorders, invasive cardiology, valvular heart diseases, intensive care in cardiology and much more.

CARDIOPROGRESS
MOSCOW
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Readership: researchers, cardiologists, general physicians, clinical pharmacologists, endocrinologists, cardiac surgeons, and allied health professionals.

About the authors

Mehman N. Mamedov — MD, PhD, Professor, Head of the Chronic Noncommunicable diseases Secondary Prevention Department, National Research Center for Therapy and Preventive Medicine, Moscow, Russia.

Sergey G. Kanorskiiy — MD, PhD, professor, Head of the Internal Medicine Department № 2, Kuban State Medical University, Krasnodar, Russia.

Ksenia K. Badeynikova — research associate; Chronic Noncommunicable diseases Secondary Prevention Department, National Research Center for Therapy and Preventive Medicine, Moscow, Russia.

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PREAMBULE

Dear colleagues!

It is known that cardiovascular diseases (CVD) are a serious medical and social problem all over the world, including in Russia. To reduce morbidity and mortality CVD prevention and treatment programs are being actively implemented. The results of several large-scale clinical studies have been published in recent years, which formed the basis for the development of international and national recommendations to reduce the burden of CVD. At the annual ESC congresses special attention is paid to the new achievements of world cardiology over the past year. In the HotLine and Clinical Trial Update sessions (the most attended events) specially selected 30-40 studies are presented. The presentation format allows participants to get objective data about a particular study. After the presentation of the results of each study, the opponents come forward with further discussion and

The present digest includes the results of the most important international clinical trials presented in 2010-2022. The authors systematized studies in 20 sections, which include risk factors, antiplatelet and anticoagulant therapy, laboratory and instrumental diagnostics, arrhythmias, invasive cardiology, valvular heart disease and intensive therapy in cardiology. At the end is a list of recommended literature.

It should be emphasized that in Russia, the results of international cardiac clinical trials are presented in this format for the first time.

The publication is intended for researchers, university professors, cardiologists, therapists, clinical pharmacologists, doctors of functional diagnostics and cardiac surgeons.

The authors express their gratitude for the interest shown in the publication. All wishes and questions can be sent by the following e-mail: mmamedov@mail.ru.

Authors

ABBREVIATIONS AND ACRONYMS

AAIR	single-lead atrial pacing
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AF	atrial fibrillation
ARB	angiotensin II receptor blockers
ATP	adenosine triphosphate
BARC	Bleeding Academic Research Consortium
BB	beta-blockers
CAD	coronary artery disease
CHA2DS2- VASc	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female)
CHADS2	CHF history, Hypertension history, Age ≥75 y, Diabetes mellitus history, Stroke or TIA symptoms previously
CI	confidence interval
COVID-19	coronavirus disease 2019
CT	computed tomography
CKD	chronic kidney disease
CHF	chronic heart failure
CPAP	continuous positive airway pressure
CVD	cardiovascular diseases
DBP	diastolic blood pressure
DDDR	dual-chamber, atrioventricular pacing
DM	diabetes mellitus
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
EF	ejection fraction
ESC	European Society of Cardiology
FFR	fractional flow reserve
FC	functional class
GRACE	Global Registry of Acute Coronary Events
HDL	high-density lipoproteins

HESTIA	Home Evaluation of Stroke Induced Aid Read
HR	hazard ratio
ICD	implantable cardioverter-defibrillator
INR	international normalized ratio
KCCQ	Kansas City Cardiomyopathy Questionnaire
LDL	low-density lipoproteins
LV	left ventricular
MI	myocardial infarction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MRI	magnetic resonance imaging
NYHA	New York Heart Association
OCT	optical coherence tomography
OR	odds ratio
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PESI	Pulmonary Embolism Severity Index
PET	positron emission tomography
RCT	randomized clinical trial
RR	relative risk
SARSCoV-2	severe acute respiratory syndrome coronavirus 2
SCORE	Systematic COronary Risk Evaluation (scale)
SBP	systolic blood pressure
SPECT	single-photon emission computed tomography
SSS	sick sinus syndrom
TIMI	Thrombolysis In Myocardial Infarction

RANDOMIZED CONTROLLED CLINICAL TRIALS

Introduction

Randomized controlled clinical trials (RSTs) have been conducted since the middle of the XX century and have traditionally been viewed as the gold standard of clinical trial design. RCTs were the response of the scientific community to experiments that were conducting on humans during the Second World War in Nazi concentration camps. RCT is a prospective study in which the first group is assigned to receive a certain intervention according to a research plan, and the control group under a standard modern treatment. RCTs involve the use of subtle and sensitive operational and statistical methods. To analyze the results of RCTs, statistical methods are used to determine the scientific validity of the conclusions obtained. RCTs are optimally suited for evaluating the treatment effectiveness and safety and provide a low probability of systematic error. The disadvantages of RCTs are the complexity of implementation and the inability to distribute the results to populations of patients who were not included in the work.

Also, there are always ethical issues that must be considered in the evaluation of any study. A distinctive feature of modern RCTs is strict adherence to ethical standards.

RCT protocol must be approved by the national and regional Ethics Committee before starting. The Ethics Committee is always should be informed about serious side effects that occur during RCT and all changes in the protocol.

Before being included in the study, a potential participant must voluntarily sign an informed consent where the purpose of the study, possible complications or inconveniences, advantages associated with the patient's participation in the study, and alternative methods of treatment are described. The patient should be informed that the decision on his participation or non-participation in this clinical trial at any stage of implementation will not affect the further tactics of his management, and he can terminate his participation in RCT at any time.

Endpoints

There are "hard" and "soft" (surrogate) endpoints evaluated in RCTs. Hard endpoints include, for example, general and cardiovascular mortality, stroke, myocardial infarction (MI). Examples of surrogate endpoints are left ventricular (LV) hypertrophy, ejection fraction (EF), plasma lipid and glucose levels, etc. Recently, the so-called composite endpoints, combining more than one measure, have become widely used in RCTs.

Another feature of modern RCTs are sub-studies within the main RCT, which use additional survey methods and allow answering questions that remained outside the framework of the main RCT.

The duration of the study (the time interval from the moment of randomization and the implementation of the intervention to the moment of evaluation of the outcome of the disease) is determined by the purpose and objectives of the study, depends on the nature of the pathology, the characteristics of the natural course of the disease, the risk of complications under study and the time required for the intervention to have a potential impact on the selected endpoints.

Inclusion and exclusion criteria

An important consideration in the design of an RCT is the subject inclusion and exclusion criteria.

Inclusion criteria are predetermined by the purpose of the study, broader ones facilitate the recruitment of patients and allow extrapolating the results obtained to a large population of patients. However, there is a danger of the formation of heterogeneous study groups of patients in initial clinical and demographic indicators and in the intervention effectiveness. Usually, RCTs include patients with moderate cases of the disease, although in patients with an initially higher risk of complications, the effect of intervention on hard endpoints can be assessed in a shorter time. A group of patients with low risk and mild course of the disease requires long-term follow-up and is potentially less promising in terms of obtaining a statistically significant effect of the intervention, whereas it may be effective.

Exclusion criteria should minimize the possibility of errors during the study (for example, exclusion from the study of patients with end-stage disease, sharply reduced liver and/or kidney function). Also, minors, women during pregnancy and lactation or who do not use contraception, oncological and mentally ill people are not included if these groups of patients are not the subject of RCT. In general, the larger the RCT and the faster it is planned to be completed, the broader the inclusion criteria should be, and fewer exclusion criteria should be used.

Study Size

A small number of patients in RCT usually does not allow achieving uniformity of the compared groups and a reliable intervention effect. A typical

baseline indicator needed to calculate the size of the RCT is the expected outcome of the disease with standard conventional treatment at the time of study planning. In addition, data from recently completed similar RCTs are very useful. The greater the expected difference in effect between the compared options treatment in the experimental and control groups, the fewer the required number of observations will be.

When conducting a study, it is very important to obtain reliable information about the intervention in the shortest period. Multicenter (often international) RCTs with a single program and methods of observation allow scientists to obtain comparable data in different medical institutions.

Randomization

The reliability of the RCT data directly depends on the comparability of the compared groups. It is categorically impossible to compare groups, one of which included patients with the analyzed intervention, and the other — those who refused to participate in RCT and received "traditional" therapy. It is also impossible to compare the results of a new treatment method in different clinics if they did not evaluate it according to one common protocol, due to differences in technical equipment, personnel qualifications, and accepted treatment standards. The method of "historical control", which involves a comparison of the studied and previously conducted treatment, has similar disadvantages.

Randomization also does not include methods in which patients are assigned to experimental and control groups in the order of admission, by the initial letters of names and surnames, by odd and even days of inclusion in the study, date of birth. With such a selection, the doctor may bias the patient with a good, in his opinion, effect of intervention in the "right" group and vice versa.

Randomization is a key point in conducting RCTs. It should ensure a random distribution of patients, independent of the desire of the doctor or any other factors, and the comparability of the compared groups according to the clinical and demographic characteristics of patients, the severity of the main disease under study, comorbidity, and therapy. During randomization, a key condition must be observed — the unpredictable nature of the distribution of patients into groups, when it is impossible to predict whether the patient will fall into the intervention group or the control group. Neither the patient nor the researcher should know which groups the patients are assigned to. This is achieved by using "blind", "double-blind" selection. "Double-blind study" is research where both the subjects or participants of a study and the researchers are oblivious of the treatment being given and the subjects receiving the treatment.

Analysis and results interpretation

The main task of statistical analysis of RCT is to establish significant differences in outcomes (endpoints) between the group with the analyzed intervention and the control group. To obtain objective information about the effectiveness of the intervention, it is necessary to include in the analysis all initially randomized patients (intention-to-treat analysis), and not only those who

were treated in strict accordance with the study protocol (on protocol analysis). The withdrawal of patients from the study for various reasons (refusal of further participation, side effects and poor tolerability of treatment, violations of the protocol by patients or researchers) should not exceed 15% of the initial number of randomized patients. In this case, the results can be considered reliable.
Currently, ethical and methodological standards have been developed for conducting RCTs. It should be remembered that placebo-controlled studies are justified only when there is no alternative method of treatment, the effectiveness of which is beyond doubt.

In 1998, a rating system for evaluating clinical trials was proposed, where the quality of clinical trials decreases with increasing sequence number of evidence. Levels are usually denoted by Roman numerals (I, II, III, IV) or letters of the Latin alphabet (A, B, C, D). The numbers indicate the level of evidence of the results of scientific research. The letters indicate the level of evidence of the accepted recommendations.

Class (level) I (A): large double-blind placebo-controlled studies, as well as data obtained from meta-analysis several randomized controlled trials.
Class (level) II (B): Small randomized controlled trials in which statistical calculations are performed on a limited number of patients.
Class (level) III (C): non-randomized clinical trials on a limited number of patients.
Class (level) IV (D): Consensus-building by a group of experts on a specific issue.
In international clinical guidelines the classes of recommendations and levels of evidence presented in the following tables are used.

Classes of Recommendation

Definition		Wording to use
Class I:	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.	Is recommended or is indicated
Class II:	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.	
Class IIa:	Weight of evidence/opinion is in favor of usefulness/efficacy.	Should be considered

Class IIb:	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.	Is not recommended

Levels of evidence

Level of evidence A	Data derived from multiply randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

THE DIAGNOSIS OF CVD

Computed tomography (CT) of the coronary arteries noninvasively detects their stenosis but does not determine whether this stenosis causes ischemia.
DeFacto (2012) study included stable patients with suspected coronary artery disease (CAD), enrolled from 17 centers, who underwent CT, invasive coronary angiography, fractional flow reserve (FFR) computed from standard coronary CT scans. Among 407 vessels from 252 patients there were identified 150 vessels of intermediate stenosis by CT, defined as 30% to 69% stenosis. For lesions of intermediate stenosis severity, accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of FFR from CT were 71%, 74%, 67%, 41%, and 90%, whereas accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of CT stenosis were 63%, 34%, 72%, 27%, and 78%. FFR from CT demonstrated significant reclassification of CT stenosis for lesion-specific ischemia.

In **CORE320 study (2012)** the prognostic importance of combined CT angiography and CT myocardial stress perfusion imaging with that of combined invasive coronary angiography and stress single photon emission CT myocardial perfusion imaging were compared. And 381 participants clinically referred for invasive coronary angiography and aged 45-85 years were enrolled. The diagnostic accuracy of the first (non-invasive) technique was noninferior to the second (invasive), in patients with coronary stenoses of 50-70% or more requiring revascularization. Combined CT angiography and CT perfusion enables similar prediction of 2-year major adverse cardiovascular events, late major adverse cardiovascular events, and event-free survival similar to that enabled by invasive coronary angiography and single photon emission CT. The evaluated noninvasive technique allows to reduce the patient's radiation dose but is not yet mentioned in the recommendations, and it is unavailable in most cardiological centers.

The highly sensitive troponin test has sex-specific thresholds. The **High-STAKES study (2013)** involved 1126 patients (46% of women) with suspected MI. MI was diagnosed by two independent cardiologists using a highly sensitive troponin I test with separate diagnostic thresholds (34 ng/L for men and 16 ng/L for women versus 50 ng/l for both sexes in daily clinical practice). As a result, the frequency of MI diagnosis significantly increased in women (from 13% to 23%, $p < 0.001$) and to a lesser extent in men (from 23% to 24%, $p = 0.021$). Women with suspected MI are less likely to be referred to a cardiologist, for coronary angiography and revascularization compared to men, which can cause errors in diagnosis and treatment. A highly sensitive troponin test can improve clinical outcomes in women with suspected acute coronary syndrome (ACS).

In the **BACC study (2015)**, two algorithms of biochemical diagnosis of MI were compared in 1045 patients with acute chest pain. The first group of patients were diagnosed with MI with troponin I level above 6 ng/l in the period 0-1 hours from the onset of symptoms or its rise to 12 ng/l after 3 hours. The second (standard) algorithm involved the diagnosis of MI at the level of troponin I from 27 ng/l. Patients with the established diagnosis were treated in the hospital, the rest were discharged home.
During 6 months of follow—up, a fatal outcome was observed in 0.79% of cases with the first and 1.73% with the second MI diagnosis tactic. When evaluating the first algorithm on two independent cohorts ($n = 4009$), its high negative (99.2–99.7%) and positive prognostic values (80.4–81.5%) were determined.

Early detection and treatment of cardiac remodeling is it is critically important since this process can be stopped at the beginning. In the **DOPPLER-CIP study (2015)**, 676 patients with stable CAD (with a positive stress test, a history of coronary revascularization) had a noninvasively determined parameter that predicts the subsequent remodeling of the heart better than others. Patients underwent at least two imaging studies, including echocardiography, magnetic resonance imaging (MRI) and single-photon positron emission CT, and received optimal drug therapy for 2 years. According to the results of the final examination, some patients had signs of cardiac remodeling and its best predictor unexpectedly turned out to be a small final LV diastolic volume.
With an initial value of this indicator less than 145 ml, the probability of remodeling was 25-40%, and with a value of more than 145 ml, it was 20% less ($p < 0.001$). The initial increase in LV wall thickness significantly increased the risk of remodeling ($p = 0.003$).

In patients with symptoms of CAD, CT of the coronary arteries improves the selection of patients for coronary angiography compared with stress testing. Similar effectiveness of the new non-invasive technology for measuring fractional reserve of blood flow using CT has not been previously established. The

PLATFORM study (2015) included 584 patients with a new pain syndrome, of which 204 had a planned noninvasive examination of the coronary arteries, and 380 had a planned invasive coronary angiography (in 187 patients it was performed directly, and 193 patients were initially measured by fractional reserve of blood flow using CT). The primary endpoint was the number of patients whose planned coronary angiography did not reveal arterial obstruction (absence of stenosis by at least 50% and fractional reserve of blood flow less than 0.80). In the group of planned invasive examination in 117 out of 193 patients, noninvasively obtained data made it possible to cancel invasive coronary angiography. In the remaining 76 patients, only 12% did not have coronary obstruction according to the invasive study, whereas among those directly subjected to invasive coronary angiography, arterial obstruction was not detected in 73% ($p < 0.0001$). The average radiation dose was similar for noninvasive and invasive examination (9.9 vs 9.4 mSv, respectively; $p = 0.20$). The frequency of myocardial revascularization with two diagnostic tactics turned out to be comparable. No ischemic events were observed for 90 days among patients who had invasive angiography canceled based on the results of a noninvasive examination of the coronary arteries. Among 204 patients who underwent a planned noninvasive measurement of the fractional reserve of blood flow using CT, the number of patients without coronary obstruction did not decrease compared to the standard examination according to invasive angiography after 3 months ($p = 0.95$). CT of coronary arteries with measurement of FFR is a possible and safe alternative to invasive coronary angiography, which reduces the frequency of invasive examination that does not detect arterial obstruction.

About 2/3 of patients undergoing coronary angiography do not have obstructive CAD. CT of the coronary arteries is a non—invasive study that allows to exclude CAD, but its effectiveness has not been established. In the **CONSERVE study (2016)**, 1503 stable patients with indications for elective coronary angiography were randomized for routine or selective angiography based on CT results. In the groups of routine and selective coronary angiography, obstructive CAD was detected in 21% and 25% ($p = 0.10$), the absence of stenosis of at least one coronary artery — in 79% and 75% ($p = 0.12$) of the examined patients, respectively. During 12 months of follow-up, events attributed to the primary endpoint (death, nonfatal MI, unstable angina, stroke, revascularization, or hospitalization due to a cardiovascular cause) were observed in 4.6% of patients in both groups ($p = 0.99$) without significant differences when comparing the frequency of each of the complications. In the group of selective coronary angiography, its frequency decreased by 78%, revascularization — by 41% ($p <0.001$), and treatment costs decreased by 50% ($p < 0.001$) without worsening outcomes.

DOCTORS (2016) is the first randomized study that evaluated optical coherence tomography (OCT) in optimizing percutaneous coronary intervention (PCI) results in 240 patients with ACS without ST segment elevation. PCI was

compared with OCT before and after it (OCT group), as well as PCI according to the results of conventional coronary angiography (angiography group). The primary endpoint — the functional result of PCI (the average fractional reserve of blood flow in the artery) was better in the OCT group (0.94 ± 0.04 vs. 0.92 ± 0.05; p = 0.005) and the value of this indicator greater than 0.90 was also achieved significantly more often (82.5% vs. 64.2% of cases) in the angiography group. There were no significant differences in the frequency of type 4a MI (33% vs. 40%; p = 0.28) with an identical incidence of PCI complications (5.8%) and contrast-induced nephropathy (1.6%) in the OCT and angiography groups.
After PCI, OCT showed incomplete stent opening in 42%, incomplete stent fit in 32% of patients, incomplete lesion coverage in 20% and edge dissection in 37.5% of cases. This led to more frequent use of additional stent dilation in the OCT group (43% vs. 12.5% in the angiography group; p < 0.0001) and provided less residual stenosis (7.0 ± 4.3% vs. 8.7 ± 6.3%; p = 0.01).
In patients with ACS without ST segment elevation PCI under the control of OCT improves FFR in the artery without increasing the frequency of complications of the procedure or acute kidney injury.

In patients with suspected CAD, invasive angiography is performed unreasonably often. The **CE-MARC 2 study** (2016) involved 1202 patients with a clinical probability of CAD of 49.5 ± 23.8%, who, after randomization, were examined in accordance with the UK standard (n = 240) using MRI (n = 481) or single-photon emission computed tomography (SPECT) (n = 481). The primary endpoint included signs of no need for coronary angiography (normal fractional reserve of blood flow (more than 0.80) or absence of stenosis ≥ 70% according to quantitative coronary angiography in 1 viewing or ≥ 50% in 2 orthogonal views of all coronary arteries with a diameter of ≥ 2.5 mm). With a median follow—up of 15.8 months, the frequency of coronary angiography was 42.5%, 17.7% and 16.2%, with unnecessary angiography - 28.8%, 7.5% (p < 0.001) and 7.1%, and the frequency of large cardiovascular complications of 1.7%, 2.5% and 2.5% in the standard management groups, MRI, and SPECT, respectively. In patients with suspected CAD, the use of MRI diagnostics reduces the likelihood of unnecessary angiography for 12 months compared to standard management without significant differences between the use of MRI and SPECT, as well as without worsening clinical outcomes.

In the **PACIFIC study (2016)**, the preferred method for noninvasive assessment of myocardial perfusion and severity of coronary stenoses was determined. Initially, 208 patients with suspected CAD underwent invasive coronary angiography to determine the fractional reserve of blood flow, which revealed hemodynamically significant coronary stenoses in 44.2% of patients. Then the examined patients were compared with positron emission tomography (PET), SPECT, CT and, to combine functional and anatomical data, their combinations (PET and CT or SPECT and CT). Comparison of the results of noninvasive studies and invasive coronary angiography showed that PET is

significantly more accurate (85%) for the diagnosis of coronary ischemia compared with CT (74%, p < 0.01) and SPECT (77%, p < 0.01). The sensitivity of noninvasive diagnostic methods of PET, CT and SPECT was 87%, 90% and 57%, and the specificity was 60%, 94% and 84%, respectively. Diagnostic accuracy did not increase when combining CT with SPECT or PET.

The benefits of systematic detection of atherosclerosis and aggressive secondary prevention (proactive strategy) compared with standard patient management were evaluated in the **AMERICA study (2016).** In the proactive strategy group (n = 263), in contrast to the standard management group (n = 258), instrumental studies of arteries (doppler ultrasonography, CT, MRI), biochemical blood analysis for early detection of multifocal atherosclerosis and the most intensive cardioprotective pharmacotherapy, non-drug measures were conducted every 6 months. After 2 years, the frequency of events of the primary endpoint (death, ischemic complication with hospitalization, acute heart failure, new cognitive dysfunction, deterioration of kidney function, new cardiac arrhythmia, malignant arterial hypertension) was 47.4% vs. 46.9% (HR (hazard ratio) 1.03 at 95% CI (confidence interval) from 0.80 to 1.34) in groups of proactive strategy and standard management. The sum of deaths, MI, stroke and any revascularization (HR 0.94 at 95% CI from 0.58 to 1.50), total mortality (HR 0.78; p = 0.37), the frequency of organ dysfunction (HR 0.97; p = 0.91), major bleeding (p = 0.73) and hospitalization (p = 0.11) in the groups of proactive strategy and routine management, respectively. The authors explained the lack of superiority of the proactive strategy by conducting optimal therapy in both groups.

In the **YEARS study (2016)**, a modified diagnostic algorithm was evaluated in 3465 patients with suspected pulmonary embolism. According to this algorithm, the determination of the D-dimer level is mandatory for all patients, after which the clinical signs of deep vein thrombosis (1 point), the presence of hemoptysis (1 point) and the doctor's conviction of the presence of pulmonary embolism (1 point) are evaluated. If the score is 0 and the D-dimer level is <1000 ng/ml, CT is not performed, and if the D-dimer level is > 1000 ng/ml, CT indicated. At 1 point or more, but the D-dimer level <500 ng/ml, pulmonary embolism is excluded, and CT is not performed, but at an indicator > 500 ng/ml, the patient is referred for CT. When using this algorithm, symptomatic venous thrombosis was observed during 90 days of follow-up in 0.43% of patients with pulmonary embolism excluded by the D-dimer level and in 0.85% of patients with pulmonary embolism excluded by CT. The authors of the work believe that the refusal of CT in patients with a low risk of pulmonary embolism will eliminate unnecessary exposure to radiation, contrast agents and reduce the costs of the healthcare system without compromising the quality of diagnosis.

Studies of highly sensitive cardiac troponin allow the use of lower thresholds for the diagnosis of MI, but it is not known whether this improves clinical

outcomes. The **High-STEACS study (2018)** included consecutive patients hospitalized with suspected ACS in Scotland. Hospitals were randomized to start using the highly sensitive troponin test early (n = 5) or 6 months later (n = 5) together with the diagnostic threshold of the 99th percentile, sex-specific (34 ng/l for men and 16 ng/l for women) obtained in a population of healthy people.

Of the 48,282 examined patients, 10,360 (21%) had troponin I concentrations above the 99th percentile of the normal values identified by conventional or highly sensitive analysis. A highly sensitive analysis reclassified 17% of patients into a group with myocardial damage that was not identified by conventional analysis, but only 1/3 of them were diagnosed with MI. During 1 year of follow-up, the primary endpoint (MI or death from cardiovascular causes) was recorded in 15% of those reclassified at the validation stage of the new technique and in 12% at the implementation stage of this test (adjusted OR (odds ratio) for implementation versus the verification phase of 1.10 at 95% CI from 0.75 to 1.61; p = 0.620).
Patients reclassified using a highly sensitive cardiac troponin I study after a negative result of a conventional test have the same probability of MI or cardiovascular death during the following year.

In the **HISTORIC study (2019)** involving 32,837 patients, various threshold levels of cardiac troponin I, determined by a highly sensitive method, were evaluated to exclude MI and safely send patients home from the emergency department without increasing the frequency of adverse cardiac events. After the initial troponin test, patients with low risk (troponin I level less than 5 ng/l) and a duration of symptoms of more than 2 hours were identified (or with a repeat test if the duration of symptoms is up to 2 hours). High-risk patients whose troponin I levels exceeded the threshold value of the 99th percentile, considering gender, were admitted to the hospital. Patients with an average risk (from 5 ng/l to the 99th percentile) were re-examined after 3 hours, and at a troponin I level of less than 3 ng/l were discharged, and the rest were hospitalized.
The use of the described method made it possible to significantly reduce the duration of stay in the emergency department compared to standard treatment (6.8 versus 10.1 hours, respectively; p < 0.001). A total of 74% of patients evaluated using the new method, compared with 53% of those examined according to the standard protocol, were discharged without hospitalization (HR 1.57 with 95% CI from 1.34 to 1.83; p < 0.001). Death from cardiac causes or MI within 12 months (the primary safety endpoint) was recorded with a frequency of 1.8% in the group of the new MI exclusion method and 2.5% in the group of the standard protocol (adjusted HR 1.02 at 95% CI from 0.74 to 1.40). Compared with patients with a troponin I concentration of 5 ng/l and higher, but less than the 99th percentile, in patients with its level of less than 5 ng/l, the risk of MI or cardiac death for 12 months was 77% lower (5.3% vs. 0.7%; adjusted HR 0.23 at 95% CI of 0.19 to 0.28), and at a level of less than 2 ng/l — 80% lower (5.3% vs. 0.3 %; adjusted HR 0.20 at 95% CI from 0.14 to 0.29).

The introduction of a new approach to the exclusion of MI can be useful both for patients and for the healthcare system. Many patients will need only one troponin I test to make a safe decision about the need for hospitalization, which will be accompanied by great economic benefits.

The **RAPID-TnT study (2019)** evaluated the possibility of safely excluding MI in patients admitted to the emergency department with suspected ACS, based on the results of an earlier determination of troponin T levels in the blood by a highly sensitive method. After randomization, the level of troponin T was determined in patients at an early date (0/1-hour) with an exclusion criterion of less than 5 ng/l (n = 1646) or according to the standard (within 0/3-hours) — with an exclusion criterion of less than 29 ng/l (n = 1642). In the group of early detection of troponin T, compared with the standard, the probability of discharge from the emergency department home was significantly higher (45.1% vs. 32.3%; p <0.001), and the average length of stay in the department was lower (4.6 hours vs. 5.6 hours, respectively; p <0.001). During the observation period of 30 days, events of the primary endpoint (death from all causes or MI) were recorded with equal frequency in the groups of early and standard determination of troponin T levels (1.0% vs. 1.0%, respectively; RR (relative risk) 1.06 at 95% CI from 0.53 to 2.11; for "not worse" p = 0.006, for superiority p = 0.867). Among patients discharged from the emergency department, the protocol for early determination of troponin T levels had a negative prognostic value of 99.6% (95% CI 99.0 to 99.9%) for a 30-day risk of death or MI.
The protocol of early (0/1-hour) determination of troponin T by a highly sensitive method, evaluated in clinical practice, promotes accelerated home discharge of patients admitted with suspected ACS, without worsening 30-day outcomes.

The Danish **DANCAVAS** trial **(2022)** randomly assigned (1:2 ratio) 46,611 adult men between the ages of 65 to 74 and living in 15 Danish municipalities to undergo screening, including coronary-artery calcium scoring, ankle–brachial blood-pressure measurements and blood testing for DM and hypercholesterolemia, or no screening. The primary outcome was death from any cause and secondary outcomes were stroke, MI, amputation due to vascular disease, aortic dissection and aortic rupture. The median follow-up was 5.6 years.

In intention-to-treat analyses, after a median follow-up of 5.6 years, 2106 men (12.6%) in the invited group and 3915 men (13.1%) in the control group had died (hazard ratio, 0.95; 95% confidence interval [CI], 0.90 to 1.00; P=0.06). The hazard ratio for stroke in the invited group, as compared with the control group, was 0.93 (95% CI, 0.86 to 0.99); for myocardial infarction, 0.91 (95% CI, 0.81 to 1.03); for aortic dissection, 0.95 (95% CI, 0.61 to 1.49); and for aortic rupture, 0.81 (95% CI, 0.49 to 1.35). There were no significant between-group differences in safety outcomes. After more than 5 years, the invitation to undergo comprehensive cardiovascular screening did not significantly reduce the incidence of death from any cause among men 65 to 74 years of age. However, the effect of the invitation

to the screening could be underestimated, since only 63% men in the invited group underwent screening.

Smart devices have shown the potential for large-scale atrial fibrillation screening but there was no comparison with conventional screening. In the **eBRAVE-AF** study **(2022)**, 5,551 policyholders with a large healthcare insurance company (average age 65 years, 31% of women), who initially did not have AF, were randomized for digital screening (n=2860) or routine management (n=2691). In the digital screening group, participants used a certified application on their smartphones to detect pulse wave anomalies. When abnormal results were obtained, an external ECG recorded for 14 days using a recorder was evaluated. The primary endpoint was AF, first diagnosed within 6 months, treated with oral anticoagulants by an independent physician who was not involved in the study. After 6 months, the participants were asked to proceed to the second phase of the study with a reverse distribution for secondary analyses. The primary endpoint of the study was reached, as digital screening more than doubled the detection rate of treatment-relevant AF in both phases of the study with a odds ratio of 2.12 (95% CI from 1.19 to 3.76; p=0.010) and 2.75 (95% CI from 1.42 to 5.34; p=0.003) in the first and second phases, respectively. The digital screening technology used provides significant advantages in detecting AF compared to conventional management and has the potential for widespread use due to its availability on conventional smartphones. Further research is needed to check whether digital screening of AF leads to better results of its treatment.

RISK FACTORS OF CVD AND PREVENTION

After 4 years of follow-up, 34436 patients remained in the large international **REACH registry (2010)**. Included patients had CAD, cerebrovascular pathology, atherosclerosis of peripheral arteries with symptoms or multiple risk factors for CVD. The most important predictors of complications according to the register were multivessel atherosclerotic lesion (the risk is 1.99 times higher compared to the presence of only risk factors), chronic heart failure (CHF) (the risk is 1.71 times higher than in its absence), ischemic events in the last year (the risk is 1.71 times higher compared to their absence), diabetes mellitus (DM) (risk 1.44 times higher compared to the absence of diabetes). The listed groups of patients with a high risk of complications require the most active therapeutic intervention.

The **RESPONSE study (2010)** evaluated the effect of a preventive program coordinated by nurses in 754 patients underwent ACS within the last 8 weeks. The preventive program was based on recommendations and focused on improving lifestyle (cessation of smoking, adequate physical activity, normalization of body weight), control of risk factors (hypertension, dyslipidemia, diabetes) and increasing compliance to drug therapy. 4 outpatient visits were performed within 6 months. The risk of death from CVD in the next 10 years was compared on the SCORE scale at the begining, after 6 and 12 months.
In the group of more active intervention (n = 377) and control (n = 377), the risk of death according to SCORE was 4.5% and 5.4% (difference of 16.9%, p = 0.029). The target indicators of blood pressure and low-density lipoprotein (LDL) levels were more often achieved during a special program, and the frequency of smoking and newly diagnosed diabetes in the compared groups did not differ significantly.
A preventive program with the participation of nurses for 6 months is able to reduce the risk of an adverse outcome after undergoing ACS.

The **EUROACTION PLUS project (2011)** involved 696 patients (137 with atherosclerosis-related diseases and 559 with risk factors of CVD, necessarily including smoking), divided into a group of active intervention involving nurses (n = 350) and the use of varenicline, as well as a group of routine medical care (n =

346). Active intervention ensured more frequent cessation of smoking after 16 weeks (51.2% of cases versus 18.8%, $p < 0.0001$), adherence to the Mediterranean diet ($p < 0.001$), recommended physical activity ($p = 0.002$), achievement of the target blood pressure level ($p = 0.03$). However, there were no differences in body weight, lipid and carbohydrate metabolism between the groups.

The objective of the **EUROASPIRE III project (2011)** was to model clinical efficacy and costs in optimizing secondary prevention of CAD in Europe. The cost-effectiveness analysis for 8 countries showed mostly positive results with an average additional cost of €16,000 per year of life with good quality for one patient. The most expensive were intensive treatment of hypertension, and intensive lipid-lowering therapy.
Only in a small part of patients with the lowest risk of recurrence of CAD complications, enhanced secondary prevention is not cost-effective.

The **PURE Register (2011)** was conducted in 17 countries of the world and included 154,996 people aged 35 to 70 years, including patients with CVD (5,650 — coronary ischemic events, 2,292 — stroke). In low-income countries, 80.2% of cardiac patients did not undergo secondary prevention with antiplatelet agents, beta-blockers (BB), angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (ARB), statins. In high-income countries, 11.2% of such patients did not receive adequate treatment. The difference in the frequency of statin prescribing reached 20-fold. Rural residents, smokers, younger patients, women, people with a low level of education, without diabetes and obesity got less adequate treatment.

The **PURE study (2012)** analyzed the influence of macro- and microeconomic influence on the frequency of CVD risk factors in 153,996 surveyed from 17 countries on 5 continents. In countries with low gross domestic product (Bangladesh, India), the population consumes fewer vegetables, fruits, proteins and fats, the caloric content of food is significantly lower, and the consumption of carbohydrates and the level of physical activity is higher. In economically developed countries, smoking cessation is more common. Differences in diet, physical activity, and smoking frequency between rich and poor are less pronounced among urban residents compared to the rural population. Consequently, prevention programs in rich and poor countries should differ.

The relationship between the powerful **earthquake in Japan (2012)** on March 11, 2011, and cases of CVD and pneumonia was assessed by analyzing 124,152 emergency medical calls in the disaster zone from February 11 to June 30, 2011. After the earthquake, there was a sharp increase in the number of calls for heart failure, ACS, stroke, cardiac arrest and pneumonia. At the same time, there was a rapid decline in the number of ACS and cardiac arrest, while cases of heart failure and pneumonia were more common for more than 6 weeks. The second increase in the frequency of stroke and cardiac arrest was registered after the

strongest aftershocks (April 7, 2011). The importance of intensive medical treatment of any CVD after large earthquakes is obvious.

The **PURE project (2013)** included 155245 people aged 35-70 years from 17 countries with high (Canada, Sweden, United Arab Emirates, n = 16110), medium (n = 104260) and low economic levels (India, Bangladesh, Pakistan, Zimbabwe, n = 34875). The highest prevalence of risk factors for cardiovascular complications was observed in "rich countries", the lowest in "poor countries" ($p < 0.0001$). Meanwhile, over 3 years of follow-up, stroke and heart failure were recorded with a frequency of 4.3, 5.1 and 6.4 per 1000 person-years, and death from cardiovascular causes — 0.5, 1.3 and 2.7 per 1000 person-years ($p < 0.0001$) in countries with high, medium and low economic levels, respectively. Early detection and effective treatment of diseases is typical for "rich countries", while poor countries are characterized by poor development of medical care.

The vital status of 786 French cyclists who participated in the **Tour de France race (2013)** for the period from 1947 to 2012 was assessed. The causes of death were analyzed from 1968 to 2012. 208 (26%) cyclists died, mainly from neoplasms (32%) and CVD (29%). Their total mortality was 41% lower than in the similar population of the French (HR 0.59, $p < 0.0001$), including lower mortality from neoplasms (HR 0.56, $p < 0.0001$) and CVD (0.67, $p = 0.004$) with a tendency to higher mortality from external causes (1.06, $p = 0.80$). The presented results demonstrate the correlation between the possible positive effect of a high level of fitness in selected healthy athletes and the potentially harmful effects of excessive exercise combined with the likely use of doping.

Increased heart rate is a recognized marker of the risk of cardiovascular complications. It has previously been shown that ivabradine improves the results of treatment of patients with stable CAD, LV dysfunction and a sinus rhythm of 70 beats per minute or more. The **SIGNIFY (2014)** study involved patients with stable CAD without CHF with a sinus rhythm of 70 beats per minute or more, in most cases with angina pectoris ≥ II functional class (FC), limiting their activity. After randomization, ivabradine was added to the recommended therapy at a dose of up to 10 mg 2 times a day (n = 9550) (target heart rate from 55 to 60 beats per minute) or placebo (n = 9552). After 3 months, the average sinus rhythm frequency was 60.7 ± 9.0 beats per minute in the ivabradine group versus 70.6 ± 10.1 beats per minute in the placebo group. With a median follow-up of 27.8 months, death from cardiovascular causes or non-fatal MI (primary endpoint) was recorded in 6.8% and 6.4% of cases ($p = 0.20$) in the ivabradine and placebo groups, respectively, without significant differences in the number of deaths from cardiovascular causes and non-fatal MI. Ivabradine intake was associated with an increase in the frequency of the primary endpoint in patients with activity-limiting angina, but not in patients without such angina. Bradycardia was observed in 18.0% and 2.3% ($p < 0.001$) of patients in the ivabradine and placebo groups,

respectively. It is likely that in patients with stable CAD with normal LV EF, an increased heart rate is a risk marker, but not a modifiable determinant of outcomes. Previous studies have shown that people with an ideal risk factor profile have a very low risk of CVD, but the causal relationship with a combination of low LDL and systolic blood pressure (SBP) levels remained unknown.

B.A. Ference et al. (2016) used data on cardiovascular risk factors from 102,773 subjects from 14 prospective cohort projects or case-control studies. LDL and SBP levels were used as tools for "natural" 2×2 factor randomization into 4 groups. During up to 32 years of follow-up, there were 14,368 major vascular events included in the primary endpoint (death from CAD, MI, stroke or revascularization). Compared with the group without LDL and SBP reduction, subjects in the group with the lowest LDL level had a 54.2% lower risk of the primary endpoint (HR 0.454), people in the group with the lowest level of SBP had a 44.7% lower risk (HR 0.553), and subjects in the group with a combination of the lowest LDL levels and SBP had an 86.1% lower risk of major vascular events (HR 0.139). The results of the study showed that a long-term simultaneous decrease in LDL by 1 mmol/L and SBP by 10 mmHg can reduce the risk of cardiovascular complications by almost 90%.

The **CAMELIA-TIMI 61 study** (2018) included patients with overweight/obesity and atherosclerotic CVD or several cardiovascular risk factors. After randomization patients were taking lorcaserin (a selective agonist of 5-HT2C serotonin receptors that regulates appetite, reduces weight with overweight and obesity) 10 mg twice a day (n = 5135) or placebo (n = 5083). After 1 year, 38.7% of patients in the lorcaserin group and 17.4% in the placebo group had weight loss of ≥ 5% (OR 3.01 at 95 % CI from 2.74 to 3.30; $p < 0.001$), and by ≥ 10% in 14.6% and 4.8% of cases (OR 3.40 at 95% CI from 2.92 to 3.95; $p < 0.001$). However, by the end of the study, the average difference in body weight of those examined in the lorcaserin and placebo group was only 1.9 kg.

With a median follow—up of 3.3 years, the primary safety endpoint - the total number of major cardiovascular complications (cardiovascular death, MI, stroke) was recorded with a frequency of 6.1% in the lorcaserin group and 6.2% in the placebo group (HR 0.99 at 95% CI from 0.85 to 1.14; $p < 0.001$ for "not worse"). Lorcaserin caused previously known side effects — dizziness, fatigue, headache, nausea, but also an increase in the number of patients with severe hypoglycemia ($p = 0.04$) and, in addition, a decrease in the risk of first—time DM - 8.5% vs. 10.3% (HR 0.81 at 95% CI 0.66 to 0.99) cases. The risk of pulmonary hypertension (1.6% vs. 1.0%; $p = 0.26$) and valvulopathy (1.8% vs. 1.3%; $p = 0.24$) did not differ statistically significantly in the lorcaserin and placebo groups, respectively.

Lorcaserin is the first body weight loss medicine with proven cardiovascular safety. In the high-risk group of overweight or obese patients, lorcaserin promotes sustained weight loss without increasing the frequency of major cardiovascular events compared to placebo.

The **PURE epidemiological study (2018)** included a 9.1-year follow-up of 138,527 participants (aged 35-70 years) from 50 countries who initially had no CVD and were divided into groups depending on the quality of their diet. Considering the previously identified reduction in mortality from the consumption of fruits, vegetables, nuts, legumes, fish, dairy products and unprocessed meat, the authors of the work created a PURE Healthy dietary score. Each diet received a score based on the quintiles of consumption of these protective components of the diet from 1 for the lowest quality to 5 for the highest quality of nutrition. The total score of the diet was determined as the sum of the consumption of seven components of protective nutrition with a minimum score of 7 and a maximum score of 35. Cardiovascular risk and mortality were compared in individuals with the highest (18 points or more) and the lowest quality of diet (11 points or less). The highest quality of the diet, compared with the lowest, was associated with a significantly lower risk of death (HR 0.75 at 95% CI from 0.68 to 0.83, p-trend in diet categories < 0.001) and a tendency to decrease the frequency of major cardiovascular events (HR 0.91 at 95% CI from 0.81 to 1.02; p-trend by diet category = 0.0413).
It is known that better nutrition is typical for countries with a high level of economic development, in which numerous factors have a positive impact on the health of the population.

To reduce the level of uric acid in plasma and treat gout, allopurinol is traditionally used. A new, more selective xanthine oxidase inhibitor, febuxostat, provides lower concentrations of uric acid, but recent results of the CARES study have called into question the safety of its long-term use in patients with CVD.
The **FREED project (2018)** involved patients aged 65 years and older with baseline plasma uric acid levels ranging from > 7 to ≤ 9 mg/dl and ≥ 1 risk factors (hypertension, type 2 DM, glomerular filtration rate 30-60 ml/min/1.73 m2) or recently developed CVD. Lifestyle modification was recommended for all patients, and after randomization, febuxostat was prescribed at 10 mg/day with a possible dose increase to 40 mg/day (n = 533) or allopurinol at 100 mg /day (n = 537) with persistent hyperuricemia (27.2% of cases), which led to a greater decrease in the average urinary acids in the first group (4.50 mg/dl vs. 6.76 mg/dl; p < 0.001). During 36 months of therapy, composite primary endpoint events (death from cardiovascular or renal disease; new or recurrent cerebrovascular complication — ischemic, hemorrhagic stroke or transient ischemic attack; new or repeated non-fatal MI, unstable angina; hospitalization for heart failure; arteriosclerotic disease requiring treatment, including aneurysm, aortic dissection or obliterating arteriosclerosis; renal insufficiency, defined as microalbuminuria or moderate proteinuria, progression of albuminuria or proteinuria, a twofold increase in plasma creatinine levels, development of end-stage renal failure or renal death; atrial fibrillation (AF); death from any other cause) were recorded with a frequency of 23.3% in the febuxostat group and 28.7% in the control group (HR 0.75 at 95% CI from 0.59 to 0.95; p = 0.017), renal insufficiency — in 16.2% vs. 20.5% (HR

0.745 with 95% CI from 0.562 to 0.987; p = 0.04), death, cerebrovascular complication or nonfatal coronary event — 4.3% vs. 4.9% of cases (HR 0.861 at 95% CI 0.492 to 1.506; p = 0.60), respectively.
There was a J-shaped relationship between the development of clinical outcomes and the achieved level of uric acid in the blood plasma, the lowest risk of primary endpoint events was observed at an index from > 5 to ≤ 6 mg/dl. Therefore, the decrease in the level of uric acid with febuxostat compared with allopurinol cannot be considered as an advantage.

The objective of the **UK Biobank study (2019)** was to assess the lifelong impact of lower LDL cholesterol and lower SBP on the risk of CVD. Among 438,952 participants registered with the British Biobank between 2006 and 2010 with follow-up until 2018, genetically determined LDL and SBP indicators were used as tools to divide participants into groups with lifelong exposure to lower LDL, lower SBP or both. Differences in LDL levels, SBP and the frequency of CVD were compared between the groups to determine their association with the risk of coronary complications during life.
During the follow-up period, the first severe coronary event (coronary death, nonfatal MI or coronary revascularization) was recorded in 24,980 people. Participants with a lower (by 14.7 mg/dl compared with the median) genetic LDL level had a reduced lifetime risk of major coronary complications (HR 0.73 at 95% CI, from 0.70 to 0.75; p < 0.001), as well as participants with a genetically lower (by 2.9 mmHg. when compared with the median) the level of SBP (HR 0.82 at 95% with CI from 0.79 to 0.85; p < 0.001). In the group with a genetic decrease in both indicators (LDL by 13.9 mg/dl and SBP by 3.1 mmHg below the median, the risk of severe coronary events was even lower (HR 0.61 at 95% CI from 0.59 to 0.64; p < 0.001). In a meta-regression analysis, the combined effect of a reduced LDL level by 38.67 mg/dl and a decrease in SBP by 10 mmHg was associated with a marked reduction in the lifetime risk of severe coronary events (HR 0.22 at 95% CI 0.17 to 0.26; p < 0.001) and cardiovascular death (HR 0.32 at 95% CI from 0.25 to 0.40; p < 0.001).
Lifelong genetic exposure to lower LDL and SBP levels is associated with lower cardiovascular risk. However, it cannot be argued that these results accurately indicate the amount of benefit that can be achieved by correcting these risk factors.

The prospective **PURE study (2019)** collected data from 155,722 participants from 21 countries aged 35 to 70 years, who were included in the work in 2005-2016 on 5 continents, except Australia, followed by an average of 9.5 years of follow-up. The causes of death in countries with low, medium and high levels of economic development, the influence of variable risk factors on the development of CVD (cardiovascular death, MI, stroke and CHF) and mortality in these types of countries were compared. According to the data obtained, CVD as a cause of death were noted in 43%, 42% and 23% of cases, and cancer - in 15%, 30% and 55% of cases in countries with low, medium and high economic levels, respectively. The age- and gender-standardized indicators of total mortality

decreased with an increase in income levels - 13.3, 6.9 and 3.4 per 1,000 person-years for countries with low, medium, and high economic levels, respectively. It was showed that low income was associated with an increase in mortality from cardiovascular, respiratory diseases, injuries, and infections, as well as with a decrease in mortality from cancer. The ratio of mortality from CVD to cancer mortality was 3.0, 1.3 and 0.4 in countries with low, medium and high economic levels, respectively. The most important cardiovascular risk factor was hypertension, followed by high LDL levels, with air pollution in third place. Smoking, poor nutrition, low level of education and abdominal obesity had a comparable effect on cardiovascular risk. In high-income countries, behavioral and metabolic risk factors determined almost the entire risk of CVD, and in middle- and low-income countries, there was a greater impact of low education and air pollution.
A significant part of cardiovascular complications can be prevented by optimal control of metabolic and behavioral risk factors at the level of individuals and households. Health policy should focus on the risk factors that are most important in specific groups of countries. According to the authors of the study, in countries with low and medium economic development, the greatest benefits can be expected from limiting smoking, controlling hypertension and investing in healthcare, including increasing the availability of medicines to correct modifiable risk factors.

An open-label, cluster-randomized trial **SSaSS (2021)** involved 20,995 people 60 years of age or older, 72.6% had a history of stroke, and 88.4% a history of hypertension, from 600 villages in rural China. The villages were randomly assigned in a 1:1 ratio to the intervention group, in which the participants used a salt substitute (75% sodium chloride and 25% potassium chloride by mass), or to the control group, in which the participants continued to use regular salt (100% sodium chloride). The mean duration of follow-up was 4.74 years. The rate of stroke was lower with the salt substitute than with regular salt (29.14 events vs. 33.65 events per 1000 person-years; rate ratio, 0.86; 95% confidence interval [CI], 0.77 to 0.96; P = 0.006), as were the rates of major cardiovascular events (49.09 events vs. 56.29 events per 1000 person-years; rate ratio, 0.87; 95% CI, 0.80 to 0.94; P<0.001) and death (39.28 events vs. 44.61 events per 1000 person-years; rate ratio, 0.88; 95% CI, 0.82 to 0.95; P<0.001). The rate of serious adverse events attributed to hyperkalemia was not significantly higher with the salt substitute than with regular salt (3.35 events vs. 3.30 events per 1000 person-years; rate ratio, 1.04; 95% CI, 0.80 to 1.37; P = 0.76). Among persons who had a history of stroke or were 60 years of age or older and had high blood pressure, the rates of stroke, major cardiovascular events, and death from any cause were lower with the salt substitute than with regular salt.

The **LOOP study (2021)** assessed the possibility of preventing stroke in high-risk individuals by screening for AF using continuous ECG monitoring and

subsequent anticoagulant treatment. After randomization of 1:3 6004 people without AF aged 70-90 years and with at least one additional risk factor for stroke (arterial hypertension, DM, stroke, or CHF), continuous ECG monitoring was performed with an implantable loop recorder facilitating the detection of asymptomatic episodes of AF (n=1501) or routine care was provided (n=4503). Anticoagulant therapy was recommended for AF episodes of 6 minutes or more. During an average follow-up period of 64.5 months, AF was diagnosed in 31.8% of participants in the continuous monitoring group versus 12.2% in the control group (HR 3.17 with 95% CI from 2.81 to 3.59; p<0.0001). Oral anticoagulant therapy was initiated in 29.7% of patients in the continuous monitoring group compared with 13.1% in the control group (HR 2.72 at 95% CI 2.41 to 3.08; p<0.0001), stroke or systemic arterial embolism were observed in 4.5% vs. 5.6% of cases (HR 0.80 at 95% CI from 0.61 to 1.05; p=0.11), major bleeding – in 4.3% vs. 3.5% of cases (HR 1.26 at 95% CI from 0.95 to 1.69; p=0.11) accordingly. In individuals with stroke risk factors, screening using an implantable loop recorder led to a threefold increase in the frequency of detection of AF and the onset of anticoagulation but was not accompanied by a significant reduction in the risk of stroke or systemic arterial embolism. These data may mean that not all types of AF deserve screening and not all cases of AF detected during screening require anticoagulation.

ARTERIAL HYPERTENSION

The **KYOTO HEART study (2010)** involved 3,031 Japanese residents with uncontrolled hypertension and a high risk of complications who, after randomization, additionally received valsartan or therapy without ARB. According to the results of an additional analysis, valsartan significantly reduced the total risk of stroke, MI, heart failure and angina pectoris in primary (by 56%) and secondary (by 37%) prevention of complications. The results of treatment in 4 groups were compared — valsartan + calcium antagonist (n = 773), valsartan + non-calcium antagonist (n = 744), non-ARB + calcium antagonist (n = 1034), non-ARB + non-calcium antagonist (n = 480), the frequency of events related to the primary endpoint of the study, accounted for 5.0%, 6.0%, 9.8% and 11.0%, respectively. At the same time, the average blood pressure level in the groups did not differ significantly. Valsartan prevented the development of stable ($p = 0.01$), but not unstable angina ($p = 0.10$).

A subanalysis of the results of the **JIKEI HEART study (2010)**, in which Japanese patients on the background of standard hypertension therapy additionally received valsartan or therapy without ARB, was conducted in patients with CAD. The use of valsartan was accompanied by a decrease in the frequency of angina by 72% ($p = 0.00008$), heart failure — by 68% ($p = 0.02402$), but the frequency of MI cases did not decrease. The blood pressure level in the comparison groups did not differ significantly, but the LV myocardial mass index according to echocardiography was significantly lower in the valsartan group ($p < 0.001$).

An additional analysis of the results of the **KYOTO HEART study (2011)**, depending on the state of the kidneys, was carried out in 2929 patients with hypertension. The total frequency of CVD in those examined with a glomerular filtration rate of less than 60 ml/min / 1.73 m2 was significantly higher than in patients with a higher value of this indicator (11% vs. 6%, RR 1.71, $p < 0.0001$). In patients with chronic kidney disease (CKD) stages 4 and 5, the primary endpoint was recorded significantly more often than with preserved renal function (respectively 30% vs. 7%, $p = 0.0001$ and 27% vs. 7%, $p = 0.02$). Valsartan significantly reduced the risk of primary endpoint events in patients with stage 3-5

CKD compared with therapy that did not include ARB (8% vs. 14%, RR 0.53, p = 0.001), including new cases of CHF (p = 0.009) and renal complications (doubling of creatinine levels or the need for hemodialysis, p = 0.036).

Of the 25,620 participants in the **ONTARGET study (2011)** (ramipril vs. telmisartan and their combinations in patients at high risk of CVD), 4,629 did not comply with the prescribed therapy regimen. Among them, the RR of cardiovascular death compared to those receiving therapy was 2.05, MI - 2.24, stroke — 2.28, hospitalization with CHF — 2.85, but new cases of diabetes — 0.66 (all differences are significant, p < 0.0001). In patients who did not comply with the studied therapy, CVD complications quickly occurred, and the developing complications themselves led to an increase in their recurrence in the future, closing a vicious circle.

A subanalysis of the **PURE study (2012)** was devoted to the epidemiology and nature of hypertension treatment according to a survey of 153996 residents of 17 countries on 5 continents. The prevalence of hypertension averaged 40.7%, which makes it possible to regard this disease as a global epidemic. Awareness of the presence of hypertension, the frequency of treatment and its effectiveness remain low, especially among the rural population of countries with a low standard of living. However, the quality of hypertension treatment in urban populations of countries with different levels of economic development is comparable.

The **AQUARIUS project (2013)** included patients with blood pressure 125-139 and < 90 mmHg and plaques in the coronary arteries with narrowing up to 20-50%. After randomization, patients received aliskiren 300 mg/day (n = 305) or placebo (n = 308). According to intravascular ultrasound in dynamics after 72 weeks, the plaque volume decreased comparably: by 0.33% and 0.11% (p = 0.08), and its total volume — by 4.0 mm3 and 2.1 mm3 (p = 0.18) in the aliskiren and placebo groups, respectively. Meanwhile, a direct renin inhibitor, along with a decrease in blood pressure, reduced the total frequency of major CVD (8.5% vs. 16.2%, p = 0.004) and non-fatal MI (0.3% vs. 2.6%, p = 0.02) compared with placebo.

As part of the **PURE-Sodium project (2013)**, 97,000 people aged 35-70 years were examined, in whom the relationship between sodium, potassium intake and blood pressure levels were assessed. According to the data obtained, a decrease in sodium intake and an increase in potassium intake can reduce blood pressure in patients with hypertension with high sodium intake and the elderly. Significantly lower blood pressure dynamics can be expected in patients with moderate or low sodium intake, young people and people without hypertension.

The study **REGARDS (2013)** assessed the effect of SBP on the frequency of CVD (stroke, CAD, total mortality) in 13,948 elderly patients with hypertension without MI and a history of stroke. In the age groups 55-64, 65-74 years, the

smallest number of strokes, cases of ischemic disease and deaths were recorded with SBP below 120-130 mmHg, increasing at higher and lower levels. At the age of 75 years and older, the minimum stroke rate was observed with SBP below 120, CAD — 120-129, fatal outcome — 130-139 mm Hg. These data do not correspond to the current recommendations for the treatment of hypertension, although they maintain the target level of SBP below 140 and its dangerous level is less than 110 mmHg. Intensive therapy of hypertension (target SBP below 120 mmHg.) may be the subject of further research.

The **ATTEMPT-CVD study (2015)** included 1228 patients with hypertension and at least one risk factor for cardiovascular complications (DM, pathology of the kidneys, cerebral or peripheral arteries). After randomization, patients received telmisartan (n = 615) or antihypertensive therapy without ARB (n = 613). After 36 months in the telmisartan group, there was a significantly greater decrease in the albumin/creatinine ratio in urine ($p < 0.001$), a smaller increase in the concentration of brain natriuretic peptide ($p = 0.044$), a greater increase in the level of adiponectin in plasma ($p = 0.041$). In addition, treatment with telmisartan was accompanied by a tendency to decrease the frequency of fatal and non-fatal cardiovascular complications (cerebral, coronary, cardiac, from the aorta/ peripheral arteries), complications of diabetes and cases of deterioration of kidney function (HR 0.71 at 95% CI from 0.45 to 1.12; $p = 0.14$). Therapy with telmisartan, compared with standard antihypertensive treatment, is accompanied by positive changes in the levels of several prognostically significant biomarkers, regardless of blood pressure control.

It was assumed that resistant hypertension (failure to achieve the target blood pressure with triple therapy — an ACE inhibitor or ARB, calcium antagonist and diuretic in full doses) is due to aldosteronism and spironolactone may be the most effective additional therapy in this case. The **PATHWAY-2 study (2015)** involved 335 patients with SBP of 140 mmHg or higher (135 mmHg or more in DM) with office measurement and 130 mmHg or higher with home self-measurement after at least 3 months of triple therapy with maximum doses of drugs. In a random sequence of 12 weeks, spironolactone (25-50 mg/day), bisoprolol (5-10 mg/day), modified-release doxazosin (4-8 mg/day) or placebo were additionally used. Doubling of the initial dose of each drug was carried out after 6 weeks of therapy. According to the average decrease in SBP at home, spironolactone was superior to placebo (by 8.70 mmHg; $p < 0.001$), two active methods of treatment (doxazosin/ bisoprolol — by 4.26 mmHg.; $p < 0.001$), separately doxazosin (by 4.03 mmHg; $p < 0.001$) and bisoprolol (by 4.48 mmHg; $p < 0.001$). Spironolactone is the most effective supplement to the therapy of resistant hypertension, supporting the idea of the role of aldosterone in it.

The **PATHWAY-3 study (2015)** involved 399 patients with uncontrolled hypertension (SBP above 140 mmHg) and obesity who had indications for treatment with diuretics. After randomization, amiloride was used at 10 mg/day (n

= 132), hydrochlorothiazide at 25 mg/day (n = 134) or a combination of them in half doses (n = 133) for 12 weeks, after which a doubled dose of drugs was treated for another 12 weeks in each group. Comparison of average glycemic levels during the oral glucose tolerance test in dynamics revealed significant differences in the amiloride and hydrochlorothiazide groups (by 0.55 mmol/L; p = 0.009) due to a decrease in the first and an increase in the second case. At the same time, the level of glycemia in dynamics did not change significantly in the combination therapy group, being lower than in the hydrochlorothiazide group (by 0.42 mmol/L; p = 0.048). The degree of decrease in SBP in the amiloride group and the hydrochlorothiazide group did not differ significantly (14.7 mmHg and 14.0 mmHg, respectively). However, the combination of these drugs reduced blood pressure by 3.4 mmHg more than hydrochlorothiazide (p = 0.007). Amiloride is noninferior to hydrochlorothiazide in antihypertensive activity, and the combination of half doses of these drugs is more effective and does not cause disorders of carbohydrate metabolism, changes in blood potassium levels.

An increase in SBP, pulse blood pressure and blood pressure in the aorta accelerates the aging of the arteries and increases the risk of cardiovascular complications. The **PARAMETER study (2015)** included 454 elderly patients with hypertension who were randomized to receive LCZ696 (ARB / non-lysine inhibitor) 200 mg once a day (n = 229) or olmesartan 20 mg / day (n = 225) for the first 4 weeks, and after doubling the dose of medicine — for another 8 weeks or more. Over the next 40 weeks, additional medicines could be added to achieve the target blood pressure. After 12 weeks, SBP on the shoulder decreased by 13.7 versus 9.9 mmHg (p = 0.02), in the aorta — by 12.6 versus 8.9 mmHg (p = 0.01), pulse blood pressure in the aorta — by 6.4 versus 4.0 mmHg (p = 0.012) in the LCZ696 and olmesartan groups, respectively. LCZ696 was also superior to olmesartan in the degree of reduction of SBP on the shoulder and in the aorta according to the results of outpatient 24-hour monitoring (p < 0.001 for both comparisons), especially clearly at night. After 52 weeks, the benefits of LCZ696 treatment persisted, the level of the N-terminal precursor of the brain natriuretic peptide decreased comparatively more (by 34% versus 20%), and there was a tendency to decrease the pulse wave propagation rate when using it. In 68% of patients in the LCZ696 group and 53% in the olmesartan group, the target blood pressure was achieved with monotherapy. With the two methods of treatment, there were no significant differences in its tolerability, as well as the frequency of cardiovascular complications.

The single-blind study of **SPYRAL HTN-OFF MED (2017)** involved patients with arterial hypertension who did not take antihypertensive drug therapy, and with office SBP ≥ 150, but < 180 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, average level of SBP at 24-hour outpatient monitoring was ≥ 140, but < 170 mmHg. After randomization during renal angiography, sympathetic denervation of the kidneys with a new four-electrode spiral catheter for ablation (n = 38) or its imitation (n = 42) was performed.

After 3 months, only in the renal denervation group there was a significant antihypertensive effect according to 24-hour outpatient monitoring (SBP -5.5 mmHg; p = 0.0031 and DBP -4.8 mmHg; p < 0.0001) and office measurement (SBP -10.0 mmHg; p = 0.0004 and DBP -5.3 mmHg; p = 0.0002). The average difference between the ablation and its imitation groups after 3 months according to the results of 24-hour outpatient monitoring was -5.0 mmHg (p = 0.0414) for SBP and -4.4 mmHg (p = 0.0024) for DBP, and according to office measurement -7.7 mmHg for SBP (p = 0.0155) and DBP -4.9 mmHg (p = 0,0077). The results of the work confirmed the possibility of lowering blood pressure by sympathetic denervation of the kidneys. Meanwhile, the target level of SBP was not achieved and pharmacotherapy in these patients is required.

J.J. Miranda presented a study conducted in Peru, in which **the substitution of table salt** was carried out to reduce blood pressure **(2019)**. Families, shops, bakeries, and restaurants in rural areas were provided free of charge with potassium chloride to replace 25% sodium chloride in the diet for 3 years. 91.2% of 2,605 registered adults participated in the work. People with CKD, heart disease, or taking digoxin were excluded due to concerns about increased potassium intake.

Blood pressure was measured 7 times every 5 months and its decrease was noted by an average of 1.23/0.72 mmHg (p = 0.004 and p = 0.022, respectively) from the average baseline level of 113.1/72 mmHg. This effect was more pronounced in 18% of people with hypertension and in individuals older than 60 years (decrease in SBP by an average of 1.92 and 2.17 mmHg, respectively). At the same time, no adverse events were observed. The cumulative probability of developing hypertension (threshold level 140/90 mmHg) decreased by 55% over the 3 years of the study compared to the control (p < 0.001).

This study shows that the strategy of replacing the consumption of sodium chloride with potassium chloride at the population level is feasible and effective. Although the average decrease in blood pressure is insignificant, it can be expected that a decrease in SBP by 2 mmHg will lead to a 10% reduction in mortality from stroke, and from CAD and other vascular complications — by 7%.

Hypertension is the main cause of CVD worldwide, but its control remains insufficient. In the open randomized controlled trial **HOPE4 (2019)**, the hypothesis of increasing the effectiveness of risk factor correction in medical care with the participation of primary care physicians and family, with the provision of effective medications to people with poorly controlled or recently diagnosed hypertension, was evaluated.

The study involved 1,371 patients from 30 communities in Colombia and Malaysia who received routine medical care (control group, n = 727) or based on the investigated approach — free antihypertensive drugs and statins, support from a family member or friend (supporter of treatment) to improve adherence to therapy and a healthy lifestyle (intervention group, n = 644).

The primary endpoint was a change in the indicator of a 10-year assessment of the risk of cardiovascular complications on the Framingham scale after 12 months in the participants of the intervention and control groups. A year later, the reduction in the risk index was -6.40% in the control group and -11.17% in the intervention group with a difference of -4.78% (95% CI from -7.11 to -2.44; $p < 0.0001$). There was an absolute decrease in SBP by 11.45 mmHg (95% CI from -14.94 to -7.97) and a decrease in LDL by 0.41 mmol/L (95% CI from -0.60 to -0.23) in the intervention group (both $p < 0.0001$). The target level of SBP (< 140 mmHg) was registered in 69% of patients in the intervention group versus 30% in the control group ($p < 0.0001$).
A comprehensive model of medical care with the participation of primary care physicians and family, considering regional peculiarities, significantly improves hypertension control. The implementation of this strategy can significantly reduce the risk of cardiovascular complications compared to the modern approach focusing on the doctor.

Pharmacological reduction of blood pressure is an effective strategy to prevent CVD in people with high blood pressure. However, the recommendations for antihypertensive therapy in some countries have features due to differences in perceptions of the threshold level of blood pressure below normal (140/90 mmHg), the excess of which requires taking medications that improve outcomes in the presence or absence of concomitant pathology.
The aim of the **BPLTTC project (2020)** was to determine the effect of antihypertensive therapy on clinical outcomes, depending on the presence of cardiovascular pathology and the initial level of SBP. The authors combined data from 48 RCTs conducted as part of the Blood Pressure Lowering Treatment Trialist' Collaboration. Each such work had to include ≥ 1000 person-years of follow-up and compare either one class of antihypertensive drugs with placebo, or different classes of drugs with each other, or a strategy of intensive treatment. The study included 348,854 observation participants who were divided into groups depending on the absence (n = 188,583) or presence (n = 160,271) of CVD, and then divided into seven groups by SBP ranges from more than 170 mmHg to less than 120 mmHg.The average age of patients at the baseline level was 65 years, and the average follow—up period was about 4 years. The combined primary endpoint was the sum of serious cardiovascular events (fatal or nonfatal stroke, fatal or nonfatal MI or CAD, or death from heart failure or hospitalization, or death from CVD).
In the general population, with a decrease in SBP for every 5 mm Hg, the total frequency of serious cardiovascular events decreased by 10% (HR 0.89 at 95% CI from 0.86 to 0.92 among persons without documented CVD at baseline; HR 0.91 at 95% CI from 0.89 to 0.94 in those who initially had CVD). Reduction of SBP for every 5 mm Hg was accompanied by a decrease in the risk of stroke by 13%, heart failure by 14%, CAD by 7% and death from CVD by 5% evenly among all seven groups of SBP ranges (less than 120, 120-129, 130-139, 140-149, 150-159, 160-169, more than 170 mmHg), regardless of the presence or absence of CVD.

Lowering blood pressure reduces the risk of CVD even in patients with "normal" blood pressure levels, including those without signs of CVD. But this does not mean that all people should be treated. Making a medical decision on the antihypertensive drug therapy requires considering the age of the person, the estimated risk of cardiovascular complications, the cost/ effectiveness / potential side effect of treatment.

The optimal target level of systolic blood pressure to reduce cardiovascular risk in elderly patients with hypertension remains unclear. In the **STEP study (2020)**, 8511 Chinese patients aged 60-80 years with hypertension received antihypertensive therapy to achieve a target systolic blood pressure from 110 to <130 mmHg (intensive treatment) or from 130 to <150 mmHg (standard treatment). After 1 year of follow–up, the average systolic blood pressure was 127.5 mmHg in the intensive care group and 135.3 mmHg in the standard treatment group. During an average follow-up period of 3.34 years, primary endpoint events (stroke, MI, hospitalization for unstable angina, acute decompensated heart failure, coronary revascularization, AF, or death from cardiovascular causes) occurred in 3.5% of patients in the intensive care group and in 4.6% in the standard treatment group (HR 0.74 at 95% CI from 0.60 to 0.92; p=0.007). In intensive treatment group, the risk of stroke (HR 0.67 at 95% CI 0.47 to 0.97), ACS (HR 0.67 at 95% CI 0.47 to 0.94), acute decompensated heart failure (HR 0.27 at 95% CI 0.08 to 0.98), coronary revascularization (HR 0.69 at 95% CI from 0.40 to 1.18), AF (HR 0.96 at 95% CI from 0.55 to 1.68), death from cardiovascular causes (HR 0.72 at 95% CI from 0.39 to 1.32) decreased. Safety and renal outcomes did not differ significantly between the two groups, but the frequency of hypotension was higher in the intensive care group. In elderly patients with hypertension, intensive treatment to achieve systolic blood pressure from 110 to <130 mmHg reduces the frequency of cardiovascular events more than standard treatment with a target systolic blood pressure from 130 to <150 mmHg.

The **TIME (2022)** study involved 21,104 patients with hypertension (average age 65.1 years) who received usual antihypertensive medication in the morning (06:00-10:00) or in the evening (20:00-00:00) after randomization. With a median follow–up of 5.2 years, the composite primary endpoint – vascular death or hospitalization for non-fatal MI or non-fatal stroke occurred in 3.4% of participants in the evening dosing group (0.69 events per 100 patient years) and 3.7% in the morning dosing group (0.72 events per 100 patient years), giving an unadjusted hazard ratio of 0.95 (95% CI 0.83 to 1.10; p=0.53). No safety concerns were identified.
Evening dosing of usual antihypertensive medication was not different from morning dosing in terms of major cardiovascular outcomes. Patients can be advised that they can take their regular antihypertensive medications at a

convenient time that minimises any undesirable effects. According to the authors, this conclusion is final, at least for drugs with a guaranteed duration of action of 24 hours. However, the study did not identify and consider special groups of patients, such as patients with non-dipper, night-peacker, over-dipper blood pressure profiles, for whom the time of taking antihypertensive medication may be of significant importance.

MANAGEMENT OF DYSLIPIDEMIA

The randomized, double-blind, placebo-controlled **ALPHA OMEGA study (2010)** included 4837 patients who underwent MI for up to 10 years. In four groups, eicosapentaenoic and docosahexaenoic acids were treated at a low dose of 400 mg/day, alpha—linolenic acid at a dose of 2 mg/day, their combination or placebo. The source of omega-3 polyunsaturated fatty acids was margarine, prescribed 20 g per day. Background treatment turned out to be very intensive — 98% of patients received antithrombotic drugs, 90% received antihypertensive drugs, and 86% of patients received lipid—lowering drugs, usually statins. During 40 months of controlled therapy, no differences were achieved between the groups in the total frequency of nonfatal cardiovascular events (MI, sudden cardiac arrest, stroke, myocardial revascularization, defibrillator implantation). However, in women treated with alpha-linolenic acid, this primary endpoint was registered 27% less frequently. In patients with DM (21% of the study participants), mortality from CAD decreased by 49% when treated with eicosapentaenoic and docosahexaenoic acids, and events associated with ventricular arrhythmias were reduced by these omega-3 polyunsaturated fatty acids by 49%, alpha-linolenic acid by 61%.
Low doses of omega-3 polyunsaturated fatty acids when using margarine do not reduce the risk of serious cardiovascular events. The positive results of such therapy in women and patients with diabetes require confirmation in new studies.

The **HCS study (2011)** evaluated the ratio of plasma triglyceride levels and glucose tolerance with cardiovascular outcomes in 514 patients with stable CAD documented by coronary angiography. The test consisted of an oral fat load: 250 ml of cream (75 g of fat), and then 75 g of glucose in 250 ml of water. The levels of triglycerides and glucose in the blood were evaluated in dynamics. Only in patients with normal glucose tolerance, elevated postprandial triglyceride levels were an independent marker of cardiovascular outcomes.

dal-VESSEL (2011) — study of the effect of dalcetrapib phase IIb on endothelial function and blood pressure. In 476 patients with CAD or its risk

factors and high-density lipoprotein (HDL) cholesterol less than 50 mg/dl, dalcetrapib 600 mg/day (n = 238) or placebo (n = 238) were used in addition to the treatment. The primary endpoint of efficacy was a change in the flow-dependent dilatation of the brachial artery after 12 weeks, compared with the initial one. The primary safety endpoint was 24-hour outpatient blood pressure monitoring at the 4th week of therapy. Patients received treatment for 36 weeks. Dalcetrapib reduced the activity of the cholesterol ester transporter protein by almost 50% and increased the level of HDL cholesterol by 31% without significantly changing the level of LDL cholesterol, nitric oxide-dependent endothelial function, markers of inflammation and oxidative stress. Dalcetrapib did not increase blood pressure, which is an important difference from the action of torcetrapib, which worsened the prognosis, as it is believed, for this reason.

The observation of participants in the lipid branch (n = 10305) of the **ASCOT study (2011)** (atorvastatin 10 mg/day versus placebo in patients with hypertension and total cholesterol levels of no more than 6.5 mmol/L) lasted on average up to 11 years. With such a follow-up period, a statistically significant decrease in total mortality by 14% (p = 0.02) was achieved in the atorvastatin group, as a result of a 15% decrease in mortality from non-cardiovascular causes (p = 0.03), mainly from infections and respiratory diseases. At the same time, cardiovascular mortality only tended to decrease by 11% (p = 0.32).

The **HPS2-THRIVE study (2012)** included residents of Europe and China who had suffered MI, stroke, atherosclerosis of peripheral arteries or DM, who after randomization received nicotinic acid (niacin) (n = 12838) or placebo (n = 12835) in addition to simvastatin at a dose of 40 mg/day. The presented safety analysis showed that myopathy developed more often in patients receiving simvastatin and niacin (0.54% vs. 0.09% in the simvastatin and placebo group), and most of these cases were observed in patients from China.
The frequency of rhabdomyolysis was 0.02% and 0.05%, respectively, the effect of the two types of therapy on liver function was comparable.

The effect of RVX-280, a substance capable of increasing the level of HDL in the blood, on the progression of coronary atherosclerosis was studied against the background of therapy with atorvastatin or rosuvatstatin under the control of intravascular ultrasound in the **ASSURE project (2013)**. For 26 weeks, the level of HDL was higher by 10.9% and 7.7% (p = 0.32), and LDL were lower by 16% and 17.6% (p = 0.72) in the RVX-280 (n = 244) and placebo (n = 80) groups, respectively. These minor differences were accompanied only by a tendency to decrease the volume of atheroma (p = 0.08) and the frequency of cardiovascular complications (p = 0.09) when treated with a new drug.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a molecule that plays a key role in the destruction of receptors for LDL, which leads to a decrease in the capture and catabolism of circulating LDL, an increase in their content in

plasma. Alirocumab is a fully human monoclonal antibody to this molecule that effectively corrects hypercholesterolemia. The **ODYSSEY COMBO II study (2014)** involved patients with a history of CVD and LDL ≥ 1.8 mmol/L (in combination with risk factors) and LDL ≥ 2.6 mmol/L, against the background of the use of the maximum tolerated daily dose of statin. After randomization, alirocumab was additionally applied 75 mg (in 18.4% of cases — 150 mg) subcutaneously once every 2 weeks (n = 479) or ezetimibe 10 mg/day (n = 241). After 24 weeks, there was a decrease in LDL by 50.6% and 20.7% (p = 0.0001) with a level of < 1.8 mmol/L in 77% and 45% of cases in the alirocumab and ezetimibe groups, respectively. The frequency of discontinuation of therapy with alirocumab or ezetimibe due to side effects (most often dizziness and myalgia) was 7.5% and 5.4 %

The **ODYSSEY FH I and FH II (2014)** study included patients with two genetic variants of heterozygous familial hypercholesterolemia and with insufficient effect of the maximum tolerated daily dose of statin or other therapy. After randomization, alirocumab 75 mg subcutaneously was added to treatment 1 time every 2 weeks, increasing its dose to 150 mg after 8 weeks if the level of LDL remained ≥ 1.8 mmol/L, or placebo. After 24 weeks, in the first genetic variant of hypercholesterolemia, alirocumab (n = 323) reduced LDL by 48.8%, placebo (n = 163) — by 9.1% (p < 0.0001), in the second variant, alirocumab (n = 167) - by 48.7%, placebo (n = 82) — by 2.8 % (p < 0.0001). As a result, the target level of LDL was achieved in more than 70% of patients and more than 80% of patients with two studied variants of heterozygous familial hypercholesterolemia with a frequency of withdrawal of alirocumab due to side effects (injection site reactions, nasopharyngitis, headache) of 3.1 % and 3.7% of cases, respectively.

The **ODYSSEY LONG TERM project (2014)** involved patients with CAD, high risk of cardiovascular complications or heterozygous familial hypercholesterolemia (17.7% of cases) and LDL levels ≥ 1.81 mmol/L while taking the maximum tolerated dose of statins and/or other lipid-lowering therapy. After 24 weeks of using alirocumab (n = 1553) 150 mg subcutaneously once every 2 weeks or placebo (n = 788), the level of LDL decreased by 61.0% and 0.8%, respectively (p < 0.0001), reaching an average of 1.25 mmol/L versus 3.08 mmol/L. Retrospectively, there was a decrease in the total frequency of coronary death, nonfatal MI, fatal and nonfatal ischemic stroke, unstable angina that required hospitalization by 54% (p = 0.0089). The frequency of discontinuation of therapy in the alirocumab and placebo groups was 6.2% and 5.5%, respectively.

Statins can increase the risk of developing diabetes, but their effect on the course of existing diabetes has not been studied enough. In the **LISTEN study (2014),** Japanese patients with type 2 DM and hypercholesterolemia were prescribed rosuvastatin 5 mg/day (n = 514) or atorvastatin 10 mg/day (n = 504) for a year after randomization. After 3 months, the level of LDL decreased in the rosuvastatin and atorvastatin groups by 39.4% and 36.4% (p = 0.0106), and after a

year — by 34.8% and 32.8%, respectively. The blood glucose level increased more after 3 and 6 months under the influence of atorvastatin (p = 0.0104), but after a year it changed equally, on average by 0.11% and 0.12%, in the rosuvastatin and atorvastatin groups, respectively. At the same time, 1.46 times more (p = 0.05) the number of patients receiving atorvastatin was enhanced with DM therapy to correct the observed hyperglycemia. Therefore, rosuvastatin is the best choice for the treatment of patients with type 2 diabetes compared to atorvastatin.

According to the results of small, randomized studies, perioperative statin therapy reduced the likelihood of developing AF after heart surgery and prevented myocardial and kidney damage. In the **STICS study (2014)**, rosuvastatin 20 mg/day (n = 960) or placebo (n = 962) were used 8 days before and 5 days after elective heart surgery. The incidence of AF was 21% versus 20% (p = 0.72) in the rosuvastatin and placebo groups, respectively. In the compared groups, there were no significant differences in plasma troponin I levels (p = 0.72) reflecting perioperative myocardial injury, as well as the duration of hospitalization, cardiac and cerebrovascular complications during hospitalization, LV function according to echocardiography, plasma creatinine levels.

The effect of prolonged high-intensity statin therapy on coronary atherosclerosis in patients with MI with ST segment elevation remained unknown. In the **IBIS4 study (2014)** in 103 such patients, the effect of rosuvastatin at a dose of up to 40 mg/day on the size and phenotype of plaques in two noninfarction-associated epicardial arteries was evaluated according to intravascular, including radiofrequency, ultrasound. After 13 months, the level of LDL decreased from 3.29 to 1.89 mmol/L (p < 0.001), HDL increased from 1.10 to 1.20 mmol/L (p < 0.001), plaque volume decreased by 0.9% (p = 0.007). The proportion of patients with plaque regression in at least one artery was 74%. The volume of the necrotic nucleus of the plaque (-0.05%; p = 0.93) and the number of radiofrequency ultrasound sections that revealed a thin plaque covering (p = 0.15) did not change significantly.
According to meta-analysis, 1 g per day of eicosapentaenoic and docosahexaenoic omega-3 polyunsaturated fatty acids significantly reduces cardiac mortality. In an experiment in animals, omega-3 polyunsaturated fatty acids in a low dose changed the composition of cardiomyocyte membranes, preventing cardiac arrhythmias, especially ventricular fibrillation. Much less is known about the effectiveness of alpha-linolenic polyunsaturated fatty acid contained in plants.

After ACS, high-intensity statin therapy is recommended. It was assumed that the addition of ezetimibe to treatment could further improve the prognosis of such patients. In the **HIJPROPER study (2016)**, patients with ACS after randomization underwent lipid-lowering therapy with pitavastatin at a dose of 2 mg/day (n = 857) or its combination with ezetimibe (n = 864), maintaining LDL levels in the range of 90-100 mg/dl or less than 70 mg/dl, respectively.

After an average of 3.9 years of follow-up, events of the primary combined endpoint (death from any cause, nonfatal MI or stroke, unstable angina, revascularization due to ischemia) occurred with comparable frequency — in 36.9% and 32.8% of patients (HR 0.89 at 95% CI from 0.76 to 1.04; p = 0.152), the total mortality was 7.0% and 4.9% (p = 0.075), and the total number of cases of cardiovascular death, MI or stroke was 6.1% and 5.9% (p = 0.921) in the group of pitavastatin and its combination with ezetimibe, respectively. Meanwhile, in the subgroup of patients with the level of the cholesterol absorption marker sitosterol 2.2 mcg/ml or more, the frequency of the primary endpoint significantly decreased (HR 0.71 at 95% CI from 0.56 to 0.91; p = 0.006). There were no significant differences in the incidence of myopathy (p = 0.99), rhabdomyolysis (p = 0.57) and cancer (p = 0.27) between the groups of mono- and combined lipid-lowering therapy.

Heterozygous familial dyslipidemia is characterized by an increase in LDL levels, insufficient effectiveness of statins and early development of CAD. Apheresis allows you to temporarily reduce the level of LDL in the blood by 50-75%, but after 1-2 weeks a repeat of the procedure is required. In the **ODYSSEY ESCAPE study (2016)** in 62 patients with heterozygous familial dyslipidemia, the effect of the PCSK9 inhibitor alirocumab at a dose of 150 mg once every 2 weeks subcutaneously (n = 41) compared with placebo (n = 21) on the frequency of standard apheresis procedures was evaluated. For the first 6 weeks, the apheresis was planned for the patient, and from 7 to 18 weeks it depended on the patient's LDL level (the procedure was not performed at an index ≥ 30% lower than that available before inclusion in the study). The primary endpoint was the frequency of apheresis from week 7 to week 18, standardized to the number of planned procedures. At week 6 in the alirocumab group before apheresis, the LDL level decreased by 53.7% and practically did not change in the placebo group (+ 1.6%; p < 0.0001). In this regard, patients, those who received alirocumab avoided 75% of the planned apheresis procedures compared to placebo, and 63.4% of patients did not require apheresis at all, and 92.7% of the frequency of procedures decreased by at least half. Alirocumab was generally safe and well tolerated.

Refractory angina, which persists despite optimal medical treatment and myocardial revascularization, is associated with an increased level of lipoprotein (a) in the blood, poorly corrected by pharmacotherapy, but reduced by apheresis. In 20 patients with refractory angina pectoris and lipoprotein (a) levels above 500 mg/l, **T.Z. Khan et al. (2016)** after randomization, apheresis (n = 10) or its imitation (n = 10) was performed weekly for 3 months. The primary endpoint of the study was the reserve of myocardial blood supply, which represented the ratio of blood flow under stress and at rest after 3 months of lipoprotein apheresis, compared with the baseline level according to MRI. The reserve of myocardial blood supply increased in the group of apheresis (from 1.45 to 1.93; p < 0.001), but not in the group of its imitation. Also, apheresis, unlike its imitation, increased the tolerance of patients to physical activity according to the results of a 6-minute

walking test, reduced the symptoms of angina pectoris and the volume of plaques in the carotid arteries, improved the quality of life according to the Seattle Angina Questionnaire.

Inclisiran is a synthetic oligonucleotide that cleaves the matrix ribonucleic acid that encodes the PCSK9 protein, reducing its activity in the liver, which causes a persistent decrease in the level of LDL in plasma. The double-blind phase II **ORION 1 study (2017)** included 501 patients with CVD caused by atherosclerosis and LDL levels > 1.8 mmol/L or a high risk of their development (DM, familial dyslipidemia) and LDL levels > 2.6 mmol/L while taking the maximum tolerated doses of statins. In eight treatment groups, patients were injected subcutaneously with inclisiran once in doses of 200, 300, 500 mg or placebo; as well as twice with an interval of 90 days with 100, 200, 300 mg of inclisiran or placebo. 1 year after one injection of inclisiran 200, 300 or 500 mg, the LDL level decreased by 31.6%, 38.1% and 39.8%, respectively ($p < 0.0001$ for all comparisons) when compared with background therapy with statins alone or their combination with ezetimibe, and 1 year after two injections of inclisiran 100, 200 or 300 mg — by 31.0%, 41.1% and 46.8%, respectively ($p < 0.0001$ for all comparisons). After the maximum decrease in LDL, it increased by an average of 2-3% per month and returned to the baseline level after 18-21 months. Serious side effects were observed in 11% of patients treated with inclisiran (mostly local reactions in the injection area), and in 8% of patients treated with placebo. The possibility of dosing inclisiran 2 times a year, the use of a low dose, moderate production costs can ensure the economic effectiveness of the drug. Soon, randomized phase III clinical trials will begin, in which its effect on the risk of death from CAD, nonfatal MI, fatal and nonfatal ischemic stroke will be evaluated.

The **EMPATHY study (2017)** involved Japanese residents with hypercholesterolemia, who suffered from DM and diabetic retinopathy, but did not have CAD. After randomization, patients received intensive (target LDL level < 70 mg/dl; n = 2518) or standard (target LDL level ≥ 100, but < 120 mg/dl; n = 2524) therapy with any statin. With an average follow-up duration of 37 months, the frequency of registration of the primary composite endpoint (cardiovascular death, cardiac, cerebral, renal, or vascular events) did not significantly decrease in the statin intensive care group (HR 0.84 at 95% CI from 0.67 to 1.07; p = 0.15) compared with the standard treatment group. Intensive statin treatment was accompanied by a decrease in the risk of cerebral complications (HR 0.52 at 95% CI from 0.31 to 0.88; p = 0.01), but not cardiac events (HR 0.93 at 95% CI from 0.65 to 1.33; p = 0.69), which is typical for Asian populations. A retrospective analysis showed a significant decrease in the frequency of the primary endpoint during intensive statin therapy in a subgroup of patients who reached the target LDL levels (HR 0.48 at 95% CI from 0.28 to 0.82; p = 0.007).

In **FOURIER** study **(2022)** the proprotein convertase subtilisin-kexin type 9 inhibitor evolocumab reduced LDL cholesterol and risk of cardiovascular events and was safe and well tolerated over a median of 2.2 years of follow-up. Therefore **FOURIER-OLE** study was conducted to investigate the long-term safety, tolerability, lipid levels, and risk of major adverse cardiovascular events in patients getting prolonged treatment with the proprotein convertase subtilisin-kexin type 9 inhibitor evolocumab. A total of 6635 patients were enrolled in FOURIER-OLE (3355 randomized to evolocumab and 3280 to placebo in the parent study). During the FOURIER-OLE follow-up period 5.0 years, patients originally randomized in the parent trial to evolocumab versus placebo had a 15% lower risk of cardiovascular death, MI, stroke, or hospitalization for unstable angina or coronary revascularization (HR 0.85 at 95% CI from 0.75 to 0.96; p=0.008), the risk of cardiovascular death, MI or stroke by 20% (HR 0.80 at 95% CI 0.68 to 0.93; p=0.003) and cardiovascular death by 23% (HR 0.77 at 95% CI 0.60 to 0.99; p=0.04) compared with placebo. Long-term LDL cholesterol lowering with evolocumab was associated with persistently low rates of adverse events for >8 years that did not exceed those observed in the original placebo arm during the parent study and led to further reductions in cardiovascular events compared with delayed treatment initiation.

Statin therapy is widely used and effectively prevents atherosclerotic CVD, but concerns persist that it causes muscle pain or weakness. The **Cholesterol Treatment Trialists' Collaboration (2022)** meta-analysis included 19 large randomized double-blind studies of statins compared to placebo (n=123,940) and 4 double-blind studies of more versus less intensive regimens (n=30,724). During an average follow-up period of 4.3 years, 27.1% of those receiving statins compared to 26.6% of those receiving placebo reported muscle pain or weakness (HR 1.03 at 95% CI 1.01 to 1.06). During the first year of statin therapy, there was a relative increase in the frequency of muscle pain or weakness (HR 1.07 at 95% CI from 1.04 to 1.10), which corresponds to an absolute frequency of excess of 11 events per 1000 person-years, that is, only one of 15 ([1,07-1,00]/1,07) these messages on therapy statins were linked to statins. After 1 year of observation, there was no increase of the frequency of the first muscle symptoms appearance in the statin group, compared with placebo (HR 0.99 at 95% CI from 0.96 to 1.02). Regimens of high-intensity statin therapy (atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day) were associated with a higher risk of muscle symptoms than regimens of low-intensity and moderately intensive statin treatment, and it was traced after 1 year compared with placebo (HR 1.05 at 95% CI 0.99 to 1.12). There was no clear evidence that the risk was different for individual statin molecules or in different clinical situations. Statin therapy leads to a small clinically insignificant increase in the median values of blood creatine kinase. Statin treatment causes a slight increase in patients' complaints of muscle pain, mostly mild. The majority (>90%) of all reports of muscle symptoms in patients who have been prescribed statins are not related to statins. The risk of muscle symptoms is much lower than the known cardiovascular benefits of statins.

CVD AND DIABETES MELLITUS

In the **TREAT project (2010)**, the use of darbepoetin (a substance that stimulates the formation of erythropoietin) in patients with type 2 diabetes did not lead to a decrease in the total frequency of deaths, the development of MI, myocardial ischemia, heart failure and stroke compared with placebo. Additional analysis of the study data made it possible to identify predictors of an unfavorable outcome in the surveyed population. Among the known factors was heart failure, the presence of which increased the risk of complications by 1.74 times ($p < 0.0001$). A direct relationship between increased levels of the N-terminal fragment of the precursor of the brain natriuretic peptide, the level of troponin T, as well as the risk of deterioration of kidney function turned out to be unexpected.

The aim of the **ALTITUDE study (2012)** was to assess the possibility of reducing the high risk of fatal and non-fatal cardiovascular and renal complications in patients with type 2 diabetes by using a direct renin inhibitor aliskiren. After randomization, patients received aliskiren at a dose of 300 mg once a day (n = 4274) or placebo (n = 4287) in addition to treatment with ACE inhibitors or ARB. With an average follow-up period of 32 months, the primary endpoint (the time before the first event — cardiovascular death, resuscitation in case of sudden cardiac arrest, MI, stroke, unplanned hospitalization for CHF, the onset of end-stage kidney disease or doubling of the initial creatinine level) was registered in 767 patients (17.9%) treated with aliskiren and 721 (16.8%) — placebo ($p = 0.14$). In the aliskiren group, there were trends towards increased stroke (3.4% vs. 2.7% in the placebo group, $p = 0.070$), total mortality (8.8% vs. 8.3%, $p = 0.388$), hyperkalemia - 6 mmol/L or more (8.8% vs. 5.6%) and arterial hypotension (12.1% vs. 8.0 %). These results show that the addition of aliskiren to a drug that inhibits the renin-angiotensin system does not improve the prognosis of patients with type 2 diabetes.

The **GRACE study (2012)** (a part of a large ORIGIN project) involved 1,184 patients with diagnosed CVD or risk factors who had impaired fasting

glycemia, impaired glucose tolerance or type 2 diabetes. After randomization, in addition to standard therapy, long-acting insulin galargin with a target glycemic level of 5.3 mmol/L, capsules with 1 g of omega-3 polyunsaturated fatty acid ethyl esters or placebo were prescribed. With an average follow—up period of 4.9 years, the main indicator (average annual change in intima media thickness in 12 carotid artery sites) in the insulin treatment group changed insignificantly - by 0.0030 ± 0.0021 mm/year (p = 0.145), although the maximum intima media thickness in the common carotid artery and common carotid artery plus bifurcation sites decreased significantly — by 0.0033 ± 0.0017 mm/year (p = 0.049) and 0.0045 ± 0.0021 mm/year (p = 0.032), respectively. The listed indicators did not differ in the groups of omega-3 fatty acids and placebo.

In a randomized study **CARDia (2012)**, the effect of coronary bypass surgery (n = 254) was compared with PCI with stenting (n = 256) in patients with DM with multivessel coronary lesion. During an average of 5.1 years of follow—up, the primary endpoint (death from any cause, MI or stroke) was recorded in 20.5% in the coronary bypass group and 26.6% in the PCI group (p = 0.11), total mortality was 12.6% and 14% (p = 0.53), the incidence of MI was 6.3% and 14% (p = 0.007), stroke — 4.3% and 3.1% (p = 0.48), and the sum of complications (death from any cause, MI, stroke, repeated revascularization) — 26% and 37.5% (p = 0.005), respectively. Although coronary bypass remains the preferred method of revascularization in DM, multivessel PCI is also possible in some patients.

A new hypoglycemic drug from the class of DPP-4 (dipeptidyl peptidase-4) inhibitors alogliptin (n = 2701) or placebo (n = 2679) was prescribed after randomization to patients with type 2 DM who had suffered MI or unstable angina 15-90 days ago. The HbA1c level in the first group was 0.36% lower. With an average follow-up duration of 18 months, the primary endpoint of the **EXAMINE study (2013)** (the sum of complications – cardiovascular death, MI or stroke) was recorded with a frequency of 11.3% versus 11.8% (HR 0.96, p < 0.001 for no less effectiveness) in the active therapy and control groups, respectively. The number of cases of hypoglycemia, cancer, pancreatitis, and the onset of hemodialysis did not differ significantly. Alogliptin does not have a cardioprotective effect, but it does not worsen the prognosis of patients with type 2 diabetes who have recently undergone ACS.

Another DPP-4 inhibitor, saxagliptin at a dose of 5 mg/day (2.5 mg for impaired renal function), was evaluated in 16492 patients with type 2 DM in a placebo—controlled study **SAVOR-TIMI 53 (2013)**. With an average duration of treatment of 2.1 years, the total frequency of cardiovascular death, MI or ischemic stroke (primary endpoint) was 7.3% and 7.2% (p = 0.99), and the number of cases of cardiovascular death, MI, stroke, hospitalization for unstable angina, coronary revascularization or heart failure was 12.8% and 12.4% (p = 0.66) in the saxagliptin and placebo groups, respectively. At the same time, DPP-4 inhibitor intake was accompanied by a significant increase in the frequency of

hospitalizations due to heart failure (3.5% vs. 2.8% in the palacebo group, p = 0.007).

The purpose of additional analysis of the results of the **PARTNER study (2013)** was to compare transcatheter (transfemoral or transapical access) and surgical replacement of the aortic valve in 275 patients with aortic stenosis and DM. In patients with diabetes, mortality from any cause during the year was lower with transcatheter than with surgery (18.0% vs. 27.4%, p = 0.04), whereas in patients without diabetes, mortality did not differ significantly (27.8% vs. 23.7%, respectively, p = 0.48). During the year, in the group of diabetic patients, the incidence of stroke was 2.1% and 2.7% (p = 0.87), renal failure requiring dialysis — 4.2% and 10.6 % (p < 0.05) with transcatheter or surgical replacement of the aortic valve, respectively.

Previously, large-scale studies of dipeptidyl peptidase-4 inhibitors (saxagliptin and alogliptin) in patients with type 2 DM showed an increased risk of heart failure, which was of concern to endocrinologists and cardiologists. The **TECOS study (2015)** evaluated the cardiovascular safety of another representative of this class of drugs — sitagliptin (n = 7332) compared with placebo (n = 7339), added to the standard therapy of type 2 diabetes and concomitant CVD. With a median follow-up of 2.9 years, sitagliptin compared with placebo did not increase the frequency of the combined primary endpoint (cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina) (HR 0.98 at 95% CI from 0.88 to 1.09; p < 0.001 for the conclusion "not worse"). The rate of hospitalization due to heart failure was 3.1% each in the sitagliptin and placebo groups (HR 1.00 at 95% CI from 0.84 to 1.20; p = 0.95), and the sum of cases of hospitalization due to heart failure or cardiovascular death - 7.3% and 7.2%, respectively (p = 0.81). In the analysis of a subgroup of 2643 patients with pre-existing heart failure, there was also no increased risk of cardiovascular complications during treatment with sitagliptin. The obtained results demonstrated the cardiovascular safety of sitagliptin therapy in patients with type 2 diabetes, including in relation to heart failure.

The **ELIXA project (2015)** included patients with type 2 diabetes who had undergone MI (83% of cases) or hospitalization due to unstable angina in the last 6 months. After randomization, in addition to standard therapy, daily subcutaneous injections of the glucagon-like peptide receptor agonist lixisenatide (n =3034) or placebo (n = 3034) were used. The primary composite endpoint (cardiovascular death, MI, stroke, or unstable angina) was recorded in 13.4% and 13.2% of cases (HR 1.02 at 95% CI 0.89 to 1.17) in the lixisenatide and placebo groups, respectively. Lixisenatide proved to be safe in the selected category of patients, including with respect to heart failure, but did not reduce the risk of cardiovascular complications in patients with type 2 diabetes.

A randomized **ASCEND study (2018)** determined the ratio of the benefits and dangers of using aspirin at a dose of 100 mg per day compared with placebo for the primary prevention of cardiovascular events in 15,480 patients with DM (in 94% of cases of type 2).
With an average follow—up period of 7.4 years, the primary composite endpoint of efficacy (first MI, stroke/transient ischemic attack or death from a vascular cause, excluding any confirmed intracranial hemorrhage) was less frequently recorded in the aspirin treatment group compared to the placebo group - 8.5% vs. 9.6% of cases (HR 0.88 with 95% CI of 0.79 up to 0.97; p = 0.01). In contrast, the events of the primary safety endpoint (the first major bleeding — intracranial hemorrhage, vision-threatening intraocular bleeding, gastrointestinal or other serious bleeding) were more likely to develop when taking aspirin (4.1%) compared with placebo (3.2%) (HR 1.29 at 95% CI 1.09 to 1.52; p = 0.003), and most of the bleeding was gastrointestinal. There were no significant differences between the aspirin and placebo groups in the incidence of gastrointestinal cancer (2.0% vs. 2.0% - RR 0.99 at 95% CI 0.80 to 1.24) or all types of cancer (11.6% and 11.5%, respectively — RR 1.01 at 95% CI 0.92 to 1.11), but to confirm/exclude the probable preventive effect of aspirin, long-term monitoring of patients will be continued. The use of aspirin prevented serious vascular events in people with diabetes and without obvious CVD, but also caused large bleeding, which offset the benefits of therapy.

The second part of the **ASCEND project (2018)** was to establish the role of omega-3 fatty acids in the primary prevention of cardiovascular events in patients with DM. After randomization, the study participants (n = 15,480) received capsules with 1 g of omega-3 fatty acids (omega-3 fatty acids group) or olive oil (placebo group) once a day. With an average follow—up period of 7.4 years and a treatment adherence rate of 76%, the primary composite endpoint - the first serious vascular event (non-fatal MI and non-hemorrhagic stroke, transient ischemic attack or vascular death) was recorded in 8.9% of patients in the omega-3 fatty acid group and in 9.2% — in the placebo group (HR 0.97 at 95 % CI from 0.87 to 1.08; p = 0.55). The total number of serious vascular complications and revascularization of any arteries was 11.4% and 11.5% (HR 1.00 at 95% CI from 0.91 to 1.09), and the frequency of death from any cause was 9.7% and 10.2% (HR 0.95 at 95% CI from 0.86 to 1.05) when taking omega-3 fatty acids or a placebo, respectively. There were no significant differences between the compared groups in the frequency of serious side effects.

Patients with stable CAD and type 2 diabetes have a high risk of cardiovascular complications, partly due to increased platelet aggregation. According to the hypothesis of the **THEMIS study (2019)**, the addition of ticagrelor to aspirin can reduce the risk of atherothrombotic events in this category of patients. A randomized double-blind study included patients aged 50 years and older with stable CAD and type 2 diabetes for taking ticagrelor (the initial dosage of 90 mg twice a day was reduced to 60 mg twice a day after receiving the data of

the PEGASUS-TIMI 54 study) and aspirin (n = 9619) or placebo and aspirin (n = 9601). Patients with a stroke or stroke were excluded from the project. Withdrawal of treatment was more common when taking ticagrelor than placebo (34.5% vs. 25.4% of cases, respectively). With a median follow-up of 39.9 months, the frequency of events of the combined primary endpoint of efficacy (cardiovascular death, MI or stroke) was lower in the ticagrelor group (7.7% compared to the placebo group of 8.5%; HR 0.90 with 95% , CI from 0.81 to 0.99; p = 0.04). The frequency of major bleeding on the TIMI scale (primary safety endpoint) was also significantly higher in the ticagrelor group (2.2% vs. 1.0% in the placebo group; HR 2.32 at 95% CI from 1.82 to 2.94; p < 0.001), as well as the frequency of intracranial hemorrhages (0.7% vs. 0.5% in the placebo group; HR 1.71 at 95% CI from 1.18 to 2.48; p = 0.005), but fatal bleeding was recorded with a comparable frequency (0.2% vs. 0.1% in the placebo group; HR 1.90 at 95% CI from 0.87 to 4.15; p = 0.11). The sum of "irreversible harm outcomes" (death from any cause, MI, stroke, fatal bleeding, or intracranial hemorrhage) in the ticagrelor and placebo groups did not differ significantly (10.1% vs. 10.8%; HR 0.93 at 95% CI from 0.86 to 1.02). In patients with stable CAD and type 2 diabetes without MI or a history of stroke, the addition of ticagrelor to standard treatment reduces the frequency of ischemic cardiovascular complications but increases the frequency of large bleeding compared with placebo. Therefore, for most patients with type 2 diabetes and established coronary atherosclerosis who meet the criteria for inclusion in the THEMIS study, the addition of ticagrelor to aspirin is not recommended.

Among the patients with stable CAD and type 2 diabetes who participated in the **THEMIS** study, approximately half (58%, n = 11,154) had a history of PCI, which indicated a high risk of ischemic cardiovascular complications. These patients usually receive aspirin, but the **THEMIS—PCI (2019)** subanalysis assessed the possibility of improving outcomes when ticagrelor was added to standard treatment. The study included patients aged 50 years and older with type 2 diabetes and stable CAD with one of three additional criteria: a history of PCI or coronary bypass surgery or angiographically documented stenosis of at least one coronary artery by at least 50%. After randomization, ticagrelor (n = 5558) or placebo (n = 5596) were added to aspirin treatment. With a median follow-up period of 3.3 years, complications that constituted the primary combined endpoint of efficacy (cardiovascular death, MI or stroke) were less frequently reported in the ticagrelor group compared to the placebo group (7.3% vs. 8.6%, respectively; HR 0.85 at 95% CI 0.74 to 0.97; p = 0.013), but the risk of cardiovascular death (3.1% vs. 3.3%, respectively; p = 0.68), as well as death from all causes (5.1% vs. 5.8%, respectively; p = 0.11) did not differ significantly.

Large bleeding was more often observed with the addition of ticagrelor than placebo (2.0% vs. 1.1%, respectively; HR 2.03 at 95% CI from 1.48 to 2.76; p < 0.0001), but there was an equal frequency of intracranial hemorrhage (in 0.6% vs. 0.6% of patients, respectively; p = 0.45) and fatal bleeding (in 0.1% versus 0.1% of patients, respectively; p = 0.83). In the ticagrelor group, a reduction in the total risk of the sum of events of "irreversible harm" (death from any cause, MI, stroke, fatal

bleeding or intracerebral hemorrhage) was achieved, which determined the "net clinical benefit" (9.3% compared to 11.0% in the placebo group; HR 0.85 at 95% CI from 0.75 to 0.95; p = 0.005) and this advantage was present regardless of the time spent by PCI.
In patients with type 2 diabetes and stable CAD with a history of PCI, the addition of ticagrelor to aspirin reduces the total risk of cardiovascular death, MI and stroke, increasing the risk of bleeding. At the same time, unlike patients without a history of PCI, ticagrelor provides a "pure clinical benefit", which indicates the expediency of its use in this category of patients with a high risk of ischemia and a low risk of bleeding.

It was known that the selective antagonist of nonsteroidal mineralocorticoid receptors finerenone has a beneficial effect on cardiorenal outcomes in patients with stage 3 or 4 CKD, type 2 DM and severe albuminuria. The **FIGARO-DKD study (2021)** involved 7437 patients with type 2 DM and stage 2-4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severe albuminuria who received maximum doses of renin-angiotensin system blockers who were randomized to receive finerenone or placebo. With a median follow-up of 3.4 years, a combination of primary endpoint events (death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for CHF) was less common in the finerenone group (HR 0.87 at 95% CI 0.76 to 0.98; p=0.03), which was primarily due to a reduced risk of hospitalization about CHF (HR 0.71 at 95% CI from 0.56 to 0.90). The overall frequency of adverse events did not differ significantly between the groups, but the frequency of termination of participation in the study due to hyperkalemia was higher when taking finrenone (1.2%) than placebo (0.4%). In patients with type 2 DM and stage 1-4 CKD, finerenone therapy improved cardiovascular outcomes compared to placebo.

In a pre-planned analysis of FIDELIO-DKD and FIGARO-DKD studies in 13,026 patients with type 2 DM and CKD called **FIDELITY (2021)**, cardiovascular and renal outcomes when taking a new selective nonsteroidal mineralocorticoid receptor antagonist finerenone or placebo at different, overlapping stages of CKD, were studied. With a median follow-up of 3 years, the primary endpoint (a combination of cardiovascular death, nonfatal MI, nonfatal stroke or hospitalization for CHF, as well as a combination of renal failure, a steady decrease in the estimated glomerular filtration rate of ≥57% of the baseline level for ≥4 weeks or renal death) was less frequently recorded in the finerenone group compared to placebo (HR 0.86 at 95% CI from 0.78 to 0.95; p=0.0018). The combination of renal outcomes was also less common when taking finerenone (HR 0.77 at 95% CI from 0.67 to 0.88; p=0.0002). The safety indicators of treatment in the groups did not differ, but hyperkalemia, which led to discontinuation of treatment, was more often observed in finerenone recipients (1.7%) than placebo (0.6%). Finerenone reduced the risk of clinically significant cardiovascular and renal outcomes compared with placebo across the entire spectrum of CKD in patients with type 2 DM.

ANTITHROMBOTIC AND ANTICOAGULATION PHARMACOTHERAPY

According to the **PLATO study (2010)**, the reversible direct P2Y12 receptor inhibitor ticagrelor is more effective clopidogrel in terms of cardiovascular death, MI, and stroke, and is also safe in patients with ACS. A genetic study conducted in 10285 project participants confirmed the idea of variable pharmacokinetics and pharmacodynamics of clopidogrel, but not ticagrelor, in the examined patients. When prescribing antiplatelet therapy, we do not know the patient's genetic profile. In addition, expensive genetic studies cannot be recommended for general clinical practice. The efficacy of ticagrelor is higher than that of clopidogrel and is independent of genetic polymorphism.
It has been suggested that clopidogrel may be ineffective in preventing cardiovascular events in patients with reduced CYP2C19 function associated with limited formation of the active metabolite of this drug. Some patients in the large, randomized, placebo-controlled CURE and ACTIVE trials underwent genetic testing. It was established that genetic polymorphism did not have a significant effect on the incidence of cardiovascular complications and bleeding in the treatment with clopidogrel. According to the results of the **CURE ACTIVE study (2010)**, the efficacy and safety of long-term therapy with clopidogrel does not depend on the genetic characteristics of patients, but this does not exclude the influence of genetic polymorphism in the treatment of acute conditions
in cardiology.

In a randomized open-label **EINSTEIN-DVT study (2010)**, another oral X factor inhibitor (rivaroxaban) was used to show that it is no worse than standard antithrombotic therapy. The study included patients with symptoms of acute deep vein thrombosis, but without symptoms of pulmonary embolism. Rivaroxaban (n = 1731) was prescribed 15 mg 2 times a day for the first 3 weeks, then 20 mg 1 time a day, enoxaparin (n = 1718) was administered 1 mg / kg 2 times a day, followed by transfer to treatment with vitamin K antagonists, INR was maintained within 2.0-3.0. After 30 days, the primary endpoint (symptoms of recurrent deep vein

thrombosis and nonfatal or fatal pulmonary embolism) was recorded in the treatment with rivaroxaban and standard therapy in 2.1% and 3.0%, and the frequency of large and small bleeding was equal to the comparison groups (8.1% each, p = 0.77). The sum of adverse events attributed to the primary endpoint and major bleeding was significantly (33%) lower in the rivaroxaban group (2.9% vs. 4.2%). There was a tendency to decrease in total mortality (2.2% vs. 2.9%) and all cardiovascular complications (0.7% vs. 0.8%) against the background of the use of a factor Xa inhibitor.
Simple monotherapy with rivaroxaban is no worse ($p < 0.0001$) than standard treatment with enoxaparin with conversion to vitamin K antagonists during initial and subsequent therapy of patients with deep vein thrombosis to prevent thromboembolism.

Available oral antiplatelet therapy has limitations in the form of variability of individual response to it and increased risk of bleeding. The new inhibitor of P2U12 (elinogrel), available in forms for oral and intravenous administration, does not require activation by liver metabolism, it has rapid, intense, competitive and reversible inhibition of platelets. The **INNOVATE-PCI study (2010)** is a randomized double—blind phase II project with active control, in which the efficacy and safety of elinogrel administered intravenously and orally to 652 patients with elective coronary angioplasty were evaluated. Antithrombotic therapy options included clopidogrel at a loading dose of 300 or 600 mg, then 75 mg/day, as well as elinogrel 80 or 120 mg intravenously, then 50, 100 or 150 mg 2 times a day orally. Elinogrel demonstrated a more pronounced dose-dependent inhibition of platelet aggregation in comparison with clopidogrel without a significant increase in the frequency of bleeding. Treatment with a new drug was more often accompanied by the appearance of shortness of breath and an increase in the level of hepatic transaminases.
The presence of two forms of elinogrel administration is of practical interest. In phase III of the study, it is planned to conduct a large study with an assessment of the effect of the drug on the endpoints.

With coronary angioplasty, stent thrombosis often occurs against the background of the action of fondaparinux. The optimal mode of additional intravenous administration of unfractionated heparin during PCI in patients with ACS without ST segment elevation receiving fondaparinux has not been established. In a double—blind randomized **FUTURA OASIS 8 study (2010)**, low (50 U/kg regardless of the use of glycoprotein IIb/IIIa platelet receptor inhibitors) and standard (85 U/kg, and in combination with IIb/IIIa receptor inhibitors - 60 U/kg) doses of unfractionated heparin were compared. Fondaparinux was used at a dose of 2.5 mg / day for an average of 3 days, 1024 patients received unfractionated heparin at a low dose, and 1002 patients received a standard dose. The primary endpoint (large, small bleeding or serious vascular complication during the intervention in the first 48 hours after angioplasty) was recorded in 4.7% and 5.8% of cases (p = 0.27) in the groups of low and standard doses of

unfractionated heparin. The frequency of major bleeding did not differ significantly (1.4% vs. 1.2%), but small hemorrhages were observed less frequently in the low-dose therapy group (0.7% vs. 1.7%, p = 0.04). After 30 days, the total frequency of events such as major bleeding in the first 48 hours, MI and revascularization of the target artery was 5.8% and 3.9% (p = 0.05), and death, MI and revascularization of the target artery was 4.5% and 2.9% (p = 0.06) in the groups of low and standard doses of unfractionated heparin accordingly. Catheter thrombosis developed rarely (0.5% and 1.0%, p = 0.15) with a low and standard dosage of unfractionated heparin.
Low dose heparin does not reduce the risk of major bleeding in PCI and vascular complications at the intervention site compared with the standard. Catheter thrombosis rarely occurs in patients with non-ST-elevation ACS who receive unfractionated heparin in the presence of fondaparinux.

In the study **TRA 2°P-TIMI 50 (2012)**, follow-up was continued for MI patients who, for the purpose of secondary prevention of atherothrombosis, received, in addition to standard therapy, a new antiplatelet drug vorapaxar at a dose of 2.5 mg/day (n = 8898) or placebo (n = 8881). With an average follow-up duration of 2.5 years, the primary endpoint of efficacy (cardiovascular death, MI or stroke) was recorded in 610 and 750 (p < 0.0001), moderate or severe bleeding — in 241 and 151 (p < 0.0001), and intracranial hemorrhage in 43 and 28 (p = 0.076) cases with taking vorapaxar or placebo, respectively. Other serious adverse events were evenly distributed between the groups. Consequently, in patients with a history of MI, vorapaxar reduces the risk of cardiovascular death and ischemic events when added to standard antiplatelet therapy, including aspirin, and lasting more than a year, but increases the risk of moderate or severe bleeding.

In the **ARISTOTLE study (2012)**, the glomerular filtration rate calculated using the Cockcroft-Gault formula in 7518 patients exceeded 80 ml/min, in 7587 it was 51 and 80 ml/min, and in 3017-50 ml/min and less. The frequency of cardiovascular complications and bleeding was higher with impaired renal function (glomerular filtration rate of 80 ml/min or less). Apixaban was more effective than warfarin in preventing stroke or systemic embolism and reducing mortality, causing less bleeding regardless of kidney function. At a glomerular filtration rate of 50 ml/min or less, the greatest reduction in the risk of bleeding was observed in the apixaban group compared to the warfarin group.

The safety and tolerability of the new oral factor Xa inhibitor darexaban in secondary prevention after ACS was studied in the **RUBY-1 study (2011)**. A total of 1279 patients who underwent ACS with or without ST segment elevation after discontinuation of parenteral antithrombotic therapy received one of six darexaban treatment regimens: 5 mg 2 times a day, 10 mg 1 time a day, 15 mg 2 times a day, 30 mg 1 time a day, 30 mg 2 times a day, 60 mg 1 time a day or placebo, in addition to dual antiplatelet therapy (aspirin and clopidogrel) within 24 weeks. The primary endpoint of the study (clinically significant bleeding) was more common

when treated with any dose of darexaban compared to placebo (total RR 2.275, p = 0.022), statistically significantly more often when using a single dose of the drug — 30 mg 2 times a day against placebo (RR 3.8, p = 0.002). Darexaban did not reduce the number of complications (death, stroke, MI, systemic thromboembolism, and severe recurrent ischemia) compared with placebo, but the study did not have sufficient statistical power to evaluate the effectiveness of the drug.

A genetic study was conducted in 2944 participants of the **RE-LY project (2012)** to identify genetic determinants of the level of dabigatran in blood plasma, which can influence the clinical effect of antithrombotic treatment of patients with AF. The genetic polymorphism detected in 32.8% of cases (CES1 SNP rs2244613 allele) was associated with a decrease in the concentration of dabigatran in plasma and a decrease in the risk of any bleeding.

The **Hukosai-VTE study (2013)** involved patients with provoked (surgical intervention or immobilization) or unprovoked venous thromboembolism — 4921 with deep vein thrombosis and 3319 with pulmonary embolism. After initial heparin therapy, patients were randomized to receive the factor Xa inhibitor edoxaban (60 mg once a day or 30 mg — with impaired renal function / low body weight) or standard warfarin treatment for 3 to 12 months. Relapse of venous thromboembolism with symptoms (primary endpoint) was recorded in 3.2% and 3.5% of cases, respectively (RR 0.89, p < 0.001 for no less effectiveness). Large and clinically significant bleeding was significantly less frequent in the edoxaban group (8.5% vs. 10.3% in the warfarin group, HR 0.81, p = 0.004).

The potential benefit of aspiration of thrombus fragments in PCI in patients with MI with ST segment elevation was first evaluated in the randomized **TASTE project (2013)**. The use (n = 3621) or refusal to use thrombus aspiration (n = 3623) was accompanied by a comparable frequency of deaths during 30 days of follow—up - 2.8% and 3.0% of cases, respectively (OR 0.94, p = 0.63).

The **TAO study (2013)** included 13229 patients with ACS without ST segment elevation who were scheduled for invasive treatment. After randomization, a direct factor Xa inhibitor otamixaban (0.08 mg/kg followed by an infusion of 0.140 mg/kg per hour) or unfractionated heparin and eptifibatide were administered intravenously (during PCI and 18-24 hours after it). Within 7 days, the primary endpoint (death or a new MI) occurred in 5.5% of patients treated with otamixaban and 5.7% with standard therapy (HR 0.99, p = 0.93), and the bleeding rate was 3.1% and 1.5%, respectively (HR 2.13, p < 0.001). These data confirm that with rapid PCI in patients with ACS, antiplatelet therapy remains the most effective.

RE-ALIGN (2013) was a phase II study involving patients with mechanical aortic or mitral heart valves implanted up to 7 days or at least 3 months before

randomization. Anticoagulant therapy was performed with dabigatran (150, 220 or 300 mg 2 times a day, depending on kidney function) or warfarin (the target range of the INR is 2.0–3.0 or 2.5–3.5, depending on the risk of thromboembolism). The study was terminated prematurely after the inclusion of 252 patients due to the high incidence of complications in the dabigatran group. The total number of strokes, transient ischemic attacks, systemic embolisms, MI or deaths was 9% when taking dabigatran and 5% — warfarin (HR 1.94, p = 0.24), major bleeding — 4% and 2%, respectively. Dabigatran affects only the activity of thrombin; warfarin affects a number of blood clotting factors. The latter is preferable in patients with mechanical heart valves.

The prospective observational study **PARIS (2013)** included 5031 patients who were prescribed double antiplatelet therapy after PCI. The consequences of its termination on the doctor recommendation, a short break for surgery or a violation of admission (non-compliance with the treatment regimen due to bleeding) were assessed by considering major coronary complications (cardiac death, definite or probable stent thrombosis, MI, revascularization of the affected artery) for 2 years. The majority (74%) of such events occurred against the background of double antiplatelet therapy, and the risk of its termination progressively decreased over time, and the variant of violation of the treatment regimen affected the risk of complications.

The **ACCOAST study (2013)** included 4033 patients with ACS without ST segment elevation who were prescribed 30 mg of prasugrel or placebo after randomization. Before PCI, patients took another 30 or 60 mg of prasugrel in the first or second groups, respectively. The frequency of occurrence of the primary endpoint of efficacy (death from cardiovascular causes, MI, stroke, emergency revascularization) with two treatment options for 7 and 30 days did not differ significantly. The work was stopped prematurely due to an increased risk of bleeding in the group of early initiation of prasugrel (after 7 days, 2.6% vs. 1.7%, p = 0.006; after 30 days, 2.9% vs. 1.5%, p = 0.002).

Complications of emergency surgical treatment in 1005 patients with cardiovascular pathology (ischemic heart disease - 68% of cases, AF — 32%, heart valve defects — 14.5%, stroke — 10%, pulmonary embolism — 7% or prosthetic heart valves — 2.5%, heart failure — 4%, cardiomyopathy — 2%), who received aspirin (58%), warfarin (24%), double antiplatelet therapy (5%) or dabigatran (0.3%), were evaluated in the **PRAGUE 14 study (2013)**. Aspirin was canceled on average 7 days before surgery, and warfarin and thienopyridines were canceled on average 8 and 4 days, respectively. The frequency of perioperative ischemic/thrombotic cardiovascular complications did not depend on the timing of discontinuation of antithrombotic therapy. However, shortening these terms increased the risk of bleeding, so the traditional tactics of canceling antithrombotic therapy 7 days before surgery should not change.

Cangrelor, a powerful fast—acting reversible inhibitor of platelet aggregation for intravenous administration, was evaluated during PCI in three RCTs **CHAMPION PCI, CHAMPION PLATFORM and CHAMPION PHOENIX (2013).** Among 24910 of their participants were patients who underwent PCI in MI with ST segment elevation (11.6%), ACS without ST elevation (57.4 %) and stable CAD (31.0%). Cangrelor reduced the total frequency of complications (death, MI, repeated revascularization, or stent thrombosis) by 19% in 48 hours (p = 0.0007) compared with clopidogrel and this advantage persisted after 30 days. The frequency of severe/life-threatening bleeding by GUSTO (Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) definition in the cangrelor and clopidogrel groups did not differ (0.2% vs. 0.2% of cases). According to ACUITY, the number of bleeds was large in the cangrelor group (4.2% vs. 2.8% in those receiving clopidorgel), mainly due to an increase in the frequency of hematomas with a size of ≥ 5 cm.

In the **ARCTIC-GENE sub-study (2013)**, genotyping of 1,390 patients undergoing PCI was performed. 935 patients were identified with rapid (456 in the standard therapy group and 479 in the platelet function monitoring group with treatment correction) and 459 with slow metabolism of clopidogrel (238 and 221 patients, respectively), depending on the variants of cytochrome CYP2C19 metabolizing the drug. There were no differences in the total frequency of ischemic complications (death, MI, stroke, stent thrombosis, emergency revascularization) and bleeding during the year between groups of patients with fast and slow metabolism of clopidogrel. The change in treatment tactics, considering the genotyping data, also had little effect on the prognosis, indicating the multiplicity of factors on which platelet reactivity depends.

The **ATLANTIC study (2014)** compared the effects of starting ticagrelor at the prehospital (in an ambulance) and inpatient (in a catheterization laboratory) stages of treatment of patients with MI with ST segment elevation. After diagnosis of MI with a duration of symptoms > 30 minutes, but < 6 hours and an estimated time before the start of PCI of less than 120 minutes, in addition to standard therapy after randomization, patients of the "prehospital" group (n = 909) started treatment with ticagrelor at a loading dose of 180 mg, then took a placebo once in the hospital. Patients of the "intrahospital" group (n = 953) received placebo in an ambulance, then 180 mg of ticagrelor in the hospital on average 31 minutes later. All patients subsequently received ticagrelor at a dose of 90 mg 2 times a day. There were no differences between the "prehospital" and "intrahospital" groups in the frequency of absence of ST segment reduction by ≥ 70% (86.8% vs. 87.6%; p = 0.63), blood flow in the infarct-related artery of the 3rd degree according to TIMI (82.6% vs. 83.1%; p = 0.82), the number of cardiovascular complications in the first 30 days (4.5% vs. 4.4%; p = 0.91). However, the frequency of certain stent thrombosis was lower in the group of prehospital initiation of ticagrelor therapy after 24 hours (0% vs. 0.8%; p = 0.008) and after 30 days (0.2% vs. 1.2%; p =

0.02). The frequency of bleeding and serious side effects in the compared groups did not differ significantly.

In patients with AF lasting more than 48 hours who underwent cardioversion, rivaroxaban (20 mg once a day or 15 mg with creatinine clearance 30-49 ml/min) (n = 1002) and warfarin at a controlled dose (n = 502) were compared in the **X–VeRT study (2014)**. Under the condition of previously performed anticoagulant therapy or exclusion of thrombosis in the atria, according to transesophageal echocardiography, early (1-5 days after randomization), in other cases, delayed (3-8 weeks) cardioversion was performed. The total incidence of stroke, transient ischemic attack, peripheral embolism, MI, and cardiovascular death (the primary endpoint of efficacy) was 0.51% and 1.02% in the rivaroxaban and warfarin groups (RR 0.50; 95% CI 0.15-1.73). Large bleeding was recorded with a frequency of 0.6% and 0.8% when taking rivaroxaban or warfarin, respectively (RR 0.76, 95% CI 0.21–2.67). Therefore, rivaroxaban is an effective, safe and convenient alternative to warfarin for cardioversion of AF.

The **OPTIDUAL project (2015)** involved 1,799 patients who had 1 or more drug-eluting stents implanted against the background of stable CHD or ACS. After 12 months of double antiplatelet therapy (aspirin and clopidogrel), 1385 patients who had not experienced severe cardiovascular/ cerebrovascular complications or bleeding were randomized to continue taking clopidogrel at 75 mg/day (extended double antiplatelet therapy for another 36 months, n = 695) or discontinue treatment with clopidogrel (aspirin group, n = 690). With a median follow-up after stenting of 33.4 months, the primary composite endpoint (death, MI, stroke or bleeding) was recorded in 5.8% and 7.5% (HR 0.75 at 95% CI from 0.50 to 1.28; p = 0.17), fatal outcome in 2.3% and 3.5% (HR 0.65 at 95% CI from 0.34 to 1.22; p = 0.18), bleeding in 2.0% and 2.0% of cases (p = 0.95) in the groups of prolonged double antiplatelet therapy and aspirin, respectively. Despite encouraging trends, a categorical conclusion about the efficacy and safety of prolonged double antiplatelet therapy cannot be formulated due to insufficient statistical data.

In the **PRAGUE-18 study (2016)**, the efficacy and safety of prasugrel and ticagrelor were compared in patients with MI with or without ST segment elevation, who underwent primary PCI. After randomization, prasugrel was used at a dose of 60 mg, then 10 mg / day (5 mg at the age over 75 years or body weight less than 60 kg) (n = 634) or ticagrelor at a dose of 180 mg, then 90 mg 2 times a day (n = 596). Within 7 days, the primary endpoint (death, recurrence of MI, urgent revascularization of the target artery, stroke, large bleeding requiring blood transfusion or prolongation of hospitalization for 7 days) was observed with equal frequency in patients receiving prasugrel or ticagrelor — 4.0% vs. 4.1% of cases, respectively (HR at 95% CI 0.98 of 0.55 up to 1.73; p = 0.939). There were no significant differences in the risk of occurrence of any of the components of the primary endpoint. Within 30 days, the total number of severe vascular complications (cardiovascular death, nonfatal MI or stroke) in the prasugrel and

ticagrelor groups was similar - 2.7% and 2.5% of cases (HR 1.06 at 95% CI from 0.53 to 2.15; p = 0.864).

The presence of erosion, rather than rupture of the atherosclerotic plaque in ACS, can probably be considered when choosing treatment for patients. The **EROSION project (2016)** evaluated the hypothesis about the possibility of stabilizing the plaque during its erosion during ACS using antithrombotic therapy without stent implantation. In an uncontrolled prospective study, antithrombotic therapy without stenting was performed in patients with MI with ST segment elevation (97% of cases) and plaque erosion diagnosed with OCT, as well as residual arterial stenosis of less than 70% according to coronary angiography. OCT was repeated after 1 month on the background of therapy with aspirin (100 mg / day) and ticagrelor (90 mg 2 times a day) to determine changes in blood clot volume. Among 405 patients with ACS, erosion of the analyzed plaque was detected in 25.4% of cases. In 47 out of 55 patients who underwent OCT in dynamics after 1 month, the volume of the thrombus decreased by more than half (primary endpoint), on average from 3.7 mm3 to 0.2 mm3 ($p < 0.001$). At the same time, 34% of patients did not have a visible blood clot. For patients with ACS caused by plaque erosion, conservative management involving antithrombotic therapy without stenting may be one of the treatment options.

The **EMANATE study (2017)** included 1,500 patients with first-time non-valvular AF who were scheduled for cardioversion. After randomization, patients received apixaban at a dose of 5 mg 2 times a day (or 2.5 mg 2 times a day in the presence of two of the following conditions: age ≥ 80 years, weight ≤ 60 kg or plasma creatinine level ≥ 1.5 mg /dl) (n = 753) or heparin and warfarin (n = 747). At the discretion of the researcher, patients could take an initial dose of apixaban 10 mg (or 5 mg, respectively) if cardioversion was immediate. Within 30 days (90 days if cardioversion was not performed) in the group of apixaban and standard anticoagulation, the number of strokes was 0 vs. 6 (p = 0.0164), major bleeding — 3 vs. 6, clinically significant bleeding — 11 vs. 13, respectively. Systemic embolisms were not observed with any anticoagulant therapy regimen. Blood clots in the auricle of the left atrium were visualized in 61 patients, and all of them received anticoagulants. Repeated examination after an average of 37 ± 11 days revealed resolution of blood clots in the apixaban and heparin/warfarin groups in 52% and 56% of cases, respectively.

The **IMPACT-AF project (2017)** involved 2,281 patients from Argentina, Brazil, China, India and Romania with AF and indications for anticoagulant therapy (risk of stroke according to CHA2DS2-VASc ≥ 2 points, rheumatic valvular defect). After randomization, an educational program was completed in the intervention group (training, distribution of printed materials, webinars, telephone contacts, adherence control, clinical visits) (n = 1184), and routine treatment was carried out in the control group (n = 1092). After 12 months, the proportion of patients using oral anticoagulants increased in the intervention group

from 68% initially to 80%, in the control group — from 64% to 67%, respectively. During the follow—up period, 11 strokes were registered in the intervention group and 21 (p = 0.043) in the control group. An educational intervention aimed at the use of oral anticoagulant therapy has led to a significant increase in the proportion of patients committed to treatment, which can improve stroke prevention in patients with AF.

The authors of the randomized double-blind placebo-controlled multicenter study **ARRIVE (2018)** evaluated the efficacy and safety of aspirin in comparison with placebo in patients with a moderate risk of the first cardiovascular event (20-30% over 10 years). The study included men aged ≥ 55 years with ≥ 2 risk factors and women aged ≥ 60 years with ≥ 3 risk factors, excluding patients with a high risk of gastrointestinal or other bleeding, as well as with DM. After randomization, patients received aspirin 100 mg per day (n = 6270) or placebo (n = 6276) 1 time per day. With a median follow-up of 60 months, the primary endpoint of efficacy — the time before the first adverse event (cardiovascular death, MI, unstable angina, stroke or transient ischemic attack) was recorded in 4.29% of patients in the aspirin group versus 4.4% in the placebo group (HR 0.96 at 95% CI from 0.81 to 1.13; p = 0.6038). Gastrointestinal bleeding (safety endpoint) developed in 0.97% of patients in the aspirin group versus 0.46% in the placebo group (HR 2.11 at 95% CI from 1.36 to 3.28; p = 0.0007), but most of them were not heavy.
The overall incidence of adverse outcomes in ARRIVE was lower than expected, which is apparently due to effective background control of risk factors, which shifted the risk in the observed cohort of the population from moderate to low, preventing the positive effect of aspirin as a means of primary prevention. Soon, in the ASPREE project, the results of using aspirin for primary prevention in the elderly again turned out to be disappointing.

The authors of the **COMMANDER HF study (2018)** suggested that treatment with the factor Xa inhibitor rivaroxaban can reduce thrombin production and improve outcomes in patients with an episode of decompensation of CHF against the background of CAD. Patients with CHF of II or III FC and LV EF ≥ 40%, ischemic heart disease and increased concentration of natriuretic peptides in plasma, without AF after randomization received, in addition to standard therapy, rivaroxaban at a dose of 2.5 mg 2 times a day (n = 2507) or placebo (n = 2515). During the average follow-up period of 21.1 months, the primary endpoint of efficacy (death from any cause, MI or stroke) was recorded in 25.0% of patients in the rivaroxaban group and in 26.2% in the placebo group (HR 0.94 at 95% CI 0.84 to 1.05; p = 0.27), there was no significant difference in mortality from all causes (21.8% vs. 22.1% respectively — HR 0.98 at 95% CI from 0.87 to 1.10) and the risk of MI (HR 0.83 at 95% CI from 0.63 to 1.08), but the incidence of stroke was lower when taking rivaroxaban (HR 0.66 at 95% CI from 0.47 to 0.95). Events of the primary endpoint of safety — fatal bleeding or bleeding into the critical space (intracranial, intraspinal, intraocular, pericardial, intraarticular, retroperitoneal, intramuscular) with the possibility of persistent disability were observed in 0.7% of

patients who took rivaroxaban, and 0.9% - placebo (HR 0.80 at 95% CI from 0.43 to 1.49; p = 0.484), and major bleeding — in 3.3% and 2.0% of cases (HR 1.68 at 95% CI from 1.18 to 2.39; p = 0.003), respectively. Apparently, antithrombotic drugs cannot improve the prognosis of patients with heart failure without AF, usually dying from a critical decrease in the pumping function of the heart and ventricular arrhythmia.

The **GLOBAL LEADERS study (2018)** included patients undergoing PCI with implantation of a biolimus A9 drug-coated stent with stable CAD or ACS. After randomization, patients were prescribed aspirin 75-100 mg/day and ticagrelor 90 mg 2 times a day for 1 month, then ticagrelor monotherapy for 23 months (experimental group, n = 7980) or standard double antiplatelet therapy (aspirin 75-100 mg/day plus clopidogrel 75 mg/day for stable CAD or aspirin 75-100 mg /day plus ticagrelor 90 mg 2 times a day for ACS) for 12 months, followed by monotherapy with aspirin for another 12 months (control group, n = 7988).
During 2 years of therapy, the composite primary endpoint of efficacy (death from all causes or non-fatal MI with a Q—wave) was recorded in 3.81% of the experimental participants and in 4.37% of the control group (HR 0.87 at 95 % CI 0.75 to 1.01; p = 0.073), death from all causes in 2.81% and 3.17% (HR 0.88 at 95% CI 0.74 to 1.06; p = 0.18), non-fatal MI with Q-wave in 1.04% and 1.29% of patients (HR 0.80 at 95% CI from 0.60 to 1.07; p = 0.14) of the compared groups, respectively. The key secondary safety endpoint (Grade 3 or 5 bleeding according to the criteria of the BARC (Bleeding Academic Research Consortium) was observed in 2.04% versus 2.12% of cases (HR 0.97 at 95% CI 0.78 to 1.20; p = 0.77) in the experimental and control groups, respectively. The use of a combination of ticagrelor and aspirin for 1 month followed by ticagrelor monotherapy for 23 months does not exceed standard antithrombotic treatment after PCI in CAD.

The **ISAR-REACT 5 study (2019)** was conducted to compare efficacy and safety of ticagrelor or prasugrel-based therapy in patients with ACS who were scheduled for invasive examination and treatment. After randomization, standard therapy was prescribed to patients in an open way, including ticagrelor (n = 2012) or prasugrel (n = 2006). Different methods of administration of loading doses of drugs were used for patients with individual variants of ACS. Patients with MI with ST segment elevation received a loading dose of ticagrelor (180 mg) or prasugrel (60 mg) immediately after randomization, whereas patients with MI without ST segment elevation/unstable angina received ticagrelor immediately after randomization, and prasugrel — after randomization and angiography.
During 1 year of follow-up, the frequency of events of the combined primary endpoint of efficacy (death, MI or stroke) was significantly higher in the ticagrelor group (9.3% vs. 6.9% in the prasugrel group; HR 1.36 at 95% CI from 1.09 to 1.70; p = 0.006).
Individual complications were recorded with the following frequency: death from any cause — in 4.5% and 3.7% of cases; MI — in 4.8% and 3.0%; stroke — in

1.1% and 1.0%, definite or probable stent thrombosis — in 1.3% and 1.0%; definite stent thrombosis — in 1.1% and 0.6 % of cases in the ticagrelor and prasugrel groups, respectively.
The safety endpoint (large bleeding type 3-5 on the BARC scale) was observed in 5.4% of patients treated with ticagrelor and in 4.8% — prasugrel (HR 1.12 at 95% CI from 0.83 to 1.51; p = 0.46).
Among patients with ACS with/without ST segment elevation, the incidence of death, MI or stroke is significantly lower among those receiving prasugrel than among those taking ticagrelor with a comparable risk of major bleeding. The data obtained confirm that prasugrel is a first-line antiplatelet therapy for patients with ACS with or without ST segment elevation. The limitations of the study were open design and observation, mostly conducted over the phone. The number of patients who were excluded from the safety analysis was 10 times higher in the prasugrel group than in the ticagrelor group, which could affect the recorded number of bleeding cases. Previously, pharmacodynamic studies have shown a similar degree of antiplatelet effect of ticagrelor and prasugrel. Therefore, the advantage of prasugrel compared to ticagrelor, exceeding the benefit of clopidogrel compared to placebo, seems implausible. The results of ISAR-REACT 5 need to be confirmed in an adequate double-blind study.

The **AFIRE open study (2019)** conducted in Japan involved 2,236 patients with AF who underwent PCI (70% of cases) or coronary bypass surgery more than 1 year ago or with angiographically confirmed CAD that does not require revascularization. After randomization, patients received monotherapy with rivaroxaban (10-15 mg 1 time per day — an analog of a dose of 20 mg for the Caucasian race) or a combination of rivaroxaban and one antiplatelet agent (aspirin in 70%, clopidogrel in 25% of cases or prasugrel).
The study was stopped at an early stage due to increased mortality in the combination therapy group. With a median follow-up period of 2 years, the sum of the events of the primary endpoint of efficacy (stroke, systemic embolism, MI, unstable angina requiring revascularization or death from any cause) in the rivaroxaban monotherapy group was no higher than in the combination therapy group (4.14% vs. 5.75% of cases per year per patient, respectively; HR 0.72 at 95 % CI from 0.55 to 0.95; for "not worse" $p < 0.001$). Rivaroxaban monotherapy was superior to combination therapy in terms of the frequency of the primary safety endpoint (large bleeding according to the criteria of the International Society on Thrombosis and Haemostasis) (1.62% vs. 2.76% of cases per year per patient, respectively; HR 0.59 at 95% CI from 0.39 to 0.89; for superiority, p = 0.01).
Rivaroxaban monotherapy is noninferior to combination therapy with rivaroxaban and an antiplatelet drug in the effectiveness of preventing ischemic complications and is safier (risk of large bleeding). These data confirm the provisions of European and American recommendations that monotherapy with an anticoagulant, such as rivaroxaban, should be used in patients with stable CAD and AF.

The open study of **POPular Genetics (2019)** included patients undergoing primary PCI who were randomized to the group of early genetic testing (n = 1242) or standard treatment with ticagrelor or prasugrel (n = 1246). In the genetic testing group, when carriers of the CYP2C19*2 or CYP2C19*3 alleles associated with impaired formation of the active metabolite of clopidogrel were identified, they were prescribed ticagrelor or prasugrel, and not carriers — clopidogrel. During 12 months of therapy, the sum of adverse clinical events — the primary combined endpoint (death from any cause, MI, certain stent thrombosis, stroke or major bleeding) was observed in 5.1% versus 5.9% of cases in the group of genetic testing and standard therapy, respectively (for "no worse" $p < 0.001$). The frequency of significant or minor bleeding according to the PLATO criteria was 9.8% in the genotype determination group and 12.5% in the standard treatment group (HR 0.78 with 95% CI from 0.61 to 0.98; $p = 0.04$).
In patients who have undergone primary PCI, the strategy of choosing oral therapy with a P2Y12 inhibitor based on the determination of the CYP2C19 genotype is noninferior to standard treatment with ticagrelor or prasugrel for 12 months in terms of preventing thrombotic events, accompanied by a lower frequency of bleeding.

The optimal duration of double antiplatelet therapy in patients with a high risk of bleeding after implantation of a drug-coated coronary stent remains unclear. In the **MASTER DAPT study (2021)**, 1 month after implantation of a coronary stent with a biodegradable polymer that releases sirolimus, 4434 patients with a high risk of bleeding were randomized to discontinue double antiplatelet therapy (reduced therapy) or continue it for at least 2 months (standard therapy). 3 primary endpoints were evaluated – a set of adverse clinical events (death from any cause, MI, stroke or major bleeding), serious adverse cardiac or cerebral events (death from any cause, MI or stroke) and large or clinically significant small bleeding. During 335 days of follow–up, a set of adverse clinical events occurred in 7.5% of patients in the reduced therapy group and in 7.7% in the standard treatment group ($p<0.001$ for no less effectiveness). Serious adverse cardiac or cerebral events were observed in 6.1% of patients in the reduced group and 5.9% in the standard therapy group ($p=0.001$ for no less effectiveness). Major or clinically significant minor bleeding occurred in 6.5% of patients with reduced and 9.4% with standard therapy ($p<0.001$ for superiority). One-month double antiplatelet therapy was not inferior to three-month or more therapy in terms of the amount of adverse clinical events and severe cardiac or cerebral outcomes, accompanied by a decrease in the frequency of large or clinically significant small bleeding.

The role of direct oral anticoagulants in comparison with vitamin K antagonists in AF after successful transcatheter replacement of the aortic valve has not been sufficiently studied. In a prospective randomized study of **ENVISAGE-TAVI AF (2021)**, 1426 patients with AF received edoxaban or a vitamin K antagonist after transcatheter aortic valve replacement. The primary endpoint of efficacy (death from any cause, MI, ischemic stroke, systemic thromboembolism,

valve thrombosis or major bleeding) was recorded with comparable frequency in the group of edoxaban and vitamin K antagonists (HR 1.05 at 95% CI from 0.85 to 1.31; p=0.01 for no less efficacy), but the primary endpoint safety (large bleeding) – more often in the group of direct oral anticoagulant (HR 1.40 at 95% CI from 1.03 to 1.91) due to more gastrointestinal bleeding. Mortality from any cause or stroke in the edoxaban group and the vitamin K antagonist group did not differ significantly (HR 0.85 at 95% CI from 0.66 to 1.11). In patients with AF after transcatheter replacement of the aortic valve, edoxaban was noninferior to vitamin K antagonists in influencing the risk of adverse clinical events, but more often caused large bleeding.

The advantage of clopidogrel monotherapy after 1-month versus 12-month double antiplatelet therapy with aspirin and clopidogrel was demonstrated in the **STOPDAPT-2 study (2021)**, but not in STOPDAPT-2 in patients with ACS; however, both studies did not have sufficient statistical power based on the recorded frequency of events. When combining these populations of patients into a general cohort of 5997 STOPDAPT-2 patients after PCI, 2993 of them were prescribed 1-month double antiplatelet therapy followed by monotherapy with clopidogrel and 3004 – 12-month double antiplatelet therapy with aspirin and clopidogrel. During the follow-up period of 12 months, the primary endpoint – a combination of cardiovascular events (cardiovascular death, MI, certain stent thrombosis or any stroke) was observed with 1-month and 12-month double antiplatelet therapy in 2.84% vs. 3.04% of cases (HR 0.94 at 95% CI from 0.70 to 1.27; p of no less efficiency = 0.001; p of superiority = 0.68). The frequency of cardiovascular complications in the groups of 1-month and 12-month therapy did not differ significantly (2.40% vs. 1.97%; HR 1.24 at 95% CI from 0.88 to 1.75; p not less effective =0.14; p superiority =0.23). The risk of bleeding was lower with 1-month versus 12-month double antiplatelet therapy (0.50% vs. 1.31%; HR 0.38 with 95% CI from 0.21 to 0.70; p superiority= 0.002) regardless of pathology – ACS or chronic coronary syndrome. With reduced double antiplatelet therapy, there was a numerical increase in the risk of cardiovascular events in patients with ACS, but not chronic coronary syndrome, although it did not reach statistical significance. Among patients without ACS undergoing PCI, 1 month of DAPT followed by clopidogrel monotherapy, compared with 12 months of DAPT with aspirin and clopidogrel, resulted in a significantly lower rate of a composite of cardiovascular and bleeding events, meeting criteria for both noninferiority and superiority.

INVICTUS study (2022) included 4,531 patients with echocardiographically-documented rheumatic heart disease and AF. Participants were eligible if they had an elevated risk of stroke (mitral stenosis with valve area ≤2.0 cm², left atrial spontaneous echo contrast or thrombus, or a CHA2DS2-VASc score ≥2). Patients were randomized to receive adjusted-dose vitamin K antagonists with goal INR of 2.0-3.0 or rivaroxaban 20 mg once daily. At a median

follow-up of 3.1 years, primary efficacy outcome events (composite of all-cause stroke, systemic embolism, myocardial infarction or death from vascular or unknown causes) in the rivaroxaban group was higher than in the vitamin K antagonist group (HR 1.25 at 95% CI from 1.10 to 1.41), including a higher risk of death in the rivaroxaban group (HR 1.23 at 95% CI from 1.09 to 1.40) and ischemic stroke (HR 1.53 at 95% CI from 1.06 to 2.20), and the frequency of bleeding in the two variants of anticoagulant therapy was similar. Vitamin K antagonists should remain the standard of treatment for AF associated with rheumatic heart disease, as they have an advantage in reducing mortality.

Oral factor XIa inhibitors may prevent pathologic thrombosis, and thus recurrent ischaemic events, without significantly increasing the risk of bleeding. In a phase 2 **PACIFIC AMI** study **(2022)** 1,601 patients (median age 68 years) within 5 days after diagnosis were treated with aspirin and ticagrelor or prasugrel, PCI. After randomization, the oral factor XIa inhibitor asundexian was added at doses of 10, 20 or 50 mg or placebo 1 time a day for 6-12 months. Asundexian caused a dose-dependent inhibition of XIa activity exceeding 90% at a dose of 50 mg. With an average follow-up period of 368 days, bleeding of type 2, 3 or 5 according to the Bleeding Academic Research Consortium occurred in 7.6%, 8.1%, 10.5% and 9.0% of patients receiving asundexian 10, 20 or 50 mg and placebo, respectively. A combination of ischemic complications (cardiovascular death, MI, stroke, or stent thrombosis) was observed in 6.8%, 6.0%, 5.5% and 5.5% of patients in the asundexian 10, 20 or 50 mg and placebo groups, respectively. In patients with recent MI, 3 doses of asundexian, when added to aspirin and a P2Y12 receptor inhibitor, dose-dependent and almost completely inhibited the activity of factor XIa without significantly increasing the frequency of bleeding, but also without reducing the frequency of ischemic events. These data support the study of asundexian at a dose of 50 mg/day in patients with MI in a phase 3 clinical trial with sufficient statistical power.

The **PACIFIC-Stroke (2022)** phase 2b study involved patients, age 45 years and older, with acute (48 hours from the onset of symptoms) noncardioembolic ischemic stroke, who received antiplatelet mono- or dual therapy and could undergo brain MRI. After randomization, 1808 participants received asundexian at a dose of 10 mg (n=455), 20 mg (n=450) or 50 mg (n=447) or placebo (n=456) 1 time per day. After 26 weeks, the primary efficacy result (the effect of "dose-effect" on the totality of cases of latent brain infarctions detected by MRI and recurrent symptomatic ischemic stroke) was observed in 19% of patients in the placebo group compared with 19% in the 10 mg asundexian group, 22% in the 20 mg asundexian group and 20% in the group of 50 mg of asundexian (p=0.80), and the primary safety result (large or clinically significant small bleeding as defined by the International Society on Thrombosis and Haemostasis) was observed in 2%, 4%, 3% and 4% of patients, respectively. Inhibition of factor XIa with asundexian in patients with acute noncardioembolic ischemic stroke did not reduce the number of latent cerebral infarcts or ischemic strokes, but also did not increase the amount of large or clinically significant small bleeding compared with placebo.

The **PANTHER (2022)** meta–analysis of 7 trails (ASCET, CADET, CAPRIE, DACAB, GLASSY, HOST-EXAM and TiCAB) – conducted in 492 centers in Europe, Asia and North America. The final study population included 24,325 patients (mean age 64.3 years, 21.7% women) with confirmed CAD, 12,178 of whom received monotherapy with P2Y12 inhibitors (clopidogrel in 62% or ticagrelor in 28% of cases) and 12,147 – aspirin monotherapy. The average duration of treatment was 557 days. The primary endpoint of the study (death from cardiovascular disease, MI or stroke) was observed in 5.5% of patients in the P2Y12 inhibitor group versus 6.3% of patients in the aspirin group (HR 0.88 at 95% CI 0.79 to 0.97; p=0.014). The frequency of major bleeding of type 3 or 5 according to the Bleeding Academic Research Consortium turned out to be similar with the compared regimens of antiplatelet therapy with a P2Y12 inhibitor or aspirin (1.2% vs. 1.4%, respectively; p=0.23). When combining ischemic and hemorrhagic outcomes, there was a lower total risk of these adverse events in the P2Y12 inhibitor group – 6.4% versus 7.2% of cases in the aspirin group (HR 0.89 at 95% CI from 0.81 to 0.98; p=0.020). After MI, PCI, stroke, coronary bypass surgery, antiplatelet therapy is indicated to prevent a repeat event. Based on the data obtained, in the secondary prevention of coronary heart disease, long-term monotherapy with a P2Y12 inhibitor is preferable to long-term monotherapy with aspirin.

STABLE ANGINA PECTORIS

CLARIFY (2012) is a prospective study lasted 1 year in which 30977 patients with stable CAD from 45 countries (77.4% men and 22.6% women) were followed up. The women included in the work were older than men, had angina attacks, hypertension, and diabetes more often, but smoked less often, were examined worse and received less quality therapy. During the year of follow-up, a comparable total number of complications (cardiovascular death, nonfatal MI or stroke) was recorded, their frequency, adjusted for the initial differences between the groups, was 1.7% versus 1.8%, deaths from any cause — 1.5% and 1.6%, fatal and nonfatal MI — 1.0% and 0.9%, but there was a high frequency of coronary revascularization (2.6% in men, 2.2% in women), the feasibility of which was not analyzed.

In 1220 patients with stable CAD included in the **FAME 2 study (2012)**, a FFR was assessed using CT during coronary angiography. Patients with functionally significant stenoses (n = 888) were randomized for PCI and optimal drug therapy (n = 447) or only optimal drug therapy (n = 441). Patients with functionally insignificant stenoses (n = 322) were treated with medication. During the year, the primary endpoint (death, MI, or emergency revascularization) was recorded in 4.3% and 12.7% of cases ($p < 0.001$) in the PCI and one drug therapy groups, respectively, which was due to a lower frequency of emergency revascularization due to the development of ACS in the first group (1.6% vs. 11.1%, $p < 0.001$). Among patients with functionally insignificant stenoses, the primary endpoint was observed in 3.0% of cases, demonstrating the adequacy of drug therapy.

The anti-inflammatory effect of colchicine makes it possible to successfully use it in the treatment of gout and hope for the effectiveness of this drug in diseases caused by atherosclerosis. It has already been shown that colchicine in a low dose significantly reduces the risk of cardiovascular complications after recently undergoing MI. The **LoDoCo2 (2020)** controlled double-blind trial involved 5,522 patients with clinically stable chronic CAD for at least 6 months who were randomized to receive 0.5 mg colchicine once a day (n = 2762) or

placebo (n = 2760) in addition to the recommended therapy. With a median follow-up period of 28.6 months, the frequency of events of the combined primary endpoint (death from CVD, spontaneous MI, ischemic stroke or myocardial ischemia requiring coronary revascularization) was significantly less frequently recorded in the colchicine group compared to the placebo group (6.8% vs. 9.6% of cases, respectively; HR 0.69 at 95% CI from 0.57 to 0.83; p < 0.001). The sum of deaths from CVD, spontaneous MI, or ischemic strokes was 4.2% in the colchicine group and 5.7% in the placebo group (HR 0.72 at 95% CI 0.57 to 0.92; p = 0.007). There was no significant effect of colchicine compared with placebo on the frequency of individual secondary endpoints: ischemic stroke, mortality from all causes or death from CVD. Serious adverse events were observed with comparable frequency in the colchicine and placebo groups, respectively, included hospitalization for gastrointestinal diseases (1.9% vs. 1.8%), for pneumonia (1.7% vs. 2.0%), for infection (5.0% vs. 5.2%) and new cases of cancer (4.3% vs. 4.4%). At the same time, there was a tendency to increase the number of deaths from non-cardiovascular causes when using colchicine compared with placebo (0.7 vs. 0.5 cases per 100 patient-years, respectively; HR 1.51 at 95% CI from 0.99 to 2.31). Colchicine in a low dose, if it is well tolerated, can be considered as a potential means of long-term secondary prevention of cardiovascular complications in patients with chronic CAD.

Measurement of the fractional flow reserve plays a certain role in the choice of treatment for coronary heart disease. In the **RIPCORD 2 study (2021)**, the hypothesis was tested that at the stage of diagnostic invasive coronary angiography, a systematic assessment of coronary artery disease under the control of a fractional flow reserve would help optimize the use of resources and improve the quality of life in comparison with the assessment using angiography alone. A total of 1100 patients with stable angina pectoris or MI without ST segment elevation were randomized for either angiography alone or angiography with a systematic assessment of all epicardial vessels with a diameter of >2.25 mm by measuring the fractional flow reserve. During one-year follow-up, there were no significant differences in the costs of hospitalization (p=0.137), the quality of life of patients according to the visual analog scale EuroQol EQ-5D-5L (p=0.88), the number of adverse clinical events (death, stroke, MI and unplanned revascularization) (p=0.64). The strategy of systematic assessment of the fractional flow reserve in comparison with a single angiography does not reduce the cost of treatment or improve the quality of life. Additional examination increased the risks for patients due to a longer procedure time, more contrast applied and a higher radiation.

Allopurinol is a urate-lowering therapy used to treat patients with gout. In **ALL-HEART** study **(2022)** patients were aged 60 years or older, with ischaemic heart disease but no history of gout. Participants were randomly assigned (1:1) to receive oral allopurinol up-titrated to a dose of 600 mg daily (300 mg daily in participants with moderate renal impairment at baseline) (n=2853) or to continue

usual care (n=2868). The primary outcome was the composite cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. There was no evidence of a difference between the randomised treatment groups in the rates of the primary endpoint. 314 (11.0%) participants in the allopurinol group and 325 (11.3%) in the usual care group had a primary endpoint (HR] 1.04 [95% CI 0.89-1.21], p=0.65). 288 (10.1%) participants in the allopurinol group and 303 (10.6%) participants in the usual care group died from any cause (HR 1.02 [95% CI 0.87-1.20], p=0.77). In this large, randomised clinical trial in patients aged 60 years or older with ischaemic heart disease but no history of gout, there was no difference in the primary outcome of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death between participants randomised to allopurinol therapy and those randomised to usual care.

ACUTE CORONARY SYNDROME

The **Italian Elderly ACS study (2011)** involved 313 patients over 75 years of age with symptoms of ACS without ST segment elevation lasting up to 48 hours, who were randomized for an early invasive or initially conservative treatment strategy. The primary endpoint (death, nonfatal MI, stroke, repeated hospitalization due to cardiovascular causes or severe bleeding) within one year after randomization) was recorded in 27.9% and 34.6% of cases ($p = 0.26$) with an early invasive and conservative strategy, respectively. However, in patients with elevated troponin levels upon admission, the total complication rate was 57% lower ($p = 0.015$) in the more aggressive therapy group.

Is withdrawal of clopidogrel associated with a higher risk of complications after hospitalization for ACS? A **study conducted in the UK** with the participation of 4,650 patients who underwent ACS with or without ST segment elevation was devoted to this issue. 53 and 54% of them continued to take clopidogrel within a year after discharge, while 84 and 89% of patients continued to take statins, respectively. During this year, the frequency of deaths and MI in those who stopped taking clopidogrel was 2.62 times higher. Withdrawal of the drug was more often noted after coronary bypass surgery, in older patients, as well as in patients who had suffered bleeding.

The report on the first data of the **PACIFIC registry (2011)** in Japan included the results of treatment of 3,597 patients with ACS. The frequency of MI with ST segment elevation was higher (59%), without ST segment elevation — lower (10%), unstable angina (31%) — similar to the indicators of the GRACE register. The frequency of PCI at the inpatient stage of treatment of 96%, 89% and 91% with three variants of ACS, respectively, also significantly exceeded the GRACE data. The total mortality in hospital (2.7%, 1.3% and 0.5%) and the total mortality for 1 year (4.8%, 6.2% and 3.6%, respectively), on the contrary, were significantly lower than in the GRACE global ACS register.

In the **TRILOGY ACS study (2012)**, 9326 patients with ACS without ST-segment elevation who had not undergone myocardial revascularization received,

after randomization, prasugrel 5-10 mg/day or clopidogrel 75 mg/day (in addition to aspirin). During an average follow-up period of 17 months, the primary endpoint (cardiovascular death, MI or stroke) among 7,243 patients under 75 years of age was observed in 13.9% and 16.0% of cases treated with prasugrel or clopidogrel, respectively ($p = 0.21$). Similar results were obtained in 2083 patients aged 75 years and older, in whom a low dose of prasugrel (5 mg/day) was compared with clopidogrel. Cardiovascular mortality ($p = 0.75$) and the frequency of major bleeding ($p = 0.27$) did not differ significantly in the two treatment options. Thus, in patients with ACS without ST segment elevation in the absence of myocardial revascularization, prasugrel was not more effective than clopidogrel.

Copeptin, a new marker of hemodynamic stress, was used in the **BIC-8 study (2013)** along with the determination of cardiac troponin to exclude MI in patients with suspected ACS. Initially, no increase in troponin levels was detected in all patients and they were divided into groups of additional observation and inpatient examination (n = 451) or copeptin determination (n = 451). At a copeptin level of ≥ 10 pcmol/l, standard ACS treatment was performed, and at an index of < 10 pcmol/l, patients were allowed to go home. After 30 days, the frequency of major cardiovascular complications in these groups did not differ (5.5% vs. 5.46%), even though 66% and 12% ($p < 0.001$) of patients were discharged directly from the emergency department in whom, respectively, copeptin was determined or not determined.

Lipid-associated phospholipase A2, an enzyme secreted by leukocytes and bound to circulating lipoproteins and macrophages of atherosclerotic plaques, is considered as a marker of arterial inflammation, a predictor of plaque destabilization and vascular complications. The study of a direct inhibitor of this enzyme, darapladib **SOLID-TIMI 52 (2014)**, included patients hospitalized for ACS in the last 30 days. After randomization, in addition to the recommended therapy, patients were prescribed darapladib (n = 6504) or placebo (n = 6522). After an average of 2.5 years of treatment, darapladib, compared to placebo, did not reduce the total number of deaths from CAD, MI, and emergency coronary revascularization due to myocardial ischemia (primary endpoint) ($p = 0.93$), cardiovascular death, MI or stroke ($p = 0.78$), as well as overall mortality ($p = 0.40$).

There were conflicting data on the efficacy and safety of bivalirudin during PCI in patients with ACS. The randomized **MATRIX study (2015)** involved 7213 patients with ACS, in whom PCI was accompanied by the administration of bivalirudin (n = 3610) or unfractionated heparin (n = 3603). In the bivalirudin group, after randomization, an extended infusion of this drug was used (n = 1799) or not (n = 1811). Serious adverse cardiovascular events (death, MI or stroke) were recorded with a frequency of 10.3% and 10.9% (HR 0.94 at 95% CI from 0.81 to 1.09; $p = 0.44$), adverse clinical events (bleeding or serious adverse cardiovascular events) - in 11.2% and 12.4% of cases (HR 0.89 at 95% CI from 0.78 to 1.03; p =

0.12) in the groups of bivalirudin and unfractionated heparin, respectively. The need for urgent revascularization of the target artery, certain stent thrombosis or serious adverse cardiovascular events (composite primary endpoint) were noted in 11.0% and 11.9% of cases (HR 0.91 at 95% CI 0.74 to 1.11; p = 0.34) in the subgroups of the use or non-use of bivalirudin infusion after PCI, respectively. In patients with ACS, bivalirudin does not reduce the frequency of major adverse cardiovascular events compared with unfractionated heparin, and prolonged infusion of bivalirudin does not reduce the risk of adverse outcomes.

The cluster randomised crossover **NZOTACS study (2019)** compared two oxygen protocols as part of routine care in 40,872 patients presenting with a suspected or confirmed ACS in ambulances and hospitals over two years in New Zealand. The high oxygen protocol recommended high flow oxygen for ischaemic symptoms or electrocardiographic changes, irrespective of the blood oxygen saturation (Sp02) level. The low oxygen protocol recommended oxygen only if Sp02 was below 90%, with a target of reaching a maximum Sp02 of 94%. ACS in dynamics was confirmed in 43% of patients, including 10% of MI with ST segment elevations. The primary endpoint was 30-day mortality obtained from a national database. The high oxygen protocol did not reduce 30-day mortality compared with low oxygen protocol (3.02% versus 3.12%, respectively, RR 0.97, 95% CI 0.86 to 1.08). At the same time, in patients with ST-segment elevation MI, the relative risk of 30-day mortality was significantly lower with high oxygen protocol (8.8% vs. 10.6% in the oxygen-restricted group; for interaction p = 0.016), which is not observed in patients with other types of ACS. Also, a numerical reduction in overall mortality was observed with high oxygen protocol in patients with low oxygen saturation recorded at the emergency stage (10.1% vs. 11.1% with limited oxygen; RR 0.88, 95% CI 0.70 1.11). The authors concluded that patients with suspected ACS who have normal blood oxygen saturation do not benefit from high oxygen protocol. ESC guidelines recommend oxygen in patients with ST-segment elevation MI and non-ST-segment elevation MI when blood oxygen saturation is below 90%, but not routinely above this level.

The prospective follow-up register **CLARIFY (2019)** analyzed data from 32,703 patients with chronic coronary syndrome from 45 countries over a 5-year follow-up period. The characteristics of patients and the relationship between their management methods, the results achieved, and their determinants were determined. The frequency of events of the combined primary endpoint (cardiovascular death or nonfatal MI) for 5 years was 8.0% (8.1% in men and 7.6% in women). The main independent predictors of complications of the primary endpoint were previous hospitalization for CHF, current smoking, AF, residence in Central/South America, MI, a history of stroke, current angina pectoris and peripheral artery disease. There was an interaction between angina pectoris and the transferred MI (p = 0.0016). In patients with a history of MI, a higher frequency of events of the primary endpoint was recorded in the presence of angina pectoris (11.8% vs. 8.2% in patients without angina pectoris; p < 0.001), whereas among

patients without MI, the frequency of events was the same in the presence of angina pectoris or without angina pectoris (6.3% and 6.4%, respectively; $p > 0.99$). The indicators of the use of measures of secondary prevention of CAD with proven effectiveness in the participants of the register were high.

The presented characteristics of patients with chronic coronary syndrome make it possible to identify a group with angina pectoris and MI, characterized by a high risk of complications, despite the active secondary prevention.

MYOCARDIAL INFARCTION

The **ACCESS register (2010)** included 9732 patients who were hospitalized in hospitals in Africa, the Middle East and South America for MI with elevation (45%) or without elevation (52%) of the ST segment. The highest mortality in 12 months after MI with ST segment elevation was observed in Africa, and the most common cause was sudden cardiac arrest. 60% of patients with MI with ST segment elevation remained without reperfusion treatment, thrombolytic therapy was performed in 30% of cases, primary coronary angioplasty — in 26% of cases. The drug treatment was more in line with the current recommendations.

The results of a 5-year follow-up of British (n = 2065) and Belgian (n = 1656) participants of the **GRACE register (2010)** who suffered unstable angina pectoris with or without ST segment elevation are presented. The high prognostic significance of the GRACE risk scale in relation to the prediction of death and MI in the next 5 years has been confirmed. The incidence of MI, stroke, the frequency of hospitalizations, as well as mortality were higher in patients who suffered MI without ST segment elevation or unstable angina, compared with patients after MI with ST segment elevation.

The **RIKS HIA study (2010)** compared the treatment methods and its results in patients hospitalized in Swedish hospitals for MI with or without ST-segment elevation. The data for 1996-1997 (n = 15248) and 2006-2007 (n = 29176) are compared. The introduction and wider use of reperfusion therapy, in particular PCI, drugs with proven prognostic efficacy (aspirin, clopidogrel, heparin and low molecular weight heparins, BB, ACE and ARB, statins) led to a decrease in 30-day and 12-month mortality after MI with ST segment elevation from 11.7% to 5.1% and with 21.9% to 12.9%. After MI without ST segment elevation, 30-day and 12-month mortality decreased from 12.9% to 6.3% and from 19.0% to 11.2%.

In the **CRISP AMI study (2011)**, 337 MI patients with ST-segment elevation without cardiogenic shock were randomized for use (n = 161) or non-use of intra-aortic balloon counterpulsation (n = 176) before primary PCI. Measured by MRI on 3-5 days after PCI, the size of MI was 42.1% and 37.5% of the total LV in

the comparison groups, respectively (the difference is unreliable). At 6-month follow-up, deaths were recorded in 1.9% and 5.2% of cases.

The randomized **HEBE III study (2010)** included 529 patients with primary MI with ST-segment elevation who, 3 hours after successful primary coronary angioplasty, were once prescribed intravenous erythropoietin at a dose of 60,000 IU (n = 263) or were not injected with this drug (n = 266). After 6.5 ± 2.0 weeks, the LV EF assessed by radionuclide ventriculography was similar in the erythropoietin group (53 ± 1%) and in the control group (52 ± 1%, p = 0.41). It was not possible to obtain evidence of a significant decrease in the size of MI under the action of erythropoietin by comparing the levels of biochemical markers of myocardial necrosis (p = 0.058). However, the sum of all cardiovascular complications decreased in the erythropoietin group — 8 vs. 19 (p = 0.032), mainly due to a decrease in cases of heart failure (1 vs. 7, p = 0.034). Erythropoietin was well tolerated, and there were no differences in hemoglobin and hematocrit levels between the groups. A single high dose of erythropoietin does not improve LV EF 6 weeks after successful primary coronary angioplasty in patients with MI with ST segment elevation but reduces the frequency of cardiovascular complications. Of interest is the use of the drug in patients with lower LV function, especially with repeated, rather than single, administration of erythropoietin.

The **IABP-SHOCK II study (2012)** involved 600 patients with cardiogenic shock that complicated MI, who were randomized for intra-aortic balloon counterpulsation (n = 301) or early revascularization (PCI or coronary bypass surgery) and optimal drug therapy (n = 299). The primary endpoint — 30-day mortality from all causes was recorded in 119 (39.7%) patients in the group of intra—aortic balloon counterpulsation and 123 (41.3%) patients in the control group (p = 0.69). There were no significant differences in the time of hemodynamic stabilization, the level of lactate in plasma (a marker of microcirculation), the dose and duration of catecholamine administration, kidney function, the frequency of major bleeding (3.3% vs. 4.4%, p = 0.51), peripheral ischemic complications (4.3% vs. 3.4%, p = 0.53), cases of sepsis (15.7% vs. 20.5%, p = 0.15) and stroke (0.7% vs. 1.7%, p = 0.28) between groups of intra-aortic balloon counterpulsation and control.

The task of the **French FAST-MI program (2012)** was to determine the factors that led to an improvement in the survival of patients with MI with ST elevation in recent years. The results of 4 registries conducted at intervals of 5 years (in 1995, 2000, 2005 and 2010), which covered 6,707 patients hospitalized with MI with ST elevation, were compared. Over 15 years, the average age of patients decreased from 66.2 to 63.3 years with a corresponding decrease in the frequency of cardiovascular complications and concomitant diseases in the

anamnesis. The proportion of young patients increased, especially women younger than 60 years (from 11.8% to 25.5%), who smoked more often (37.3% vs. 73.1%) and were obese (17.6% vs. 27.1%). The time from the onset of symptoms to hospitalization significantly decreased, the number of patients receiving reperfusion therapy increased (from 49.4% to 74.7%), due to an increase in the frequency of primary PCI (from 11.9% to 60.8%). The early use of recommended medications, especially low-molecular-weight heparins and statins has increased significantly. Total mortality in 30 days decreased from 13.7% to 4.4%, standardized mortality — from 11.3% to 4.4%. Multivariate analysis, considering clinical characteristics in addition to the use of reperfusion therapy, showed a steady decrease in 30-day mortality over 15 years, with a ratio of 0.39 ($p < 0.001$) when comparing data in 2010 and 1995.

An additional analysis of the results of the **ATLAS ACS 2-TIMI 51 study (2012)** included only patients who underwent MI with ST segment elevation, who after randomization received, in addition to standard therapy, rivaroxaban 2.5 mg 2 times a day, rivaroxaban 5 mg 2 times a day or placebo. The primary endpoint of efficacy (cardiovascular death, MI or stroke) was less frequently recorded in all patients taking rivaroxaban (8.4% vs. 10.6% in the placebo group, $p = 0.019$), including when using an anticoagulant of 2.5 mg (8.7% vs. 10.6%, $p = 0.047$) and 5 mg 2 times a day (8.2% vs. 10.6%, $p = 0.051$) compared to placebo. Only a dose of 2.5 mg 2 times a day reduced cardiovascular mortality (2.5% vs. 4.2%, $p = 0.006$) and overall mortality (3.0% vs. 4.7%, $p = 0.008$) when compared with placebo. Rivaroxaban in general increased the frequency of major bleeding not associated with coronary bypass surgery (2.2% vs. 0.6%, $p < 0.001$) and intracranial hemorrhages (0.6% vs. 0.1%, $p = 0.015$), but not fatal bleeding (0.2% vs. 0.1%, $p = 0.51$). The last complication developed in 1 and 8 cases ($p = 0.018$) when treated with an anticoagulant of 2.5 mg or 5 mg 2 times a day, respectively.

The choice of treatment tactics for MI without ST segment elevation in the randomized **FAMOUS-NSTEMI study (2014)** was carried out considering the results of the assessment of the FFR ($n = 176$) or initially without considering this indicator (only according to coronary angiography, $n = 174$). FFR < 0.80 was an indication for PCI or coronary bypass surgery. The proportion of patients for whom drug therapy was initially selected was higher in the group in which the results of determining the FFR were considered (22.7% vs. 13.2%; $p = 0.022$). Considering the FFR led to a change in tactics (drug treatment, PCI, or coronary bypass surgery) in 21.6% of patients. After 12 months, the frequency of revascularization remained lower in the treatment selection group under the control of the FFR (79.0% vs. 86.8%; $p = 0.054$). There were no statistically significant differences in health and quality of life indicators between the compared groups.

The randomized **NOMI study (2014)** included patients with MI with ST segment elevation without manifestations of heart failure in the first 2-12 hours from the onset of symptoms. To reduce myocardial damage before the start of PCI

and 4 hours after the onset of reperfusion was performed (n = 125) or not performed (n = 125) mask inhalation of nitric oxide with oxygen. According to MRI data, 48-72 hours after the procedure, the average MI size was 18% versus 19.4% of the LV myocardial mass (p = 0.44) in those receiving and not receiving nitric oxide, respectively. Its positive effect on the volume of necrosis was significantly higher in the group of patients who did not receive nitroglycerin infusion (n = 132) compared with those who received this drug (n = 93). In the nitric oxide group, after 4 months, there was a better recovery of LV function (p = 0.048), there was a tendency to decrease the total frequency of death, recurrence of myocardial ischemia, stroke, and re-hospitalization (p = 0.10).

The drug TRO40303 was evaluated in the **MITOCARE study (2014)** in relation to the reduction of reperfusion injury in patients who underwent revascularization in MI with ST segment elevation. Within 6 hours of the onset of the pain syndrome, patients received intravenously TRO40303 at a dose of 6 mg / kg (n = 83) or placebo (n = 80) before the onset of primary PCI. There were no significant differences in the dynamics of creatinekinase and troponin I in the two groups. The size of MI was also comparable according to the results of MRI (17% vs. 15% of LV mass), LV EF on the first day (46% vs. 48%) and after 30 days (51.5% vs. 52.2%) in the TRO40303 and placebo groups, respectively.

In the **ALBATROSS study (2015)**, 1,603 patients with MI, in 92% of cases without heart failure, were randomized for standard therapy (n = 801) or additional aldosterone blockade (n = 802), which included intravenous administration of 200 mg of canrenoate followed by spironolactone 25 mg/day for 6 months. The primary endpoint (death, ventricular fibrillation/ventricular tachycardia, heart failure) was recorded in 12.2% and 11.8% of cases (RR 0.97; p = 0.81) in the groups of standard treatment and additional aldosterone blockade. The latter was accompanied by a more frequent development of hyperkalemia (more than 5.5 mmol/L) — 3% versus 0.2% of cases in the control (p < 0.0001). In a large subgroup of patients with MI with ST segment elevation (n = 1229), additional aldosterone blockade provided a significant reduction in mortality (HR 0.20 with 95%, CI from 0.06 to 0.70; p = 0.004).

Experimental and clinical data suggested that cyclosporine is able to reduce reperfusion injury of the myocardium, the size of the developing MI and postinfarction LV remodeling. The **CIRCUS study (2015)** involved 970 patients with anterior MI with ST segment elevation who underwent PCI within 12 hours from the onset of symptoms and after randomization received cyclosporine (2.5 mg per kilogram of body weight intravenously) or placebo before coronary recanalization. The primary composite endpoint included death from any cause, aggravation of heart failure during primary hospitalization (or re-hospitalization for heart failure), or LV remodeling (an increase in the final LV diastolic volume after a year by 15% or more). A year later, 59.0% and 58.1% of primary endpoint events were registered among the examined in dynamics in the cyclosporine group (n =

395) and placebo group (n = 396) (HR 1.04 at 95% CI from 0.78 to 1.39; p = 0.77). Cyclosporine did not reduce the frequency of individual clinical components of the primary endpoint, as well as relapses of MI, unstable angina and stroke. In patients with anterior MI with ST segment elevation undergoing primary PCI, intravenous administration of cyclosporine, compared with placebo, is not accompanied by an improvement in clinical outcomes and does not prevent LV remodeling for 1 year.

After a large MI, degradation of the extracellular matrix and overload of cardiomyocytes with calcium are noted, leading to myocardial remodeling, despite PCI. The **PRESERVATION I study (2015)** included 303 patients, usually with anterior MI with ST segment elevation (lesion volume of more than 20% of LV) and LV EF of less than 35%, who were randomized 2-5 days after PCI in a 2:1 ratio for intracoronary administration of 4 ml of 1% dissolved in water sodium alginate and 0.3% calcium gluconate converted into gel, or 0.9% sodium chloride solution. It was assumed that the injected gel could replace the damaged extracellular matrix and provide temporary support in the healing process, preventing LV remodeling. LV final diastolic volume index (primary endpoint), determined by 3D echocardiography after 6 (up to 12) months, equally increased in both groups. There were also no significant differences in the quality of life index, the distance in the 6-minute walking test, the FC of CHF, the frequency of death, re-hospitalization, repeated MI, revascularization, stent thrombosis, life-threatening arrhythmia, myocardial rupture during the observation period of 6 (up to 12) months.

The hypothesis of the possibility of limiting the size of MI using a combination of N-acetylcysteine and nitroglycerin was evaluated in a pilot randomized **NACIAM study (2016)** in 112 patients with MI with ST segment elevation. All patients, except for emergency PCI and a low dose of nitroglycerin (2.5 mcg/min), received an intravenously high dose of N-acetylcysteine (20 mg/min for 1 hour, then infusion at a rate of 10 mg/min for 47 hours) or placebo. The size of MI (primary endpoint) was determined by MRI on day 5 and after 3 months, which showed its decrease in patients receiving N-acetylcysteine by 33% and 50%, respectively, compared with placebo (p = 0.02). N-acetylcysteine in twice increased the area of the saved myocardium (60% vs. 27%; p < 0.001), but there was only a tendency to decrease the level of creatine kinase in the blood (p = 0.08) and there was no improvement in the function of the left ventricle. The incidence of hypotension, bleeding, and contrast-induced nephropathy did not differ in the compared groups. During 2 years of follow-up, patients treated with N-acetylcysteine had fewer repeated hospitalizations due to cardiac causes and deaths (2 cases vs. 16; p < 0.01). The results obtained require confirmation in a large, randomized project with an assessment of clinical outcomes.

DETO2X-AMI (2017) is a RCT based on data from a nationwide Swedish registry. Patients with suspected MI and oxygen saturation in the blood ≥ 90% were randomly prescribed mask inhalation of oxygen (n = 3311) or air (n = 3318)

with a flow volume of 6 liters per minute for 6-12 hours. The average oxygen saturation at the end of inhalation reached 99% among those who inhaled oxygen and 97% — air, hypoxemia developed in 1.9% and 7.7% in the compared groups, respectively. The median of the highest troponin level during hospitalization was 946.5 ng/l with oxygen and 983.0 ng/l with air. The primary endpoint (death from any cause within 1 year after randomization) was observed in 5.0% of patients receiving oxygen inhalation and in 5.1% — air inhalation (HR 0.97 at 95% CI 0.79 to 1.21; p = 0.80). Repeated hospitalization with MI within 1 year was observed in 3.8% of cases among those receiving oxygen and 3.3% — air (HR 1.13 at 95% CI from 0.88 to 1.46; p = 0.33). Routine supplementation of oxygen in patients with suspected MI without hypoxemia is not accompanied by a decrease in mortality from all causes for 1 year. The results of DETO2X-AMI have already been considered in the recommendations of the European Society of Cardiology (ESC) for the treatment of MI with persistent ST segment elevation in 2017.

It is known that remote ischemic conditioning with transient ischemia and reperfusion, applied on the arm, can reduce the size of necrosis in patients with ST-segment elevation MI undergoing primary PCI. The **CONDI-2/ERICPPCI study (2019)** evaluated the possible effect of remote ischemic preconditioning on the frequency of cardiac death and hospitalization for heart failure over a period of 12 months. Patients with suspected ST-segment elevation MI eligible for PCI were randomized to receive standard treatment (including simulation of remote ischemic conditioning — control group, n = 2701) and remote ischemic conditioning group (n = 2700) before PCI. The procedure of remote ischemic conditioning involved the creation of intermittent ischemia and reperfusion of the limb, induced by four cycles of inflating the cuff to measure blood pressure (inflation) for 5 minutes and releasing air from the cuff (deflation) also for 5 minutes. The researchers responsible for collecting data and evaluating the results did not have information about the distribution of treatment options among patients.
Within 12 months after PCI, the frequency of events of the combined primary endpoint (cardiac death or hospitalization for CHF) in the control group and the ischemic conditioning group did not differ significantly (8.6% and 9.4%, respectively; HR 1.10 at 95% CI from 0.91 to 1.32; p = 0.32). No serious adverse events of remote ischemic conditioning were observed.
Remote ischemic conditioning does not reduce the risk of an adverse outcome (cardiac death or hospitalization for CHF) 12 months after primary PCI in patients with MI with ST segment elevation. In this regard, the authors of the work recognized the impractical application of the studied methodology in practice.

In the **DANAMI-2 study (2019)** conducted in Denmark, 1,572 patients with MI with ST segment elevation were randomized for primary PCI or fibrinolysis. Over the course of 16 years, death or re-hospitalization for MI (combined primary endpoint) was observed in 58.7% versus 62.3% of cases (HR 0.86 with 95% CI 0.76 to 0.98) in the groups of primary PCI and fibrinolysis, respectively. There were no differences in mortality from all causes, but cardiac mortality was

significantly lower in the primary PCI group (18.3% vs. 22.7% in the fibrinolysis group; HR 0.78 at 95% CI from 0.63 to 0.98). The advantage of primary PCI in comparison with fibrinolysis in patients with MI with ST segment elevation persists after 16 years of follow—up - the total risk of death or re-hospitalization for MI is reduced.

The **DAPA study (2019)**, which began in 2004, was prematurely discontinued in 2013 due to the slow recruitment of patients who underwent MI with ST segment elevation, in whom it was planned to show a decrease in mortality in the implantable cardioverter-defibrillator (ICD) implantation group (n = 131) compared with the drug-only treatment group (control, n = 135). With an average follow-up period of 9 years in the ICD and control groups, respectively, mortality from all causes was 24.4% vs. 35.5% (HR 0.58 at 95% CI from 0.37 to 0.91; p = 0.02), cardiac mortality — 11.5% vs. 18.5% (HR 0.52 at 95% CI from 0.28 to 0.99; p = 0.04), including mortality from heart failure — 8.4% vs. 12.6% and sudden cardiac death — 3.1% vs. 5.9%.
The limitations of this work were insufficient statistical power, transitions of patients from group to group during the study, controversial inclusion criteria according to modern concepts.

Cardiac autonomic dysfunction after myocardial infarction identifies patients at high risk despite only moderately reduced left ventricular ejection fraction. **SMART-MI-DZHK9 (2021)**, a prospective investigator-initiated, randomized, multicentre, open-label, diagnostic trial at 33 centres in Germany and Austria included patients after acute MI with LV EF of 36-50%. Patients with abnormal periodic repolarization dynamics (≥5·75 deg^2) or abnormal deceleration capacity (≤2·5 ms) were randomly assigned (1:1) to telemedical monitoring with implantable cardiac monitors or conventional follow-up. During median follow-up of 21 months, serious arrhythmic events were detected in 60 (30%) patients of the implantable cardiac monitor group and 12 (6%) patients of the control group (hazard ratio 6·33 [IQR 3·40-11·78]; p<0·001). An improved detection rate by implantable cardiac monitors was observed for all types of serious arrhythmic events: atrial fibrillation 6 min or longer (47 [23%] patients vs 11 [6%] patients; p<0·001), atrioventricular block class IIb or higher (14 [7%] vs 0; p<0·001) and ventricular tachycardia or ventricular fibrillation (nine [4%] patients vs two [1%] patients; p=0·054). In patients at high risk after MI and cardiac autonomic dysfunction but only moderately reduced LV EF, telemedical monitoring with implantable cardiac monitors was highly effective in early detection of subclinical, prognostically relevant serious arrhythmic events.

MI is a common cause of out-of-hospital cardiac arrest, but the benefits of early coronary angiography and revascularization in resuscitated patients without ECG signs of ST segment elevation remained unknown. In the **TOMAHAWK (2021)** study, 554 patients successfully resuscitated with out-of-hospital cardiac arrest of possibly coronary genesis and without ST segment elevation in the post-

resuscitation period were randomized for immediate coronary angiography (immediate angiography group) or initial intensive therapy with delayed or selective angiography (delayed angiography group). The primary endpoint (death from any cause within 30 days) was observed with comparable frequency in the immediate and delayed angiography group (HR 1.28 at 95% CI from 1.00 to 1.63; p=0.06). The total frequency of death or severe neurological deficit was more often observed in the immediate angiography group (HR 1.16 at 95% CI from 1.00 to 1.34). The peak level of troponin release, the frequency of moderate or severe bleeding, stroke and renal replacement therapy were similar in the compared groups. Among resuscitated patients with community-acquired cardiac arrest without ST segment elevation, the strategy of immediate angiography has no advantages over the strategy of delayed or selective angiography with respect to the 30-day risk of death from any cause.

In the **SECURE** study **(2022),** 2,499 patients (average age 76 years) with myocardial infarction within the previous 6 months underwent randomization and were assigned to a polypill-based strategy or usual care. The polypill treatment consisted of aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg). With a median follow-up of 36 months, a primary-outcome event (cardiovascular death, nonfatal type 1 MI, nonfatal ischemic stroke, or urgent revascularization) occurred in 118 of 1237 patients (9.5%) in the polypill group and in 156 of 1229 (12.7%) in the usual-care group (HR, 0.76; 95% CI, 0.60 to 0.96; P = 0.02). A key secondary-outcome event (composite of cardiovascular death, nonfatal type 1 MI, or nonfatal ischemic stroke) occurred in 101 patients (8.2%) in the polypill group and in 144 (11.7%) in the usual-care group (hazard ratio, 0.70; 95% CI, 0.54 to 0.90; P = 0.005). Medication adherence as reported by the patients was higher in the polypill group than in the usual-care group and adverse events were similar between groups. Treatment with a polypill containing aspirin, ramipril, and atorvastatin within 6 months after MI resulted in a significantly lower risk of major adverse cardiovascular events and higher medication adherence, therefor the results of the SECURE study may be important for secondary prevention in patients with recent MI.

ATRIAL FIBRILLATION

The **REALISE-AF Global Registry (2010)** evaluated the current treatment of 15523 patients with various forms of AF in North America and Western Europe. Most patients had a permanent form of AF, so it is not surprising that in the register, the strategy of reducing the frequency of ventricular contractions was chosen in 58% of cases. Compared with previous reports, there was a slight improvement in the quality of antithrombotic therapy for the prevention of thromboembolism.

In a randomized placebo-controlled study of **ANTIPAF (2010)**, the possibility of the effect of olmesartan on the paroxysmal AF in patients without structural changes in the heart was evaluated. Olmesartan at a dose of 40 mg / day was received by 214, placebo — by 211 patients. Parallel use of other ARB, ACE inhibitors and antiarrhythmic drugs was not allowed. Transtelephone electrocardiogram (ECG) monitoring was performed regardless of the presence of arrhythmia symptoms. On average, there were 207 (1.12 per day) transtelephone ECG recording sessions per patient. No significant differences were found in the number of days with AF ($p = 0.77$), the time before the recurrence of arrhythmia and its transformation into a persistent form, the quality of life of patients and the number of hospitalizations in the olmesartan and placebo groups. Only the time before the forced resumption of amiodarone therapy was shorter when taking placebo ($p = 0.0365$). ARB therapy does not reduce the number of AF episodes in patients with documented paroxysmal AF without organic heart pathology. Therefore, such treatment cannot be recommended for the prevention of AF if it is not indicated to patients due to other reasons.

Patients with AF have an increased risk of stroke. Warfarin, effectively reducing its frequency, increases the risk of bleeding, and its effect should be monitored regularly, since it changes under the influence of several factors. Many patients cannot use warfarin for a long time, and the only available alternative is aspirin, which slightly reduces the risk of stroke.

Apixaban, an oral inhibitor of coagulation factor Xa, was studied in a double-blind randomized **AVERROES project (2010)** with active control. The study included 5,600 patients with documented AF and at least one stroke risk factor who did not receive warfarin. Apixaban was prescribed 5 mg 2 times a day (n = 2809), aspirin — 81-325 mg / day (n = 2791). The average score on the stroke risk scale in patients with AF (CHADS2) was 2.0. The study was stopped prematurely with an average duration of therapy of 1 year due to the apparent superiority of apixaban. The primary endpoint (stroke or systemic embolism) was recorded 57% less frequently in the Xa factor inhibitor group (1.7% vs. 4.0%, p = 0.000004). The frequency of major bleeding with apixaban and aspirin was 1.5% and 1.2% (p = 0.33), hemorrhagic stroke — 0.2% in both groups (p = 0.79), all strokes — 1.5% and 3.3% (p < 0.001), MI — 0.7% and 0.8% (p = 0.57), total mortality — 3.4% and 4.4% (p = 0.07), respectively. There were no cases of hepatic toxicity or other serious side effects of the new drug. Apixaban is significantly superior to aspirin in its ability to prevent stroke and systemic thromboembolism in patients with AF who cannot be treated with vitamin K antagonists.

In the **ARISTOTLE study (2011)**, apixaban (n = 9120), usually 5 mg 2 times a day, or warfarin (n = 9081), at a dose that maintained INR of 2.0–3.0, were used in 18201 patients with AF from 39 countries after randomization, for an average of 1.8 years. The use of apixaban reduced the RR of stroke or systemic embolism by 21% (p = 0.011), the risk of bleeding by 31% (p < 0.001) and overall mortality by 11% (p = 0.047). Hemorrhagic stroke in patients receiving apixaban developed 49% less frequently (p < 0.001). Warfarin reduces the risk of stroke in patients with AF by about 70%, but only about half of patients receive this drug. Treatment with warfarin requires regular blood tests to regulate its dose, the rejection of certain foods and medications that alter the anticoagulant effect of the drug. Warfarin also increases the risk of bleeding, including intracranial hemorrhage. Apixaban, an oral X factor inhibitor that does not require blood clotting control, is the first drug that surpassed warfarin in terms of efficacy, safety, and even reducing overall mortality. However, given the problem of the cost of treatment, a new anticoagulant may not be prescribed to patients with good control of the INR with warfarin. The results of the ARISTOTLE study (2011) in 18201 patients with AF were analyzed to clarify the superiority of apixaban over warfarin in terms of stroke prevention and systemic embolism (primary endpoint), depending on the quality of maintaining an INR within 2.0–3.0. When registering the target values of this indicator in less than 58.0% of cases (n = 4538), apixaban reduced the frequency of occurrence of the primary endpoint by 23%, 58.0–65.7% (n = 4535) — by 20%, 65.7–72.2% (n = 4533) — by 21%, more than 72.2% (n = 4538) — by 19%, all differences are unreliable. Regardless of the quality of warfarin treatment, apixaban proved to be more effective and safer against the development of ischemic and hemorrhagic complications.

In the **ROCKET-AF study (2011)** in 14,264 patients with AF, the efficacy and safety of rivaroxaban (20 mg/day or 15 mg/day with creatinine clearance 30-

49 ml/min) and warfarin at a dose that maintained an INR in the range of 2.0–3.0 were compared, depending on renal function. In patients with creatinine clearance of 30-49 ml / min, the primary endpoint (stroke or systemic embolism) was recorded with a frequency of 2.32 per 100 patient-years when taking rivaroxaban at 15 mg / day compared with 2.77 per 100 patient-years when treated with warfarin (the difference of 16% is unreliable). There was no significant superiority of rivaroxaban in the effect on the frequency of bleeding (p = 0.76) and intracranial hemorrhages (p = 0.54), but the number of fatal hemorrhages with its use was significantly lower (p = 0.047).

Among the participants of the **RE-LY project (2011)** who suffered from AF, 6952 patients (38.4%) received aspirin or clopidogrel according to indications in addition to the compared therapy with dabigatran or warfarin. The primary endpoint (stroke or systemic embolism) was not significantly less frequently recorded during treatment with dabigatran at a dose of 110 mg 2 times a day in combination with and without antiplatelet therapy (RR 0.93 and 0.87, respectively, p = 0.7377 for interaction). The frequency of bleeding also did not differ significantly (RR 0.82 and 0.79, respectively, p = 0.7945 for interaction). Dabigatran at a dose of 150 mg 2 times a day significantly exceeded warfarin in reducing the frequency of the primary endpoint, especially among patients who did not receive antiplatelet drugs (RR 0.52 vs. 0.80; p = 0.0578 for interaction). The frequency of major bleeding in patients receiving high-dose dabigatran or warfarin was similar regardless of the use or non-use of antiplatelet agents (RR 0.93 and 0.94, respectively, p = 0.8746 for interaction). However, in general, the frequency of bleeding increased 1.6 times when any of the anticoagulants were combined with antiplatelet therapy.

The **Atrial Fibrillation Ablation Pilot Study (2011)** included the evaluation of radiofrequency catheter ablation in 1,391 patients with AF in 10 European countries in 2010-2011. In 2/3 of cases, paroxysmal AF was diagnosed, in 38% there was no organic heart damage. In 86% of cases, arrhythmia was accompanied by symptoms, which was an indication for ablation. More than 1/3 of patients actively expressed a desire to have a sinus rhythm without taking antiarrhythmic drugs. Ablation was accompanied by complications in 7.7% of cases, including cardiac perforation (0.8%) and cardioembolic event (0.6%). At discharge, 91.4% of patients registered sinus rhythm, 87.4% of patients were prescribed warfarin, 67% — antiarrhythmic drugs.

It was planned to include more than 50,000 patients with non-valvular AF from 50 countries in the **GARFIELD register (2011**) to assess the quality of prevention of cardioembolic complications in real clinical practice. The first results of the register (n = 9288) showed that 55% of the surveyed score 2 or more points on the CHADS2 scale, 81% - score score 2 or more points on the CHA2DS2-VASc scale. However, only 33% and 36% of such patients receive anticoagulant therapy, respectively.

The **global register of AF (2011)** included 15174 patients from 47 countries of the world to identify regional differences in the etiology and nature of treatment of this arrhythmia. Hypertension is the most common underlying disease in AF in all regions, rheumatic heart disease remains one of the important causes of this arrhythmia in India, Africa, the Middle East, and China. The frequency of prescribing oral anticoagulants in patients with non-valvular AF with 2 or more points on the CHADS2 scale varied from 65% in the USA to 10% in China Against the background of anticoagulant therapy, the values of the INR from 2.0 to 3.0 were recorded with a frequency of 67% in Western Europe to 34% in India. The principles of AF treatment adopted in the USA and Western Europe are not followed in other countries.

The **PRAGUE-12 study (2012)** included patients with AF who underwent surgery for CAD or valvular defects, who additionally underwent (n = 117) or did not undergo (n = 107) the MAZE ablation procedure in the left atrium. The primary endpoint of efficacy (sinus rhythm without AF episodes during daily Holter ECG monitoring after a year) was recorded in 60.2% of patients in the ablation group versus 35.5% in the control group (p = 0.002). The combined safety endpoint (death, MI, stroke or renal failure in the first 30 days) was observed in 10.3% (ablation group) versus 14.7% (control, p = 0.411). There were trends towards a decrease in overall mortality (p = 0,800) and stroke frequency (p = 0.319) during the year in ablated patients. By the end of the study, sinus rhythm in the ablation group was significantly more often detected in patients with long-term persistent (53.2% vs. 13.9%, p < 0.001), but not with paroxysmal (61.9% vs. 58.3%) or persistent (72% vs. 50%) AF.

Long-term use of oral anticoagulants is indicated for the prevention of stroke in many patients with AF and mechanical heart valves. After coronary stenting, they are recommended to take triple therapy (oral anticoagulant, aspirin and clopidogrel), which threatens the development of hemorrhagic complications. Such patients were included in the **WOEST study (2012)**, in which, after randomization, a double — oral anticoagulant and clopidogrel (n = 279) or the triple (n = 284) antithrombotic therapy was performed. During the year of follow—up, significantly fewer bleedings (19.5% vs. 44.9%, p < 0.001) and deaths (2.6% vs. 6.4%, p = 0.027) were recorded in the dual therapy group in combination with a favorable profile of other important safety indicators - the frequency of MI (3.3% vs. 4.7%) and stent thrombosis (1.5% and 3.2%).

The observational scientific program **AFib Alation Pilot (2012)** included 1410 patients with AF from European countries (Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Netherlands, Poland, Spain) who underwent ablation procedure to restore sinus rhythm. Perioperative complications developed in 7.7% of cases, including severe ones — in 1.7%. According to the evaluation results, after 3 months, ablation was recognized as successful in 74% of

patients, but 32% of patients continued taking antiarrhythmic drugs. During the first year after ablation, complications, more often vascular, were rarely observed in 1300 patients available for observation (2.6%). Only 4 deaths were registered — one as a result of hemorrhagic stroke, another from non-cardiac vascular causes and two for an unknown reason.

Within the framework of the **RE-LY AF register (2012)**, the outcomes of AF treatment for 1 year were evaluated in 15432 patients from 47 countries of the world. During the follow-up period, the mortality rate of those included in the register was 11.5%, including 11.4% in North America, 8.2% in Western Europe, 18.5% in Latin America and 21.5% in Africa. At the same time, mortality among patients with rheumatic heart defects and non-valvular AF was comparable (10.6% vs. 11.7%). The annual stroke rate was 3.2% in North America, but much higher in China (7.1%), Southeast Asia (7.8%) and Africa (9.1%). The increased risk of stroke in these regions could not be associated with the presence of rheumatic heart defects and anticoagulant therapy, meanwhile, in patients with non-valvular AF, it directly depended on the number of CHADS2 scores (0-1,7 %; 1-2,7 %, 2-3,7 %, 3-6,9 %, more than 3-8.8%).

Most recurrences of AF after isolation of the pulmonary veins are due to the restoration of conduction between them and the left atrium. The **UNDER-ATP study (2015)** evaluated the possibility of reducing the risk of AF recurrence by additional application of radiofrequency energy during the first ablation procedure in the areas induced by the introduction of adenosine triphosphate (ATP). After randomization, 2113 patients with paroxysmal, persistent or long-term persistent AF were subjected to isolation of the pulmonary veins using ATP (n = 1112) or according to the standard procedure (n = 1001). The primary endpoint was a reccurence of atrial tachyarrhythmia lasting more than 30 seconds or requiring repeated ablation, hospitalization, as well as the use of class I or III antiarrhythmic drugs in the period from 90 days to 1 year after ablation. In the pulmonary vein isolation group with the use of ATP (0.4 mg/kg body weight), conduction between the pulmonary veins and the left atrium was induced in 307 patients (27.6%) but was eliminated by the additional application of radiofrequency energy in 302 cases (98.4%). For 1 year, events of the primary endpoint were not recorded with a similar frequency — in 68.7% of patients in the group of pulmonary vein isolation using ATP and in 67.1% of patients in the group of standard pulmonary vein isolation (adjusted HR 0.89 at 95% CI from 0.74 to 1.09; p = 0.25).

A significant part of early reccurences after AF ablation is due to postoperative vulnerability in the left atrium. The **EAST-AF study (2015)** evaluated the ability of antiarrhythmic drugs used during the first 90 days after ablation,reduce the risk of early recurrence of AF, reduce left atrial remodeling and improve long-term clinical outcomes. After radiofrequency catheter ablation, 2038 patients with paroxysmal, persistent, or long-term persistent AF were randomized for 90-day treatment with class I or III drugs (n = 1016) or refusal of their use (n =

1022). The primary endpoint included a reccurence of atrial tachyarrhythmia lasting 30 seconds or more, the need for repeated ablation, hospitalization, or the use of class I or III antiarrhythmic drugs from 90 days to 1 year after ablation. During the first 90 days after ablation, the absence of reccurences of atrial tachyarrhythmia was more often noted in the antiarrhythmic pharmacotherapy group (59.0 % vs. 52.1 % in the control — HR 0.84 with 95 % CI from 0.73 to 0.96; p = 0.01), however, in the subsequent follow-up period, the number of patients with no primary endpoint events in the compared groups did not differ significantly (69.5% and 67.8%, respectively; adjusted HR 0.93 at 95% CI from 0.79 to 1.09; p = 0.38). The use of antiarrhythmic drugs for 90 days after AF ablation reduces the frequency of recurrence of atrial tachyarrhythmias during treatment but does not lead to an improvement in clinical outcomes in the later phase of follow-up.

Unlike vitamin K antagonists, new oral anticoagulants have a short half-life, which requires high adherence to treatment. The randomized **AEGEAN study (2015)** involved patients with AF who received apixaban after an educational program (information booklet, special keychain, mobile phone reminders, access to a virtual coagulology clinic, n = 579) or receiving routine information about the disease and its treatment (n = 583). Compliance with the apixaban intake regimen 2 times a day was monitored using an electronic device in the drug package. For 24 weeks, patients regularly took anticoagulant daily in 88.3% and 88.5% of cases (p = 0.89), did not interrupt its reception for 30 days in 91.1% and 90.5% of cases (p = 0.76) in the groups of the educational program and control, respectively. The work did not reveal additional benefits of the educational program in the treatment of apixaban in patients with AF.

The prospective open trial **RACE 3 (2017)** included patients with symptoms of recently persistent AF and/or CHF. After randomization, the patients underwent conventional treatment (n = 126) or applied aggressive correction of risk factors (n = 119). The latter included cardiological rehabilitation (physical activity, restriction of sodium intake, caloric intake of food with a body mass index ≥ 27 kg/m2, fluid restriction depending on the severity of CHF, regular counseling about adherence to these measures), mineralocorticoid receptor antagonists, statins, ACE inhibitors and/or ARB to the maximum tolerable doses (target blood pressure < 120 mmHg). After at least 3 weeks of treatment, electrical cardioversion was performed, continuing therapy for 12 months. The primary endpoint — registration of sinus rhythm at least 6/7 of the time during the 7-day Holter monitoring of the ECG at the end of the follow-up year was observed in 63% of patients in the group of conventional treatment and in 75% (p = 0.021) of patients in the group of aggressive correction of risk factors. The advantage achieved in the second group may be due to the positive effect of therapy on atrial remodeling.

To participate in the **CASTLE AF study (2017)**, patients with symptomatic paroxysmal or persistent AF and CHF with a LV EF < 35% were selected. All

patients had an implanted cardioverter-defibrillator, which allowed continuously monitor the ECG. After randomization, patients underwent radiofrequency catheter ablation of AF (isolation of pulmonary veins with additional linear ablation at the discretion of the operator) (n = 153) or received conventional therapy (n = 184) with follow-up from 3 to 60 months. With a median follow-up of 37.8 months, the frequency of the primary endpoint (death from any cause or hospitalization due to worsening of CHF) was significantly lower in the ablation group (28.5%) compared with the control group (44.6%, relative risk — HR 0.62 with 95% CI from 0.43 to 0.87; p = 0.007). Mortality from all causes was recorded in 13.4% of cases after catheter ablation versus 25% with conventional therapy (HR 0.53 at 95% CI from 0.32 to 0.86; p = 0.011). The frequency of hospitalization for CHF was 20.7% in the catheter ablation group and 35.9% in conventional therapy (HR 0.56 at 95% CI from 0.37 to 0.83; p = 0.004). Mortality and the number of hospitalizations due to CVD in patients undergoing ablation were lower by 51% (p = 0.008) and 28% (p = 0.05), respectively. Previously, there was no evidence that ablation or antiarrhythmic drugs reduce mortality and the frequency of hospitalizations of patients with AF. CASTLE AF results showed benefits of maintaining sinus rhythm in patients with AF and early-stage CHF.

The **CAPTAF project (2017)** included 155 patients with AF who, could not maintain a sinus rhythm (with monotherapy with antiarrhythmic drugs), and had at least one symptomatic episode of paroxysmal AF in the previous 2 months or at least two symptomatic episodes of persistent AF that required cardioversion during the previous 12 months. All patients were equipped with an implantable heart rate monitor. After randomization, catheter isolation of the pulmonary veins was performed (n = 79) or antiarrhythmic drug therapy was performed in accordance with current recommendations (n = 76). The positive change in the general state of health according to Short Form 36 over the next 12 months (primary endpoint) turned out to be significantly greater in the ablation group — 11.0 units versus 3.1 in the drug treatment group (p = 0.0084). The severity of AF symptoms according to the European Heart Rhythm Association classification decreased more after 12 months after the use of ablation (from 3.0 ± 0.7 to 1.6 ± 0.8) than antiarrhythmic drugs (from 2.9 ± 0.7 to 2.1 ± 1.1; p = 0.0079). At the same time, there were no statistically significant differences in reducing the burden of AF in the compared groups. The authors of the work suggested that the better quality of life in the ablation group could be due to the absence of side effects caused by antiarrhythmic drugs. They believe that the quality of life, rather than the number of episodes of AF lasting more than 30 seconds, should be the primary endpoint in future therapy studies to preserve sinus rhythm.

In the **REHEARSE-AF project (2017)**, AF screening was performed in people aged ≥ 65 years without this arrhythmia with a CHA2DS2-VASc index ≥ 2, using an AliveCor Kardia heart monitor (n = 501) or standard management (n = 500) after randomization. The heart monitor recorded an ECG by applying two fingers of the right and left hands to it, transmitted it to an iPod with WiFi support.

Such a diagnostic procedure was performed 2 times a week for 12 months, supplemented by the registration of an ECG when symptoms appeared with its automatic decoding, consultation with a physiologist and/or cardiologist. The primary endpoint — detection of AF was recorded in 19 patients in the cardiac monitor group and 5 in the standard management group (HR 3.9 at 95% CI from 1.4 to 10.4; p = 0.007). 6 versus 10 strokes/transient ischemic attacks/systemic embolisms were registered when using a heart monitor and in the control group, respectively (HR 0.61 at 95% CI from 0.22 to 1.69; p = 0.34). The device used for the remote interpretation of the ECG makes it possible to detect AF more often in outpatient settings in elderly people with an increased risk of stroke.

A randomized open trial of **phase 3b ENTRUSTAF PCI (2019)** involved patients with AF requiring oral anticoagulation who underwent successful PCI for stable CAD or ACS. Within 4 hours to 5 days after PCI, patients were randomized to receive edoxaban (60 mg once a day) and a P2Y12 receptor inhibitor (clopidogrel, prasugrel or ticagrelor at the discretion of the researchers) for 12 months (n = 751) or a vitamin K antagonist in combination with a P2Y12 receptor inhibitor and aspirin (100 mg 1 time per day) for 1-12 months. The dose of edoxaban was reduced to 30 mg once a day in the presence of one or more factors (creatinine clearance 15-50 ml / min, body weight 60 kg or less, simultaneous use of strong P-glycoprotein inhibitors). The primary safety endpoint (large or small clinically significant bleeding) for 12 months occurred in 17% (20.7% cases per year) of patients in the edoxaban group and 20% of patients (25.6% cases per year) in the vitamin K antagonist group (HR 0.83 at 95% CI 0.65 to 1.05; for "not worse" p = 0.0010, for superiority p = 0.1154). The annual incidence of the primary endpoint of efficacy (cardiovascular death, stroke, systemic embolism, MI or certain stent thrombosis) was 7.3% in the edoxaban group and 6.9% in the vitamin K antagonist group (HR 1.06 at 95% CI from 0.71 to 1.69). When performing PCI in patients with AF, double antithrombotic therapy based on edoxaban is noninferior in safety (risk of bleeding) to standard triple antithrombotic therapy based on a vitamin K antagonist without significant differences in the frequency of ischemic events.

Over the past two decades, it has not been possible to obtain evidence of the superiority of the strategy of maintaining sinus rhythm compared with the strategy of controlling the frequency of ventricular contractions in relation to the risk of cardiovascular complications in patients with AF. In an open study of **EAST-AFNET 4 (2020)** with a blind assessment of the outcomes of elderly patients (average age 70 years) with AF diagnosed no more than 1 year before inclusion in the work, and CVD (including those who had a transient ischemic attack/stroke or having their risk factors) were randomized for early control of sinus rhythm (n = 1395) or routine treatment (n = 1394) in accordance with current recommendations. Early control of sinus rhythm included early treatment with antiarrhythmic drugs or AF ablation (in 19.4% of patients within 2 years), cardioversion if necessary. The usual care was initially limited to the control of the frequency of ventricular contractions with the transition to the control of the sinus rhythm if necessary to reduce uncontrolled symptoms of AF.

With an average follow-up period of 5.1 years, events of the combined primary endpoint (death from cardiovascular causes, stroke, hospitalization with worsening of the course of heart failure or ACS) were significantly less frequently observed in the early sinus rhythm control group compared with the conventional treatment group (HR 0.79 at 96% CI from 0.66 to 0.94; p = 0.005), there was a lower risk of its individual components — death from cardiovascular causes (HR 0.72 at 95% CI from 0.52 to 0.98) and stroke (HR 0.65 at 95% CI from 0.44 to 0.97), but the average number of nights spent in the hospital did not significantly differ between the groups (5.8 ± 21.9 and 5.1 ± 15.5 days per year per patient, respectively; p = 0.23). The primary combined endpoint of safety (death, stroke, or serious adverse events associated with therapy to preserve sinus rhythm) was recorded with equal frequency due to a greater number of serious adverse events of treatment that maintained sinus rhythm early (4.9% vs. 1.4% of patients receiving conventional care); more often than other side effects, drug therapy was observed bradycardia. Clinical symptoms and LV function did not differ significantly between the groups after 2 years.
Early therapy to maintain sinus rhythm in patients with AF and CVD can reduce the risk of cardiovascular complications more effectively than standard treatment. Therefore, it should be offered to all patients with newly diagnosed AF and a high risk of cardiovascular events.

Oral anticoagulants are not used enough to prevent stroke in elderly patients with AF due to a misconception about the rarity of cardioembolic stroke and excessive fear of bleeding. In a prospective **IMPACT-AFib study (2020)** funded by the US Food and Drug Administration, patient selection and follow-up were conducted using insurance company databases. The project included 47,333 patients aged 30 years or more (78 years on average) with AF and indications for use oral anticoagulants (CHA2DS2-VASc score of 2 points or more, an average of 4.5 points). The work did not include patients who had been prescribed oral anticoagulants in the previous 12 months or who had been hospitalized due to

bleeding in the previous 6 months. Patients were randomly assigned to an intervention group (the patient and his doctor received one regular mail message for educational purposes at the beginning of the study) or to a control group in which standard medical care was provided. The primary endpoint (initiation of oral anticoagulants within 12 months) was recorded in 9.89% of patients in the intervention group and 9.80% in the control group (adjusted OR of 1.01 at 95% CI from 0.95 to 1.07). It was found that a numerically larger number of patients initiated oral anticoagulants immediately after receiving the information letter, but over time this effect weakened. There were no significant differences in the frequency of clinical outcomes, including ischemic stroke and major bleeding, in the compared groups.
Sending information once is not an effective way to increase the level of use of oral anticoagulants in the population of elderly patients with AF. To get an answer to the question about the possible benefits of several newsletters of information or subsequent contacts with patients, further research is required.

In patients with AF and CHF, strict and regular monitoring of ventricular contractions by atrioventricular junction ablation and biventricular pacing exceeds pharmacological control of heart rate in terms of reducing the risk of hospitalization for CHF. In the **APAF-CRT (2021)** study in 133 patients with severe symptoms of persistent (>6 months) AF, a narrow QRS complex (≤110 ms) and at least one hospitalization for CHF over the past year, the effect of ablation + biventricular pacing and pharmacological control of ventricular contractions was compared. With a median follow-up of 29 months, the first method of therapy significantly reduced mortality from all causes (HR 0.26 at 95% CI from 0.10 to 0.65; p=0.004). The benefit of ablation + biventricular pacing was the same in patients with LV ejection fraction <35% and >35%. The sum of mortality from all causes or hospitalization for CHF was also significantly lower in the group of ablation + biventricular pacing (HR 0.40 at 95% CI from 0.22 to 0.73; p=0.002) compared with pharmacological control of the frequency of ventricular contractions. Consequently, ablation + biventricular pacing is superior to pharmacotherapy in reducing mortality in patients with persistent AF and narrow QRS complexes who were hospitalized for CHF, regardless of the initial LV ejection fraction.

Left atrial fibrosis plays an important role in the pathophysiology of AF and has been associated with poor procedural outcomes of catheter ablation of AF. The **DECAAF II study (2021)** in 15 centers in the USA, Europe and Australia assessed the relationship between atrial tissue fibrosis and the subsequent outcome of the first catheter ablation of paroxysmal (65%) or persistent (35% of cases) AF. The degree of fibrosis blindly for attending physicians was classified as stage 1 (<10% of the atrial wall), 2 (≥10%-<20%), 3 (≥20%-<30%) and 4 (≥30%). The cumulative frequency of AF recurrence adjusted for 10 demographic and clinical variables was assessed by fibrosis stages on the 325th and 475th days after the 90-day blind period in 260 patients. The estimated uncorrected cumulative frequency

of arrhythmia recurrence by day 325 for stage 1 fibrosis was 15.3%, stage 2 – 32.6%, stage 3 – 45.9% and stage 4 – 51.1%; by day 475 – 15.3%, 35.8%, 45.9% and 69.4%, respectively. Similar results were obtained after covariate adjustment. Among patients with AF who underwent catheter ablation, atrial tissue fibrosis assessed by delayed-amplification magnetic resonance imaging is independently associated with the likelihood of recurrence of this arrhythmia.

Percutaneous closure of the left atrial appendage is an alternative to chronic oral anticoagulation to reduce stroke risk in patients with nonvalvular atrial fibrillation. In **AMULET IDE (2021)** study 1878 patients with nonvalvular atrial fibrillation at increased risk of stroke were randomly assigned (1:1) to undergo percutaneous implantation of a left atrial appendage occluder with the Amulet occluder or Watchman device. The Amulet occluder was noninferior to the Watchman device for the primary safety end point (14.5% versus 14.7%; difference=-0.14 [95% CI, -3.42 to 3.13]; $P<0.001$ for noninferiority). Procedure-related complications were higher for the Amulet occluder (4.5% versus 2.5%), largely related to more frequent pericardial effusion and device embolization and decreased with operator experience. The Amulet occluder was noninferior to the Watchman device for the primary effectiveness end point (2.8% versus 2.8%; difference=0.00 [95% CI, -1.55 to 1.55]; $P<0.001$ for noninferiority), and the composite of stroke, systemic embolism, or cardiovascular/unexplained death (5.6% versus 7.7%, difference=-2.12 [95% CI, -4.45 to 0.21]; $P<0.001$ for noninferiority). Left atrial appendage occlusion was higher for the Amulet occluder than for the Watchman device (98.9% versus 96.8%; difference=2.03 [95% CI, 0.41-3.66]; $P<0.001$ for noninferiority; $P=0.003$ for superiority). The Amulet occluder was noninferior for safety and effectiveness of stroke prevention for nonvalvular atrial fibrillation compared with the Watchman device and superior for left atrial appendage occlusion.

CONDUCTION AND RHYTHM DISORDERS

Bradycardia in patients with sick sinus syndrome (SSS) can be corrected using various pacing regimens. Two modern methods of it - frequency adaptive single atrial (AAIR) and frequency adaptive dual chamber (DDDR) were compared in a randomized study **DANPACE (2010)**. The work included 1415 patients with SSS, normal QRS complex and without atrioventricular block.
After randomization, patients were implanted with pacemaker devices in the AAIR (n = 707) or DDDR (n = 708) mode, the average follow-up was 5.4 ± 2.6 years. The primary endpoint (death from any cause) was 29.6% in the AAIR group and 27.3% in the DDDR group (p = 0.53). Paroxysmal AF occurred 21% less frequently (p = 0.024) in the dual-chamber pacing group. There were no significant differences in the incidence of permanent AF, stroke, or heart failure between groups. Reoperations to change the pacemaker regimen by 50% less frequently (p < 0.001) were required in patients from the DDDR group.
Although the overall mortality of patients with SSS during pacing in the AAIR and DDDR modes does not differ significantly, the second of them will reduce the risk of AF and reoperations.

High heart rate is a risk factor for worse outcome, including in patients with CHF. BB is the standard therapy for CHF, but in some cases, the achievement of target doses of these drugs is limited by side effects and the heart rate remains elevated. The randomized, double-blind, placebo-controlled **SHIFT study (2010)** included patients with symptoms of CHF II-IV FC according to New York Heart Association (NYHA) of ischemic or non-ischemic etiology, LV EF of 35% or less, sinus rhythm of 70 bpm or more who have been hospitalized for decompensation within the last 12 months. In addition to standard therapy for CHF, which included BB in 90% of cases, ivabradine (n = 3241) at a dose of up to 2.5, 5 or 7.5 mg 2 times a day or placebo (n = 3264) was prescribed. The primary endpoint included death from cardiovascular causes and hospitalization for CHF. With a mean follow-up of 22.9 months, it was recorded in 793 (24.5%) patients in the ivabradine group and in 937 (28.7%) patients who received placebo, the difference was 18% (p < 0.0001). Hospitalizations due to worsening CHF were observed in

15.9% and 20.6% of cases, respectively (26% difference in favor of ivabradine, $p < 0.0001$).
In the I(f) channel blocker group, deaths due to heart failure occurred 26% ($p = 0.014$) less often, mortality from cardiovascular causes decreased by 9% ($p = 0.128$), from any cause - by 10% ($p = 0.092$), the total number of hospitalizations — by 11% ($p = 0.003$). The listed effects of ivabradine were observed regardless of gender and age, taking BB, the etiology and severity of CHF, the presence of DM and arterial hypertension. Tolerability of ivabradine, as in previous studies, was good - bradycardia, accompanied by symptoms, was recorded in 4.6% and 1% of cases, visual symptoms - in 2.8% and 0.5% of cases when taking ivabradine and placebo, respectively.
With an initially higher heart rate, the differences in the frequency of registration of the primary end point were most pronounced.
An additional analysis of the obtained results confirmed the important role of heart rate in the pathophysiology of CHF. The risk of events related to the primary endpoint was 3% higher with an increase in heart rate by 1 bpm and by 16% with an increase of 5 bpm. Meanwhile, the effectiveness of ivabradine is not associated only with a "mechanical" decrease in heart rate, suggesting the presence of pleiotropic effects in this drug.

An additional analysis of the results of the **PRoFESS study (2012)** was carried out in 20165 participants with ischemic stroke (mean age 66.1 ± 8.6 years) to determine the relationship between resting heart rate and prognosis, as well as the neuropsychiatric status of patients. A direct correlation was established between heart rate and total, cardiovascular, and non-cardiovascular mortality, as well as the absence of such a relationship with recurrent stroke and MI. Normal heart rate was associated with better neurological status after ischemic stroke according to the modified Rankin scale and the Barthel index, less cognitive impairment according to the Mini-Mental State Examination test.

In the **SMART-AV study (2011)**, in 426 patients with CHF III-IV FC according to NYHA, who received resynchronization therapy, the prognostic role of electrical delay (the interval from the beginning of the QRS complex of the surface ECG to the first large peak of the LV electrogram) was analyzed in relation to the reverse development LV remodeling. A large amount of electrical dyssynchrony was directly and independently of other factors associated with the likelihood of reverse development of remodeling (more than 15% reduction in end-systolic volume) of the LV.

The follow-up of 177 patients with bradycardia and preserved LV EF participating in the **PACE study (2011)** was continued up to 2 years. During the second year, in patients with single-chamber right ventricular electrical stimulation, LV remodeling progressed, its EF continued to decrease, and in patients with biventricular stimulation it did not change significantly, as a result of

which the intergroup difference in the indicator reached 9.9%, the final LV systolic volume differed by 13. 0 ml
The impact of ivabradine on the quality of life of 1944 patients with systolic CHF and a sinus rhythm at rest of 70 per minute or more participating in the **SHIFT study (2011)** was carried out using the Kansas City Cardiomyopathy Questionnaire (KCCQ). Ivabradine significantly improved the overall ($p < 0.01$) and clinical ($p = 0.02$) components of quality of life compared with placebo, which was associated both with a decrease in the frequency of cardiovascular death and hospitalizations for CHF, and with a decrease in heart rate.

Vegetoregulatory therapy by stimulation of the vagus nerve on the right (n = 29) or left (n = 31) in the neck was evaluated in the **ANTHEM-HF study (2014)** in patients with CHF II/III FC according to NYHA and LV EF ≤ 40% receiving optimal pharmacotherapy. Electrical stimulation was performed with current pulses of 2.0 ± 0.6 mA with a natural frequency (10 Hz) and was well tolerated regardless of the side of stimulation, rarely causing mild dysphonia, cough, or pain in the oropharynx. After 6 months of vegetoregulatory therapy, LV EF increased by an average of 4.5%, LV end-systolic volume decreased by 4.1 ml, the NYHA FC improved in 77% of patients, the distance of a 6-minute walk was lengthened by 56 and 77 m with left and right-sided electrical stimulation, respectively.

In patients with atrioventricular block and low heart rate, right ventricular electrical stimulation is used, which can have a negative effect on the structure and function of the heart. In the **BIOPACE study (2014)**, these patients (mean age 73.5 years) were randomized to receive right ventricular (n = 908) or biventricular pacing (n = 902). After an average of 5.6 years of follow-up, the time to death or hospitalization for CHF (primary endpoint) tended to decrease in the biventricular pacing group (–13%; $p = 0.08$). There was no significant reduction in the overall incidence of these events in patients with LV EF ≤ 50% (–8%; $p = 0.47$) and > 50% (–12%; $p = 0.21$). It is necessary to note the dysfunction of an expensive biventricular pacemaker in 14.8% of cases in the absence of such a problem with right ventricular pacing.

INVASIVE INTERVENTIONS IN ARRHYTHMOLOGY

The **PACE project (2010)** compared the effects of biventricular (n = 89) and right ventricular (n = 88) pacing in patients with bradycardia who had an LV EF of 45% or more. Systolic dyssynchrony of the left ventricle, established by the results of Doppler studies, was detected less frequently in patients with a biventricular than with a right ventricular pacemaker after a month (15% of cases vs. 52%, $p < 0.001$). The presence of early systolic dyssynchrony was associated with a significant decrease in LV EF after 12 months.

The results of the CARE HF study on the use of resynchronization therapy in patients with CHF were first presented in 2005. Of the 813 patients initially included in the project, by the fall of 2009, 309 survived and remained available for follow-up. Among them, according to the **CARE HF LTFU project (2010)**, resynchronization therapy reduced mortality by 23% ($p = 0.007$) compared with control. Survival may be even better if resynchronization therapy devices with the added function of a defibrillator are used.

Patients with implantable cardioverter defibrillator should be examined in the clinic once every 3 months, which is in no way associated with clinical events and malfunctions of the device. In the **EVATEL study (2011)**, 1501 patients with ICD were randomized to either conventional (n = 750) or active surveillance (n = 751), which involved the transfer of information about the condition and function of the ICD to a specialized center by telephone. The primary endpoint was the sum of all-cause deaths, hospitalizations for cardiovascular causes, and ineffective or inappropriate ICD shocks. It was registered in 28.5% of cases in the control group and in 30.2% in the active observation group (the difference is not significant). In addition, there were no statistically significant differences between groups in time to first events of the primary endpoint ($p = 0.71$) and one-year survival ($p = 0.31$). The number of unnecessary ICD shocks was lower in the active control group (4.7%) compared to the standard observation group (7.5%, $p = 0.03$).

In the **ECOST study (2011)**, 433 patients undergoing secondary prevention of sudden cardiac death with an ICD were randomized to automatic transmission of information from the device (n = 221) or standard observation at clinic visits every 6 months (n = 212). At 27 months, events classified as the primary endpoint (death from any cause, severe cardiovascular complications, side effects, and ICD-related complications) occurred in 38.5% and 41.5% of cases in the remote and standard control groups, respectively. Significant differences were also not obtained when comparing the incidence of deaths (9.0% vs. 9.4%) and severe cardiovascular complications (5.4% vs. 6.6%). However, inappropriate ICD shocks were less frequently recorded in the active control group (5.0% vs. 10.4%, p = 0.03), which saved the energy of the device's batteries.

An additional analysis of the results of the **IRIS study (2011)**, involving 898 patients who received ICDs in the early stages after MI, was carried out to determine the reasons for the lack of reduction in overall mortality. It was found that ICD did not affect the incidence of sudden and non-sudden cardiac death in patients who did not receive reperfusion therapy. The ICD can reduce the risk of sudden arrhythmic death in the first 2 years after MI, but at the same time it increases the risk of death from other causes, especially significantly after shocks of the device. Meanwhile, ICD shocks more often occur in patients with a large size of MI, more frequent registration of non-sustained ventricular tachycardia, more severe CHF, less active treatment with BB.

The **DECAAF project (2013)** included 260 patients with AF (65% with its paroxysmal form), who underwent high-resolution MRI to determine the degree of atrial fibrosis 30 days before and 90 days after the catheter ablation procedure. According to the results of Holter monitoring of the ECG, arrhythmia relapses were observed in 33.8% of patients. The success rate of ablation (no recurrences within a year) was inversely related to the severity of atrial fibrosis: 85% - at stage 1 (fibrosis < 10%), 64% - at stage 2 (fibrosis ≥ 10 - < 20%), 54% - in stage 3 (fibrosis ≥ 20–<30%) and only 31% in stage 4 (fibrosis ≥ 30%). Ablation around the orifices of the pulmonary veins proved to be less effective than ablation of the fibrous tissue itself, with a significant spread of the latter.

When conducting resynchronization therapy with LV stimulation with a bipolar electrode, it is often not possible to achieve simultaneous contraction of the ventricles. The **MORE-CRT study (2014)** compared quadruple LV electrical stimulation with a QuarterTM electrode (n = 720) with traditional bipolar stimulation (n = 348). Survival without intra- and postoperative complications within 6 months (primary endpoint) was observed in 85.97% and 76.86% of cases using four- and two-pole electrodes, respectively (p = 0.0001) - a RR reduction of 40.8%. Intraoperative complications were observed in 5.98% versus 13.73% (p < 0.0001) of cases in the groups of quadruple and bipolar LV electrical stimulation, respectively.

Resynchronization therapy is recommended for patients with CHF and wide QRS complexes, but the optimal zone of electrical stimulation of the right ventricle is being specified. The **SEPTAL-CRT study (2014)** included patients with LV EF ≤ 35% and QRS > 120 ms, who, after randomization, underwent electrical stimulation of the right ventricle in the region of the apex (n = 92) or the interventricular septum (n = 90). After 6 months, there were no significant differences in the decrease in the end systolic volume of the left ventricle (29.3 ± 44 and 25.3 ± 39 ml; p = 0.79), increase in LV EF, the frequency of hospitalizations for CHF, overall mortality (3, 0 and 3.8%; p = 0.77), the frequency of complications of the electrical stimulation procedure between the groups of apical and septal stimulation, respectively.

In patients with persistent AF, additional methods of ablation are recommended in addition to the procedure of catheter isolation of the pulmonary veins to maintain a stable sinus rhythm. In the **STAR AF 2 study (2014)**, after randomization, only pulmonary vein isolation (n = 64), pulmonary vein isolation and additional ablation based on 3D electrophysiological mapping (n = 263), pulmonary vein isolation and linear ablation in the left atrium were performed (n=259). The average duration of the catheter ablation procedure was 167, 229 and 223 minutes (p < 0.001) in each of the three groups, after 18 months, 59%, 48% and 44% of patients were free from AF lasting more than 30 seconds (primary endpoint) (p = 0.15), including 48%, 37% and 33% (p = 0.11) of patients without drug antiarrhythmic therapy, respectively. In patients with persistent AF, the addition of pulmonary vein isolation ablation before elimination of complex electrograms or linear ablation prolongs the procedure time but does not provide better prevention of arrhythmia recurrence.

The **EuroEco study (2014)** compared the cost of managing 303 patients with implanted cardioverter-defibrillators who were randomized to use home telemonitoring technology or traditional health care visits. Despite the higher cost of home telemonitoring itself, when using it, patients required fewer visits to the doctor (3.79 ± 1.67 vs. 5,53 ± 2,32; p < 0,001) with a slight increase in unscheduled visits (0.95 ± 1.50 vs. 0.62 ± 1.25; p < 0.005), more non-office (1.95 ± 3.29 versus 1.01 ± 2.64; p < 0.001) and Internet contacts (11.02 ± 15.28 vs. 0.06 ± 0.31; p < 0.001), more discussions in the clinic (1.84 ± 4.20 vs. 1.28 ± 2.92; p < 0.03), but fewer hospitalizations (0.67 ± 1.18 versus 0.85 ± 1.43; p = 0.23) with their slightly shorter duration (6.31 ± 15.5 versus 8.26 ± 18.6 days; p = 0.27). As a result, the cost of home telemonitoring and traditional monitoring of patients with implanted cardioverter-defibrillators did not differ significantly.

In the first months after catheter ablation of AF, recurrence of arrhythmia is often noted, but the long-term results of prescribing short-term drug antiarrhythmic therapy have not been studied enough. In the **AMIO-CAT study (2014)**, amiodarone (800 mg/day for 2 weeks, 400 mg/day for 3 and 4 weeks, 200 mg /day from 5 to 8 weeks, n = 108) or placebo (n = 104) were used in patients with

paroxysmal or persistent AF after catheter isolation of the pulmonary veins, supplemented by linear ablation. Documented episodes of AF lasting more than 30 seconds from 4 to 6 months after ablation were observed in 39% and 48% of patients in the amiodarone and placebo groups, respectively (p = 0.18). At the same time, in the first 3 months after ablation, those receiving amiodarone had a significantly lower frequency of recurrence of AF (34% vs. 53%; p = 0.006), arrhythmias requiring hospitalization (p = 0.006) and cardioversion (p = 0.0004). Despite the developing side effects of amiodarone, it did not ultimately reduce the quality of life of patients (Short Form-36 questionnaire) due to its antiarrhythmic effect.

In patients with large MI, drug therapy and rapid restoration of blood flow in the affected area do not guarantee the prevention of cardiac remodeling. It was assumed that electrical stimulation, which coordinates heart contractions and can reduce the load on the damaged area, can prevent postinfarction myocardial remodeling. A total of 126 patients with a QRS duration ≤ 120 ms in the first 10 days of the onset of the first major MI were randomized in the **PRomPT study (2015)** to biventricular (n = 41), LV pacing (n = 40), and controls (no pacing; n = 45). According to echocardiography data, LV end-diastolic volume increased after 18 months compared to baseline by 16.7 ± 30.5 ml in the combined electrical stimulation group versus 15.3 ± 28.6 ml in the control group (p = 0.92). There were no significant differences between groups in changes in end-systolic volume and LV EF, quality of life measures (Minnesota Living with Heart Failure (MLHFQ) and European Quality of Life-5 Dimension questionnaires), NYHA FC. The increase in distance in the 6-minute walk test was similar in the comparison groups. During the 18-month follow-up period, the incidence of death or hospitalization for heart failure in the combined pacing and control groups was 17.4% and 21.7%, respectively (p = 0.59). Therefore, pacing does not prevent remodeling after major MI.

In long-standing persistent AF, isolation of the pulmonary veins is often insufficient for successful ablation. In the **BELIEF study (2015)**, 173 patients with long-term persistent AF underwent standard pulmonary venous isolation (n = 88) or supplemented with electrical isolation of the left atrial appendage (n = 85) after randomization, with a mean procedure duration of 77 versus 93 minutes, respectively. Patients who underwent electrical isolation of the left atrial appendage were significantly more likely to be free of AF during the follow-up year (56% versus 28%, RR 1.92; p = 0.001). Patients of both groups with recurrent AF underwent repeated ablation, which included isolation of the left atrial appendage. At a 2-year follow-up, AF was not recorded in 76% of patients with initial isolation of the left atrial appendage and in 56% of patients in whom it was performed during re-intervention (p = 0.003). Isolation of the left atrial appendage in long-term persistent AF seems reasonable and requires pathophysiological justification.

With standard pacing, displacement, disruption of the integrity and function of the electrode, development of infection, perforation of the heart, venous occlusion, tricuspid regurgitation are possible. In the **LEADLESS II study (2015)**, 300 patients in need of permanent single-chamber pacing were non-surgically (transfemorally catheterized) implanted in the right ventricle with a fully self-contained leadless pacemaker with a cylindrical shape 42 mm long and 6 mm in diameter. The primary efficacy endpoint was acceptable threshold (2.0 V or less with a duration of 0.4 ms) and pacing amplitude at 6 months, and the primary safety endpoint was the absence of serious device-related adverse events at 6 months. The primary endpoints of efficacy and safety were achieved in 90% and 93.3% of patients, respectively. Within 6 months, device displacement (1.7%), cardiac perforation (1.3%), and pacing failure requiring device replacement (1.3% of cases) were noted. Subsequently, the device was implanted in another 226 patients, and the rate of complications tended to decrease. The estimated battery life is 15 years. The issue of tactics in case of failure of such a pacemaker has not been resolved - to remove the device or introduce another new one.

The **OptiLink HF study (2015)** evaluated the role of early detection of fluid retention in the lungs, determined by an implanted cardioverter-defibrillator or a three-chamber pacemaker with defibrillator function, capable of measuring intrathoracic impedance. The project involved patients with an average LV EF of 27%, CHF II/III NYHA FC and a high risk of decompensation. After randomization, 505 patients underwent, and 497 did not, monitor stagnation in the pulmonary circulation with data transfer to a cardiologist. Only 37% of the time with dangerous levels of lung congestion, patients reported worsening symptoms, and physicians changed treatment for patients only 47% of the time when they received a warning of severe congestion. At a mean follow-up of 18 months, there were no significant differences in the total number of deaths and hospitalizations for CVD (primary endpoint) - 45.0% vs. 48.1% (RR 0.87; 95% CI from 0.72 to 1.04; p = 0.13), apart from death from any cause (6.2% vs. 8.5%; RR 0.89; 95% CI 0.62 to 1.28; p = 0.52) and hospitalization due to CVD (42.4% vs 44.5%; RR 0.89; 95% CI 0.73 to 1.08; p = 0.22) in the congestion monitoring groups and rejection accordingly. The applied monitoring of congestion in the pulmonary circulation improved patient-physician interaction but did not significantly affect the prognosis of patients receiving optimal CHF therapy.

The prognostic effectiveness of the preventive use of ICD has been convincingly proven in patients with systolic CHF of ischemic genesis. Due to the improvement of pharmacotherapy and the widespread use of resynchronizing therapy, the results of treatment of systolic CHF have improved significantly, which requires a reassessment of the role of ICD in modern conditions. In the **DANISH study (2016)**, 1116 patients with symptoms of systolic CHF (LV EF ≤ 35%), unrelated to CAD, received (n = 556) or did not receive ICD (n = 560, control group) after randomization in addition to conventional treatment. In both groups, 58% of patients underwent resynchronizing therapy. With a median

follow—up period of 67.6 months, the primary endpoint (death from any cause) was recorded in 21.6% of cases with ICD and in 23.4% with conventional treatment (RR 0.87 with 95% CI from 0.68 to 1.12; p = 0.28), sudden cardiac death — in 4.3% and 8.2% (HR 0.50 at 95% CI from 0.31 to 0.82; p = 0.005), infectious complications due to ICD implantation — in 4.9% and 3.6% (p = 0.29) patients, respectively. According to the analysis in subgroups, ICD reduced the overall mortality of patients only under the age of 68 years (HR 0.64 at 95% CI from 0.46 to 0.91; p = 0.01). In systolic CHF of non-ischemic genesis, ICD effectively prevents sudden cardiac death, but in patients with a high risk of non-sudden death, it does not reduce overall mortality, which requires considering age and concomitant diseases when deciding on the use of ICD.

The **REM-HF study (2016)** involved 1,650 patients with CHF and an implanted electronic device for resynchronizing therapy, a similar device with the function of a defibrillator or ICD. Patients were randomized for remote monitoring (n = 824) or routine treatment (n = 826). Remote monitoring provided weekly transmission to the attending physician of information about the patient (thoracic impedance, cardiac arrhythmias, heart rate variability, etc.). Based on this information drug therapy, lifestyle, frequency of additional visits to the clinic or visits to the doctor at home, hospitalizations for emergency care could change. The usual treatment involved remote monitoring every 3-6 months in addition to standard CHF therapy. With an average follow-up period of 2.8 years, the primary endpoint (death from any cause or unplanned hospitalization for CVD) was recorded with a frequency of 42.4% in the weekly remote monitoring group and 40.8% in the usual treatment group (HR 1.01 at 95% CI from 0.87 to 1.18; p = 0.87) with a tendency to reduce overall mortality (HR 0.83 at 95% CI from 0.66 to 1.05; p = 0.42). Remote monitoring may be useful for evaluating the operation of implanted devices, but weekly detailed analysis of the condition of patients with CHF does not improve their prognosis.

All participants in the **MORE-CARE study (2016)** suffered from severe systolic CHF and had an extended QRS complex, and therefore received an implantable device for resynchronizing therapy with a defibrillator function. 8 weeks after implantation of the device, patients were randomized for remote monitoring and visits to the clinic (n = 437) or only clinical visits (n = 428). With a median follow-up period of 24 months, the primary combined endpoint (death, hospitalization due to a cardiovascular cause or caused by a device) was recorded with equal frequency in the remote monitoring and routine monitoring group (HR 1.02 at 95% CI from 0.80 to 1.30; p = 0.89). However, in the remote monitoring group, savings in healthcare resources were achieved — a decrease in the number of planned/emergency hospitalizations and clinical visits by 38% (p < 0.001), mainly due to a significant (41%) decrease in the frequency of clinic visits, without compromising patient safety.

CARDIAC SURGERY AND INTERVENTIONAL CARDIOLOGY

The **MULTI STRATEGY project (2010)** performed the longest three-year follow-up of 736 patients who underwent ST-segment elevation MI and PCI with stent implantation. Patients were randomized into 4 groups to receive different inhibitors of platelet glycoprotein IIb/IIIa receptors, abciximab or tirofiban, and either sirolimus-treated or plain metal stents. Differences in treatment tactics did not significantly affect overall mortality, MI, and stent thrombosis. However, the use of simple metal stents 2.29 times more often ($p = 0.0006$) led to the need for repeated coronary interventions.

Follow-up of 2603 participants in the **ISAR TEST 4 (2010)** study who were implanted with stents with a biodegradable platform or continuously releasing antiproliferative agents (sirolimus or everolimus) was continued up to 2 years. As with the one-year follow-up, there were no differences in the incidence of cardiovascular death, MI in the area of the stented artery, the need for repeated revascularization, and stent thrombosis. Therefore, the use of stents with a biodegradable platform that releases antiproliferative drugs for a shorter time does not provide benefits according to a two-year follow-up.

When performing coronary artery bypass surgery, as a rule, one internal mammary artery is used. The technique of bilateral use of the internal mammary arteries is supposedly able to improve more effectively the long-term prognosis of coronary artery bypass grafting, but it is technically more difficult and is accompanied by a greater risk of death in the early postoperative period.
In the **ART study (2010)**, 3102 patients were randomized to single (n = 1554) and bilateral (n = 1548) mammary coronary artery bypass grafting. The second method of operation required more time (on average, 23 minutes) and more prolonged artificial ventilation of the lungs. After 30 days, mortality in the comparison groups was identical (1.2% each), it did not differ significantly and after a year - 2.4% versus 2.5% with single and bilateral techniques, respectively. Reconstruction after

surgical trauma of the sternum after 6 weeks was required in 0.5% and 1.5% of cases. The frequency of MI at 30 days and 1 year was similar.
There does not appear to be any benefit from bilateral mammary coronary artery bypass grafting after 1 year.

The use of everolimus-eluting stents has been shown to improve clinical outcomes compared to paclitaxel-eluting stents. Long-term comparison of implant results stents coated with everolimus or sirolimus have not previously been performed. In **LESSON I (2010)**, patients were implanted with either everolimus (n = 1601) or sirolimus (n = 1532) stents during coronary angioplasty. The mean duration of dual antiplatelet therapy in each group was 12 months. The primary endpoint (the sum of events such as death, MI and revascularization of the target artery) over 3 years of follow-up was recorded in the everolimus or sirolimus stent groups in 14.9% and 18.0% of cases (p = 0.056), mortality from all causes — in 6.0% and 6.5% (p = 0.59), MI — in 3.3% and 5.0% (p = 0.017), revascularization of the target artery — in 7.0% and 9, 6% (p = 0.039), respectively, certain stent thrombosis was 70% less common (p = 0.01) when using everolimus-eluting stents. The improvement in outcomes with everolimus-eluting stents is to some extent associated with a reduction in the incidence of MI due to stent thrombosis. The limitation of the study is its observational nature and the performance in one center.

Previous studies have shown that low molecular weight heparin enoxaparin causes fewer hemorrhagic complications compared with unfractionated heparin during coronary angioplasty. The **ATOLL randomized trial (2010)** directly compared intravenous enoxaparin at a dose of 0.5 mg/kg (with or without inhibitors of glycoprotein IIb/IIIa platelet receptors) and unfractionated heparin (50–70 U/kg with IIb/IIIa inhibitors or 70–100 U/kg without IIb/IIIa receptor inhibitors) before primary angioplasty in 910 patients with ST-segment elevation MI. In the enoxaparin group, there were 17% fewer (p = 0.07) events related to the primary endpoint (death, complications of MI, angioplasty failure, major bleeding) and 40% fewer (p = 0.01) of the sum of such events. complications such as death, relapse of ACS, repeated revascularization. The use of low molecular weight heparin compared with unfractionated heparin was accompanied by a decrease in all-cause mortality (3.8% vs. 6.3%), major bleeding (4.5% vs. 4.9%), and small hemorrhages (7.0% vs. 8.9%).
According to the results of the first randomized comparison of two types of anticoagulant therapy during primary angioplasty in patients with ST elevation MI, enoxaparin is superior to unfractionated heparin in the ability to reduce the risk of ischemic and hemorrhagic events.

The ISAR-REACT 3 study showed that intravenous administration of unfractionated heparin at a dose of 140 U/kg is accompanied by a greater number of bleedings compared with the use of the direct thrombin inhibitor bivalirudin during coronary artery stenting. The **ISAR-REACT 3A project (2010)** included

2505 patients without elevated levels of myocardial necrosis markers undergoing coronary angioplasty who were prescribed unfractionated heparin at a reduced dose (100 IU/kg). The results of treatment were compared with data obtained in ISAR-REACT 3 using a high dose of unfractionated heparin (n = 2281) or bivalirudin (n = 2289). Events related to the primary endpoint (death, MI, emergency target artery revascularization within 30 days, or major bleeding) were reported less frequently with the low dose of heparin compared with the high dose (7.3% vs. 8.7%, p = 0.045), as well as major bleeding (3.6% vs. 4.6%, p = 0.11), overall mortality was similar between the groups. The results of treatment with a low dose of heparin were no worse than with bivalirudin.
In fact, the dose of unfractionated heparin used in this study was not low since intravenous administration of this drug at a dose of 70–100 units/kg is currently recommended in addition to inhibitors of platelet glycoprotein IIb/IIIa receptors.

A new drug, an oral thrombin receptor antagonist on platelets (E5555, atopaxar), was studied in a randomized, double-blind, placebo-controlled, phase II J-**LANCELOT study (2010)** in Japanese patients. Patients with ACS (n = 241) or high-risk CAD (n = 263) received atopaxar at doses of 50, 100 or 200 mg/day or placebo. The sum of cases of any bleeding when taking atopaxar and placebo was comparable in patients with ACS (6.6% vs. 5.0%) and the same in patients with CAD (1.5% each). In direct proportion to the dose of atopaxar, the risk of bleeding, transient liver dysfunction, and prolongation of the QTc interval increased. A phase III study using the new drug atopaxar will clarify the feasibility of its use as an alternative to existing antiplatelet therapy.

The **RESET study (2011)** included 3197 CAD patients who were implanted with everolimus- eluting XIENCE V stents (n = 1597) or sirolimus- eluting SYPHER stents (n = 1600). The primary end point (re-revascularization of the target artery) was recorded in 4.3% and 5.0% of cases in the compared groups, respectively ($p < 0.0001$ to prove that the new XIENCE V stents are no worse than the old SYPHERs). In diabetic patients treated with insulin, the new stent model provided a reduction in the frequency of repeated revascularization of the target artery (p = 0.03). There were no significant differences in the frequency of deaths (p = 0.23) and MI (p = 0.42). Late stent thrombosis was rare in both groups. The patency of the vessels according to the results of repeated coronary angiography after 8–12 months did not differ significantly.

The **SYNTAX study database (2011)** analyzed a Japanese cohort of 2981 CAD patients with three-vessel coronary disease who underwent PCI (n = 1825) or coronary artery bypass grafting (n = 1156). The primary endpoint of death from any cause, MI, or stroke at 3 years of follow-up was more common in the PCI group (adjusted RR 1.47, p = 0.004), mainly due to increased risk of MI (RR 2.39, p = 0.004). The incidence of cardiac death was not significantly different (RR 1.30, p = 0.28), although the risk of death from any cause was significantly higher after PCI (RR 1.62, p = 0.005).

The **PRODIGY study (2011)** included patients with stable CAD or ACS with both non-elevation and ST-segment elevations. A total of 1970 patients were randomized 4 into groups in a 1:1:1:1 ratio for implantation of everolimus (XIENCE V), paclitaxel (TAXUS), zotarolimus (ENDEAVOR) or bare metal third-generation stents. The pooled rates of death, MI, and stroke (primary endpoint) were compared between 24-month (n = 987) and 6-month (n = 983) dual antiplatelet therapy with aspirin and clopidogrel. For 2 years, it was registered with a frequency of 10.1% and 10.0% (RR 0.98, p = 0.91) in the compared groups. There were no significant differences in the incidence of death, MI, acute cerebrovascular event or stent thrombosis between the two groups.
The frequency of bleeding was 2.17 times higher (p = 0.037) with longer dual antiplatelet therapy.

In the **EXAMINATION study (2011)**, 1498 patients with ST-segment elevation ACS during primary PCI were treated with second-generation everolimus drug-eluting stents (XIENCE V, n = 751) or bare metal stents (VISION, cobalt chromium, n = 747). The events included in the primary endpoint (death from any cause, MI, and repeat coronary revascularization) were avoided at 1 year of follow-up in 88% of patients with everolimus covered and 85.6% of patients with bare stents (p = 0.16). Repeated revascularization of the target artery was not required in 96.1% and 93% of cases, respectively (p = 0.007). Definite and definite/probable thrombosis of the XIENCE V stent occurred with a frequency of 0.5% and 0.9%, of an uncovered stent - 1.9% and 2.6% with a statistical significance of differences in favor of a new stent in both comparison cases (p = 0.01).

An observational prospective cohort study of 12,339 patients compared the thrombosis rates of three types of stents (2011): everolimus-eluting (n=4212), sirolimus-eluting (SYPHER, n=3819), or paclitaxel-eluting (TAXUS Express, n=4308). Stent thrombosis (primary endpoint) occurred in 1.4%, 2.9% (RR 0.41, p < 0.0001) and 4.4% (RR 0.33, p < 0.0001) of cases, respectively. The most recent thrombosis, in the period from 1 to 4 years, was observed with a frequency of 0.6%, 1.6% (RR 0.33, p = 0.006) and 2.4% (RR 0.24, p < 0 .0001) cases, respectively.

The largest randomized study **PROTECT (2012)** included patients with unstable angina, MI or stable CAD who were implanted with stents with zotarolimus (n = 4357) or sirolimus (n = 4352). Dual antiplatelet therapy was used at discharge in 97%, for 1 year in 88%, for 2 years in 37%, and for 3 years in 30% of patients. The primary endpoint (definite or probable stent thrombosis within 3 years) was recorded in 1.4% and 1.8% (p = 0.22), and death and major non-fatal MI were recorded in 5.3% and 6.0 % of cases in groups with stents with zotarolimus or sirolimus, respectively. In the first year, there was a trend towards a

decrease in the incidence of certain stent thrombosis (p = 0.06) in those who received a sirolimus-eluting stent.

According to the current recommendations, in the absence of cardiogenic shock, revascularization of only the artery causing the development of MI is indicated. In the **PRAMI randomized trial (2013)**, patients with ST-elevation MI underwent recommended and additionally preventive PCI on other stenotic arteries (n = 234) or only recommended PCI (n = 231). Work was stopped early at a mean follow-up of 23 months, when the primary endpoint (cardiac death, non-fatal MI, or refractory angina) was 65% less common in group 1 (RR 0.35, p < 0.001).

In **26 randomized trials of outcomes after coronary stenting (2013)**, in 43904 patients, the proportion of women was only 26.3% (n = 11557). Bare-metal stents were implanted in 9.6% of cases, processed early-generation stents in 36.1%, and new-generation stents in 54.3% of cases. Within 3 years, the incidence of death from any cause, MI or stent thrombosis was 10.7%, 8.5% and 7.6% (p < 0.001), target artery revascularization was 18.5%, 7.6% and 6 .0%, (p < 0.001), which indicates the efficacy and safety of new generation stents in women.

The **IABP-SHOCK II project (2013)** was a continuation of the follow-up of patients with MI who were randomized to receive (n = 301) or not (n = 299) intra-aortic balloon pumping for cardiogenic shock in addition to early revascularization and optimal medical therapy. Overall mortality (primary endpoint) in the counterpulsation and control groups at 12 months of follow-up was 52% and 51%, respectively (RR 1.01, p = 0.91). There were no significant differences in recurrent MI, revascularization or stroke, or quality of life between the two treatment options for cardiogenic shock.

Improvements in stent design that affect wall thickness, polymer surface, and drug release have led to improved clinical outcomes with drug-eluting stents. The **BIOSCIENCE study (2014)** compared the efficacy and safety of a new ultra-thin cobalt-chromium sirolimus-eluting sirolimus stent from a biodegradable polymer with a thin everolimus-eluting stent from a durable polymer in patients with stable CAD or ACS. In 1063 patients with sirolimus-eluting and 1056 patients with everolimus- eluting stents, the cumulative complication rates (cardiac death, MI in the target artery, revascularization - primary end point) at 12 months were 6.5% and 6.6% (p = 0, 0004 for no less efficiency), the incidence of stent thrombosis was 0.9% and 0.4% of cases (p = 0.16), respectively. There was a decrease in the number of primary endpoint events in patients with biodegradable stents in the subgroup of patients with ST elevation MI (3.3% vs. 8.7%; p = 0.024).

According to guidelines, primary PCI in patients with ST-elevation MI was limited to the infarct-associated artery. In the **CvLPRIT study (2014)**, such patients after randomization underwent revascularization of only the infarct-related (n = 146) or all arteries with hemodynamically significant stenoses (n = 150). At

12 months, the pooled rates of all-cause death, re-MI, heart failure, and revascularization for myocardial ischemia (primary endpoint) were significantly lower in the total revascularization group (10.0% vs. 21.2%; p = 0.009). There was also a trend towards a decrease in overall mortality (1.3% vs. 4.1%; p = 0.14), the frequency of recurrent MI (1.3% vs. 2.7%; p = 0.39), heart failure (2 .7% vs. 6.2%; p = 0.14), repeat PCI (4.7% vs. 8.2%; p = 0.20) without increased risk of stroke, bleeding, or contrast-induced nephropathy with total revascularization.

Patients with ST-segment elevation MI, which develops when an atherosclerotic plaque with a large necrotic core is destabilized, have a delay in arterial healing with worsening of long-term results of stenting. It is assumed that the use of bioresorbable stents contributes to better endothelialization and restoration of the vasomotor function of the artery in the long term. In the **ABSORB STEMI TROFI II study (2015)**, ST-elevation MI patients were randomized to primary PCI with implantation of everolimus-treated bioresorbable ABSORB stents (n = 95) or everolimus-eluting cobalt-chromium XIENCE stents (n = 96).
After 6 months, using OCT, the shortcomings of arterial repair in the stent area (presence of areas not covered by the endothelium, unopened areas, intraluminal filling defects) were assessed with the calculation of the integral index.
Six months later, the integral indicator of healing disorders in the stent area was lower in the ABSORB group 1.74 versus 2.80 in the XIENCE group (p < 0.001 for the conclusion “not worse”). The sum of adverse outcomes (cardiac death, MI, or the need for repeated revascularization in the area of the target artery) was 1.1% and 0.0% (p = not significant), definite subacute stent thrombosis was 1.1% and 0.0% of cases (p = not significant), 91.4% and 91.7% of patients (p = not significant) were angina-free in the ABSORB and XIENCE groups, respectively. Primary PCI on the artery causing ST-elevation MI using a bioresorbable stent results in almost complete healing of the arterial wall after 6 months, providing results no worse than after implantation of a metal drug-eluting stent.

The **ABSORB Japan study (2015)** included patients with stable and unstable angina pectoris, painless myocardial ischemia, who were randomized in a 2:1 ratio for implantation of everolimus-eluting bioresorbable ABSORB stents (n = 266) or everolimus-eluting XIENCE cobalt-chromium stents (n = 134). The methods for monitoring the state of the stent were coronary angiography, intravascular ultrasound, OCT, and CT.
During the follow-up period of 12 months, stent failure (cardiac death, MI or ischemia in the area of the target artery with the need for repeated revascularization) was observed in 4.2% and 3.8% of cases (p < 0.0001 for the conclusion "not worse"), defined / probable stent thrombosis — in 1.5% and 1.5% of patients (p = 1.0), identified restenosis — in 1.1% and 1.5% of patients (p = 1.0), narrowing of the lumen of the artery in in the target area according to angiography after 13 months was 0.13 ± 0.30 mm and 0.12 ± 0.32 mm (p < 0.0001

for the conclusion “not worse”) in the ABSORB and XIENCE groups, respectively.

The **NIPPON project (2016)** included 3775 patients with stable CAD or MI who underwent PCI with implantation of drug-eluting stents and a bioresorbable polymer. After the intervention, dual antiplatelet therapy was carried out for 18 (n = 1391) or 6 months (n = 1381) with registration of adverse clinical and cerebral events (death from any cause, MI with or without Q wave, cerebrovascular complications, major bleeding), the frequency of which was 1.45% versus 1.92% (p = 0.37), respectively.
When assessed separately, there were also no significant differences in the incidence of deaths (p = 0.48) and major bleeding (p = 0.54) in groups with different durations of dual antiplatelet therapy. According to the authors of the work, the use of new models of drug-eluting stents can reduce the risk of thrombosis and reduce the required duration of dual antiplatelet therapy, while simultaneously minimizing the incidence of stent thrombosis and hemorrhagic complications.

Monitoring of platelet function allows individualization of antiplatelet therapy to improve its risk-benefit ratio. The **ANTARCTIC study (2016)** included 877 patients aged 75 years and older who underwent emergency PCI for ACS. All patients received prasugrel at a dose of 5 mg/day and, after randomization, 442 patients continued this therapy, while in 435 patients it could be changed considering monitoring of platelet reactivity 14 days after randomization and 14 days after the first treatment adjustment. In the monitoring group, patients with platelet reactivity within the target levels continued to take prasugrel at 5 mg/day, with high platelet reactivity, its dose was increased to 10 mg/day, and with low reactivity, patients were transferred to clopidogrel at a dose of 75 mg/day.
The primary endpoint was a combination of cardiovascular death, MI, stroke, stent thrombosis, emergency revascularization, and BARC type 2, 3, or 5 hemorrhagic complication. During 12 months of follow-up, the listed complications were observed in 27.6% of patients in the monitoring group and in 27.8% of patients in the standard treatment group (RR 1.003; 95% CI 0.78 to 1.29; p = 0.98), and the frequency of bleeding did not differ (RR 1.04; p = 0.77). Control of platelet function with correction of antiplatelet therapy does not improve clinical outcomes in elderly patients undergoing PCI for ACS.

According to guidelines for myocardial revascularization, drug-eluting stents are preferred over bare-metal stents. In the **NORSTENT study (2016)**, patients with stable CAD (n = 2636) or ACS (n = 6377) were randomized to PCI with modern everolimus or zotarolimus-eluting stents (n = 4504) or bare metal stents (n = 4509). After a median follow-up of 6 years, the primary composite endpoint (death from any cause and non-fatal spontaneous MI) occurred at a rate of 16.6% in patients with drug-eluting stents and 17.1% in patients with bare-metal stents (RR 0.98 at 95% CI 0.88 to 1.09; p = 0.66) without significant differences between

groups in the frequency of components primary endpoint. At the same time, after implantation of drug-eluting stents, the frequency of repeated revascularization (RR 0.76; 95% CI 0.69 to 0.85; p < 0.001) and certain stent thrombosis (0.8% and 1.2% respectively, p = 0.0498). The Seattle Angina Questionnaire found no difference in physical limitation, angina incidence, or quality of life in the matched groups. The largest randomized trial in history of modern drug-eluting stents showed that, compared with bare-metal stents, they do not reduce the risk of death from any cause and non-fatal spontaneous MI, but reduce the frequency of revascularization and stent thrombosis.

The use of venous bypasses is often accompanied by restenosis and rapid atherosclerosis of the implanted vessels. The **BASKET-SAVAGE study (2016)** could answer the question about the preferred type of stent for failed vein grafts. After randomization, patients received Taxus Liberte drug-eluting stents (n = 84) or bare metal stents (n = 89). The primary composite endpoint (cardiac death, non-fatal MI, target vessel revascularization) was less common in the drug-eluting stents group, 2.3% vs. 17.9% (p<0.001) at 1 year and 12.4% vs. 29.8% of cases (p = 0.0012) after 3 years compared with the group using bare metal stents, respectively. The noted advantage was provided by a four-fold reduction in the frequency of target vessel revascularization after implantation of treated stents (4.5% vs. 19.1%; p < 0.001), while significant differences in the risk of death (4.5% vs. 95) or no non-fatal infarction were not observed (6.7% vs. 15.5%; p = 0.081).

In PCI in the area of bifurcation lesions of the coronary arteries, the optimal stenting technique remained the subject of discussion. The **BBK II study (2016)** compared the long-term results of Culotte technique drug-eluting stent implantation (n = 150) or T-stenting (n = 150) in patients with stable or unstable CAD with a bifurcation lesion requiring a lateral branch of a stent (n = 150). At 9 months after PCI, the maximum percentage of stenosis in the bifurcation lesion according to quantitative coronary angiography (primary endpoint) after stenting by the Culotte method was less than after T-stenting (21 ± 20% vs. 27 ± 25%; p = 0.038), mainly due to differences in the degree of stenosis of the lateral branch (16 ± 20% vs.
16 ± 25%; p = 0.029); frequency of binary restenosis — 6.5% versus 17% (p = 0.006); the need for repeated targeted revascularization of the bifurcation within a year of 1 year — 6.0% versus 12.0% (p = 0.069), respectively. The sum of long-term complications after PCI (cardiac death, MI in the target artery or its repeated revascularization) was 6.7% and 12.0% (p = 0.11) in the Culotte technique and T-stenting groups, respectively. In CAD patients with bifurcation lesions, Culotte stenting is associated with a significantly lower rate of angiographic restenosis compared to T-stenting.

The **ART study (2018)** included 3102 patients who were randomized to receive standard coronary artery bypass grafting using one artery and two veins (n

= 1554) or two internal mammary arteries and one vein (n = 1548). During the follow-up period, the primary end point of the study (10-year mortality) was observed in 329 cases of standard coronary artery bypass grafting and 315 in patients who were initially planned to use two arterial bypass grafts (RR 0.96; 95% CI 0.82 to 1, 12). There were no significant differences between groups in the overall incidence of severe cardiovascular events (death, MI, stroke) over 10 years. The results of the study were misrepresented by the fact that more than a third of patients underwent surgery opposite to that originally scheduled. The outcomes of coronary artery bypass surgery using two internal mammary arteries were also significantly influenced by the experience of surgeons - more experience was associated with a decrease in mortality.
According to the authors of the work, using two arteries is preferable in about 80% of cases. In patients with severe obesity, DM, this technique is associated with a high risk of infectious complications.

The safety and efficacy of angioplasty of coronary arteries with a diameter of less than 3 mm using balloons coated with the highly lipophilic drug paclitaxel was evaluated in the **BASKET-SMALL 2 study (2018)**. Patients with indications for PCI were randomized to angioplasty with a drug-eluting balloon (n = 382) or implantation of a second-generation drug-eluting stent (n = 376). Dual antiplatelet therapy was carried out in accordance with current recommendations. At 12 months after PCI, the primary endpoint (sum of major cardiac events—cardiac death, non-fatal MI, and target artery revascularization) was 7.5% in the treated balloon group and 7.3% in the drug-eluting stent group. (RR 0.97; 95% CI 0.58 to 1.64; p = 0.9180). Probable or definite stent thrombosis developed in 0.8% vs. 1.1% (HR 0.73; 95% CI 0.16 to 3.26), major bleeding in 1.1% vs. 2.4% of cases (RR 0.45; 95% CI 0.14 to 1.46) in the paclitaxel-coated balloon and drug-eluting stent groups, respectively. The results of the work showed that the use of a balloon coated with paclitaxel can be an alternative to implantation of a second-generation drug-eluting stent in the elimination of stenoses in small-diameter coronary arteries.

The hypothesis of the **VERDICT study (2018)** was that very early (up to 12 hours from onset of symptoms) invasive diagnosis and revascularization might be beneficial for patients with non-ST-segment elevation ACS.
Patients with clinical suspicion of ACS, ischemic changes on the ECG or elevated levels of myocardial necrosis biomarkers were prescribed dual antiplatelet therapy, fondaparinux and BB, after which patients were randomized to receive early (n = 1075) or standard (n = 1072) invasive therapy. In 32% of the examined patients, CAD was not detected. During a median follow-up of 4.3 years, the primary endpoint (all-cause death, recurrent MI, heart failure, or refractory ischemia) occurred in 27.5% of patients in the early group and 29.5% in the standard invasive treatment group. (RR 0.92; 95% CI 0.78 to 1.08; p = 0.29). In a pre-planned subanalysis, the subgroup of patients with a GRACE score >140 achieved a reduction in the sum of events in the primary endpoint (RR 0.81, 95% CI 0.67 to

1.00). Very early invasive diagnosis and treatment of all patients with non-ST-segment elevation ACS does not reduce the risk of death from any cause, non-fatal recurrence of MI, hospitalization for heart failure, or refractory myocardial ischemia, but seems reasonable in the subgroup of patients assessed by GRACE > 140.

In ST-elevation MI, PCI in the region of the artery that caused the development of this complication reduces the risk of cardiovascular death or recurrent MI. The **COMPLETE study (2019)** evaluated the hypothesis of an additional reduction in the risk of such events with simultaneous PCI in other stenosing coronary artery lesions.

The authors randomized patients with MI and multivessel CAD who successfully underwent PCI of the artery that caused the development of MI to complete revascularization with PCI of all angiographically significant lesions — at least 70% stenosis of the vessel diameter or 50-69% stenosis with a low fractional blood flow reserve (n = 2016), or refusal of complete revascularization (n = 2025). At a median follow-up of 3 years, adverse outcomes included in the primary composite endpoint (cardiovascular death, MI) were significantly less common in the total revascularization group compared with PCI of one artery (7.8% vs. 10.5 % of cases, respectively; RR 0.74; 95% CI 0.60 to 0.91; p = 0.004), as well as the sum of severe cardiovascular events - cardiovascular death, MI or ischemia-induced revascularization (8, 9% versus 16.7% of cases, respectively; RR 0.51; 95% CI 0.43 to 0.61; p < 0.001). Complete revascularization was beneficial whether performed during hospitalization or several weeks (up to 45 days) after discharge. That is, complications occurred after a considerable time and could be successfully prevented. There were no significant differences between groups regarding the safety of PCI procedures and other outcomes, including stroke, stent thrombosis, major bleeding, acute kidney injury, and severe CHF.

The present work is the first large, randomized study demonstrating a reduction in the risk of severe cardiovascular events with total coronary revascularization compared with PCI of only one artery, which caused the development of MI, in patients with ST-segment elevation MI associated with multivessel CAD. At the same time, the decrease in the frequency of events of the combined primary endpoint was due to a lower number of cases of MI without ST segment elevation, but not mortality from CVD. The study did not have the statistical power to obtain a difference in mortality. The COMPLETE project confirmed the value of total coronary revascularization already contained in current guidelines for the treatment of ST-segment elevation MI.

The SYNTAX trial compared the outcomes of PCI with first-generation Taxus paclitaxel-eluting stents versus coronary artery bypass grafting at up to 5 years of follow-up in patients with de novo 3-vessel disease or stenosis of the left main coronary artery. The **SYNTAX Extended Survival (SYNTAXES) project (2019)** assessed the impact of these two interventions on overall mortality at 10 years of intention-to-treat follow-up.

From 2005 to 2007, 1800 patients were randomized to PCI (n = 903) or bypass (n = 897). After 10 years, the primary endpoint (death from any cause) was recorded in 27% of patients after PCI and 24% after coronary artery bypass grafting (RR 1.17; 95% CI 0.97 to 1.41; p = 0.092). Among patients with 3-vessel disease, 28% versus 21% died (RR 1.41; 95% CI 1.10 to 1.80), and with stenosis of the left main coronary artery — 26% versus 28% after PCI and coronary artery bypass grafting (0.90 at 95% CI 0.68 to 1.20), respectively. The presence of DM did not significantly affect the results obtained. After 10 years, there is no significant difference in all-cause mortality after PCI with implantation of first-generation paclitaxel-eluting stents and coronary artery bypass grafting. At the same time, coronary artery bypass grafting provides a significant survival advantage in patients with 3-vessel disease, but not with stenosis of the left main coronary artery.

The **SWEDEHEART registry (2019)** assessed the effect of long-term use of secondary prevention after coronary artery bypass grafting (statins, BB, renin-angiotensin-aldosterone system blockers and antiplatelet agents) on mortality. The study included all patients who underwent coronary artery bypass surgery in Sweden from 2006 to 2015 and survived 6 months or more after discharge (n = 28,812). Statins 6 months after discharge received 93.9%, and after 8 years 77.3% of patients, BB - 91.0% and 76.4%, blockers of the renin-angiotensin-aldosterone system - 72.9% and 65.9 %, antiplatelet agents — 93.0% and 79.8% of patients, respectively. All these classes were less likely to be dispensed to patients aged 75 years and older. After adjusting for age, gender, comorbidities, and use of other secondary prevention agents, treatment with statins (RR 0.56; 95% CI 0.52 to 0.60), renin-angiotensin-aldosterone system blockers, was associated with a lower risk of mortality (RR 0.78, 95% CI 0.73 to 0.84) and antiplatelet agents (RR 0.74, 95% 0.69 to 0.81) ($p < 0.001$ for all comparisons). However, there was no association between BB use and risk of death (RR 0.97; 95% CI 0.90 to 1.06; p = 0.54).

The frequency of use of secondary prevention after coronary artery bypass grafting is high in the early stages after surgery but decreases significantly over time. Treatment with statins, renin-angiotensin-aldosterone system blockers, and antiplatelet agents is important after coronary artery bypass grafting, while the need for routine use of BB is questionable.

Angina may persist in about a third of patients despite successful myocardial revascularization with PCI and standard antianginal therapy. Trimetazidine is an antianginal agent that improves energy metabolism in ischemic myocardium, suggesting a positive effect on symptoms and outcomes in recent PCI patients.

The **ATPCI randomized, double-blind, placebo-controlled trial (2020)** included patients who underwent elective PCI for stable angina or urgent PCI for unstable angina or non-ST elevation MI less than 30 days prior to randomization. After randomization, patients received oral modified-release trimetazidine 35 mg twice daily (n = 2998) or placebo (n = 3009) in addition to standard therapy.

With a mean follow-up of 47.5 months, the rate of the composite primary efficacy endpoint (cardiac death; hospitalization for a cardiac complication; recurrence or persistence of angina pectoris requiring the addition, substitution, or dose increase of at least one antianginal drug; relapse or persistence of angina pectoris requiring coronary angiography) did not differ significantly between the trimetazidine and placebo groups (RR 0.98; 95% CI 0.88 to 1.09; p = 0.73). Individual analysis did not reveal significant differences in the frequency of primary endpoint components between matched groups. Similar results were obtained when dividing patients into categories of planned or urgent PCI. The frequency of adverse events in the trimetazidine and placebo groups was the same.
Routine oral trimetazidine 35 mg twice daily for several years in addition to optimal medical therapy is safe but does not improve outcomes or symptoms in patients after successful PCI for acute and chronic coronary syndromes.

In international multicenter randomised trial **ACST-2 (2021)** 3625 asymptomatic patients with severe carotid artery stenosis but no recent stroke or transient cerebral ischaemia were included, to compare long-term effects of either carotid artery stenting or carotid endarterectomy. Patients were randomly allocated, 1811 to carotid artery stenting and 1814 to carotid endarterectomy, with good compliance, good medical therapy, and a mean 5 years of follow-up. Overall, 1% had disabling stroke or death procedurally (15 allocated to carotid artery stenting and 18 to carotid endarterectomy) and 2% had non-disabling procedural stroke (48 allocated to carotid artery stenting and 29 to carotid endarterectomy). Kaplan-Meier estimates of 5-year non-procedural stroke were 2·5% in each group for fatal or disabling stroke, and 5·3% with carotid artery stenting versus 4·5% with carotid endarterectomy for any stroke (rate ratio [RR] 1·16, 95% CI 0·86-1·57; p=0·33). Combining RRs for any non-procedural stroke in all carotid artery stenting versus carotid endarterectomy trials, the RR was similar in symptomatic and asymptomatic patients (overall RR 1·11, 95% CI 0·91-1·32; p=0·21). Serious complications are similarly uncommon after competent carotid artery stenting and carotid endarterectomy, and the long-term effects of these two carotid artery procedures on fatal or disabling stroke are comparable.

In some randomized controlled trials for invasive treatment of CAD, transradial and transfemoral approaches were compared, with the former accompanied by lower mortality. The meta-analysis **The Radial Trialists' Collaboration (2022)** included pooled data from seven trials with a total of 21,600 patients, of which 10,775 were randomised to transradial approach and 10,825 were randomised to transfemoral approach. The median age of participants was 63.9 years, 31.9% were women, 95% presented with acute coronary syndrome, and 75.2% underwent PCI. The primary endpoint (mortality from all causes in 30 days) was recorded less frequently with transradial (1.6%) compared with transfemoral (2.1%) access (HR 0.77 at 95% CI from 0.63 to 0.95; p=0.012), less often with it there was also large bleeding within 30 days (1.5% against 2.7%; HR 0.55 at 95% CI from 0.45 to 0.67; p<0.001). The analysis of mortality in the subgroups showed

consistent results except for the baseline hemoglobin level, which indicates the superiority of transradial access in patients with significant anemia, but not with mild anemia or its absence. After adjustment, transradial access remained associated with a 24% reduction in the relative risk of all–cause mortality and a 51% reduction in major bleeding. In the invasive treatment of CAD, transradial access is associated with lower mortality from all causes and the frequency of large bleeding within 30 days compared with transfemoral access. The positive effect of transradial access on mortality can be traced in patients with anemia. Reducing the risk of major bleeding only partially explains the mortality decreasing.

ACUTE AND CHRONIC HEART FAILURE

The open non-randomized **STAR project (2010)** evaluated the immediate and long-term results of intracoronary stem cell transplantation in patients who underwent MI and coronary angioplasty with stenting. A total of 391 patients received medical therapy for an average of 8.5 years before inclusion in the study. In 191 cases, cell therapy was performed, 200 patients — control group, the average value of the LV EF and FC of CHF according to the classification of the NYHA was initially 29% and 36%, 3.22 and 3.06, respectively. A comprehensive examination, including assessment of hemodynamics using quantitative ventriculography, spiroergometry, Holter ECG monitoring, was performed after 3, 12 and 60 months. Almost all patients received standard therapy for CAD and CHF (aspirin, ACE inhibitors, BB, statins, diuretics, and in some cases digoxin). After 5 years, 184 patients survived in the stem cell group and 168 in the control group ($p < 0.01$), LV EF was 37% and 32%, respectively. Only in patients receiving cell therapy, CHF FC decreased, maximum oxygen consumption increased at rest and during exercise, and the volume of the LV cavity decreased. There were no side effects of the new treatment method.
It is likely that intracoronary administration of stem cells can prolong the life of patients with postinfarction LV dysfunction. However, confirmation of this position in large, double-blind, RCT is required. The mechanism of the positive effect of stem cells is not well understood and there are no convincing data on their transidentification into cardiomyocytes.

The development of hyperkalemia (5.5 mEq / l or more) is very likely in patients with CKD, when treated with aldosterone antagonists and ACE inhibitors, is associated with a worse prognosis. RLY5016, a non-absorbable polymer that binds potassium ions and is well tolerated, is currently being studied. The hypothesis of the **PEARL HF study (2010)** was the possibility of preventing hyperkalemia in patients with CHF and CKD receiving aldosterone antagonists by prescribing a new drug, RLY5016. The study included patients with plasma potassium levels of 4.3–5.1 meq/l, CKD (glomerular filtration rate less than 60 ml/min), in 73% of cases with diabetes, treated with ACE inhibitors or ARB, BB, with documented hyperkalemia in the last 6 months, forcing to interrupt the

prescribed therapy. Patients had CHF I or II FC according to the classification of the NYHA, the average value of the LV EF was 40 ± 12%. After randomization, 55 patients received RLY5016 at a dose of 30 g/day, 49 received placebo. In all cases, spironolactone was prescribed at a dose of 25 mg/day, which was increased to 50 mg/day at a plasma potassium level of not more than 5.1 meq/l. Before treatment, the level of potassium in the compared groups did not differ significantly, after 4 weeks of therapy it decreased by 0.22 meq/l when taking RLY5016 and increased by 0.23 meq/l when using placebo ($p < 0.001$). Hyperkalemia developed in 7% and 25% of the examined patients ($p = 0.015$), the dose of spironolactone could be increased to 50 mg/day in 91% and 74% of cases, respectively ($p = 0.019$). The frequency of side effects of RLY5016 and placebo was similar (7% vs. 6%).
RLY5016 can be used in combination with renin-angiotensin-aldosterone system blockers in patients with CHF and CKD who are at high risk of hyperkalemia. Of interest is a long-term study of a new drug in patients with more severe CHF with an assessment of its effect on mortality.

In the **EMPHASIS-HF study database (2011)**, the results of adding eplerenone (25–50 mg/day, n = 1360) or placebo (n = 1373) to the treatment of CHF were additionally analyzed in patients of 5 subgroups with the highest risk of complications. The primary endpoint is death from any cause or hospitalization for CHF. Among patients older than 75 years, it was recorded in 23.6% of those receiving eplerenone and 32.7% of placebo ($p < 0.004$), in patients with diabetes - 21.6% and 35.2% ($p < 0.0001$), in patients with a glomerular filtration rate less than 60 ml / min / 1.73 m2 - 24.4% and 34.5% ($p = 0.0001$), in those examined with an LV EF of less than 30% - 19.3% and 27.3 % ($p < 0.0001$), in patients with SBP less than 123 mm Hg. — 20.6% and 29.4% ($p < 0.0001$). In each of these subgroups, eplerenone significantly ($p < 0.05$) increased the incidence of hyperkalemia (greater than 5.5 mmol/L). However, there was no significant increase in the incidence of severe hyperkalemia (greater than 6.0 mmol/L), hyperkalemia leading to discontinuation of eplerenone, hospitalization for hyperkalemia, or deterioration of renal function.

Echocardiography at baseline and after 8 months of treatment was performed in 411 participants in the **SHIFT study (2011)**. The decrease in the LV end systolic volume index in the ivabradine and placebo groups was 7.0 and 0.9 ml/m2 ($p < 0.001$), the end diastolic volume index was 7.9 and 1.8 ml/m2 ($p = 0.002$), respectively, did not depend on the frequency of the use of BB, the etiology of CHF, the initial LV EF. The latter increased by 2.4% with ivabradine and decreased by 0.1% with placebo ($p<0.001$). The incidence of cardiovascular death and hospitalizations for CHF was higher among patients with an end-systolic LV volume index of more than 59 ml/m2 at baseline ($p = 0.04$). Patients with the greatest decrease in LV end-systolic volume index had the lowest number of adverse outcomes. Thus, ivabradine reverses LV remodeling in patients with LV systolic dysfunction.

The **European CRT survey (2011)** included 2438 patients with CHF from 13 European countries who underwent resynchronization therapy. During the year, 81% of patients reported improvement, 4% worsening, and 16% no improvement. Mortality during this time was 9.8% and its predictors were more severe CHF and its ischemic etiology, AF. Better survival was observed in women and in patients who were implanted with devices for resynchronization therapy with defibrillator function.

The angiotensin receptor and neutral endopeptidase inhibitor neprilysin LCZ696 affects the natriuretic peptide system. The **PARAMOUNT study (2012)** included patients with symptoms of CHF II-IV FC according to the classification of the NYHA and an LV EF of 45% or more against the background of standard therapy, in whom, after randomization, LCZ696 was titrated to 200 mg 2 times a day (n = 149) or valsartan - up to 160 mg 2 times a day (n = 152). The new drug provided a significant decrease in the level of NT-proBNP after 12 weeks (605 pg / ml versus 835 mg / ml in those treated with valsartan, p = 0.005), but not after 36 weeks of therapy (p = 0.20), reduced the volume of the left atrium, FC CHF, according to the classification of the NYHA, was well tolerated by patients.

Stimulation of aldosterone receptors leads to hypertrophy, fibrosis and diastolic dysfunction of the myocardium, increased stiffness of the vascular wall. **Aldo-DHF (2012)**, the first major study of an aldosterone antagonist in diastolic CHF, included patients with NYHA FC II/III symptoms and an LV EF of 50% or more. After randomization, spironolactone at a dose of 25 mg/day (n = 213) or placebo (n = 209) was added to standard CHF therapy. After 12 months, in the aldosterone antagonist treatment group, diastolic dysfunction, LV hypertrophy and remodeling significantly decreased, blood pressure and NT-proBNP levels in blood plasma decreased, but the maximum oxygen consumption, quality of life and CHF FC according to NYHA did not change. Serious side effects and deaths were not recorded.

A sub-analysis of the results of the **SHIFT study (2012)** included 1186 patients with moderate or severe CHF and LV systolic dysfunction who were hospitalized for decompensation on the background of standard therapy supplemented with ivabradine or placebo. Among them, 472 patients were hospitalized at least 2, and 218 - 3 times or more. Ivabradine was associated with a 25% reduction in the number of hospitalizations for CHF (p = 0.0002) during an average of 22.9 months of follow-up. At the same time, ivabradine reduced the risk of a second or third hospitalization with decompensated CHF by 34% (p < 0.001) and 29% (p = 0.012), respectively, and reduced the frequency of hospitalization for any reason and for all CVDs. This action of ivabradine against the background of the recommended CHF therapy improves the quality of life of patients and significantly reduces the costs of healthcare systems.

Follow-up of 419 participants in the **REVERSE study (2012)** who suffered from CHF I/II FC according to the classification of the NYHA, with a QRS duration of 120 ms or more and an LV EF of 40% or less, continued up to 5 years. In addition to optimal drug therapy, patients received resynchronization therapy in the pacemaker/defibrillator mode. After 3, 4 and 5 years, 95%, 89% and 86% of patients survived. The total number of deaths and hospitalizations for CHF over an average of 54.8 ± 13.0 months was only 28.1%, which confirms the advisability of a wider use of resynchronization therapy in patients with mild CHF.

The **IN-TIME study (2013)** included patients with CHF II / III FC according to the classification of the NYHA, more often on the background of CAD (69%), with an LV EF ≤ 35%, who were implanted cardioverter-defibrillator (42% of cases) or device for resynchronization therapy with defibrillator function (58% of patients). Patients were randomized to wireless remote control (n = 333) or standard medical control (n = 331). Within 12 months, worsening of the Packer score (primary endpoint) was observed in 18.9% and 27.5% ($p < 0.05$), death in 3.4% and 8.7% ($p < 0.012$) cases, respectively. Patient-initiated wireless monitoring using implanted devices can improve the outcome of heart failure treatment, mainly due to the timely detection of cardiac arrhythmias.

Omecamtiv mecarbil, a selective myosin activator, was evaluated in hospitalized patients with acute heart failure in the **phase II ATOMIC-AHF study (2013)**. The drug was administered intravenously for 48 hours at doses that maintained its plasma concentration of 115 (n = 103), 230 (n = 99) or 310 ng / ml (n = 101), clinical effects were compared with placebo (n = 303). A significant decrease in the number of patients with weakening of dyspnea (primary endpoint) was provided only by the maximum dose of the drug (51% of cases vs. 37% in the placebo group, p = 0.03). Omecamtiv mecarbil increased cardiac output not by increasing systole, but by increasing its duration, decreased heart rate, did not affect blood pressure levels, and did not cause ventricular proarrhythmia. However, in the new drug group, MI was recorded in 2.3% of cases versus 1.0% in the placebo group.

The **EchoCRT study (2013)** included patients with CHF III/IV NYHA FC, LV EF ≤ 35%, QRS duration less than 130 ms, and echocardiographic evidence of LV mechanical desynchronization. All patients were implanted with cardioverter-defibrillators with the function of three-chamber electrical stimulation - resynchronization therapy (n = 404) or without it (n = 405). The study was terminated early at a mean follow-up of 19.4 months, when the primary endpoint (death from any cause or first hospitalization for worsening heart failure) was 28.7% versus 25.2% (p = 0.15), and overall mortality was 11.1% versus 6.4% (p = 0.02) in the resynchronization therapy and control groups, respectively. Therefore, resynchronization therapy is not indicated for QRS durations less than 130 ms.

As part of the **RAFT study (2013)**, the role of BB was evaluated in patients with CHF II/III FC according to the classification of the NYHA, LV EF ≤ 30% and a QRS duration of more than 120 ms with implanted cardioverter-defibrillators (with or without resynchronization therapy). When treated with any of the 3 BB - bisoprolol (n = 489), carvedilol (n = 629) or metoprolol (n = 356), the primary endpoint (death or hospitalization for heart failure) occurred significantly more often at a dose of the drug less than 50% from target. This relationship was more pronounced in patients who did not receive resynchronization therapy.

In the **RELAX-AHF study (2014)**, the recombinant human vasoactive peptide hormone serelaxin at a dose of 30 mg/kg per day (n = 581) compared with placebo (n = 580) reduced dyspnoea in patients with acute heart failure and overall mortality after 180 days (RR 0.63, p = 0.019). Subgroup analysis showed that the benefit of serelaxin was most pronounced in patients over the age of 75 years who were first hospitalized for heart failure, patients with AF, in the absence of lymphopenia, and in those who did not receive BB, ACE inhibitors, or aldosterone antagonists.

Analysis of the results of the **ASTRONAUT study (2013)** in patients with systolic CHF who additionally received aliskiren or placebo was carried out depending on the presence (n = 662) or absence of diabetes (n = 953). The risk of death from any cause within 12 months of aliskiren was reduced in non-diabetic patients (RR 0.69, 95% CI 0.50 to 0.94) but increased in diabetic patients (RR 1.64, 95% CI from 1.15 to 2.33).

Kidney function is often impaired in patients with CHF and its deterioration is associated with a poor prognosis. Using the database of the **SHIFT study (2013)**, an analysis was made of the effect of ivabradine on renal function. Ivabradine did not reduce the glomerular filtration rate, did not increase plasma creatinine levels, that is, did not worsen kidney function in patients with systolic CHF, and improved the prognosis of patients, regardless of the initial presence of kidney dysfunction.

ACE inhibitors remained the main treatment for CHF with reduced LV EF for almost 3 decades, and enalapril has been shown to reduce the risk of death in these patients. Neprilysin is a neutral endopeptidase that degrades endogenous vasoactive substances (natriuretic peptides, bradykinin and adrenomedullin). Inhibition of neprilysin increases the levels of these substances, which counteracts the excess neurohormonal activation responsible for vasoconstriction, sodium retention, and maladaptive remodeling. The **PARADIGM-HF project (2014)** involved patients with CHF of any FC, mostly, II/III FC according to the classification of the NYHA, with an LV EF of 40% or less, who, against the background of the recommended therapy, were randomized for additional administration of experimental drug LCZ696 (a combination of valsartan and the neprilysin inhibitor sacubitril) 200 mg 2 times a day (n = 4187) or enalapril 10 mg

2 times a day (n = 4212). The study was terminated early at a median follow-up of 27 months due to the clear benefit of LCZ696. The primary endpoint (cardiovascular death or hospitalization due to CHF) was recorded 20% ($p < 0.0000002$) less often, death from a cardiovascular cause was also 20% ($p = 0.00004$), hospitalization due to CHF - by 21% ($p < 0.001$), and mortality from any cause - by 16% ($p < 0.001$) less often in the LCZ696 treatment group. Treatment with LCZ696, compared with enalapril, was more commonly associated with hypotension and mild angioedema, but less frequently with renal failure, hyperkalemia, and cough. The superiority of LCZ696 over enalapril in reducing the risk of death and hospitalization for CHF suggests that the new drug can replace ACE inhibitors and ARB in the treatment of CHF.

It is assumed that under sympathetic hyperactivation, characteristic of CHF, an increase in vagal influences on the heart can equalize neurohumoral imbalance and reduce the progress of the disease. The first randomized trial to evaluate this idea, **NECTAR-HF (2014)**, involved 96 patients with symptomatic CHF who underwent electrical stimulation of the right vagus nerve in the neck (mean pulse amplitude 1.24 mA at the beginning and 1.42 mA after 3 months, frequency 20 Hz) or simulated stimulation. After 6 months, the decrease in LV end-systolic diameter (primary endpoint) was 0.04 ± 0.25 cm in the treatment group and 0.08 ± 0.32 cm in the control group ($p = 0.60$). Other echocardiographic parameters, maximum oxygen consumption during exercise, and the level of the N-terminal precursor of the brain natriuretic peptide also did not differ in the groups of real and imaginary vagal stimulation. There was a statistically significant improvement in the quality of life according to the MLHFQ ($p = 0.049$) and the physical component according to SF-36 ($p = 0.016$), FC of the NYHA ($p = 0.032$) in the therapy group. Unexpectedly, infectious complications occurred frequently (7.4% of cases). As a result, it was not possible to demonstrate a significant effect of right-sided electrical stimulation of the vagus on cardiac remodeling and exercise tolerance in patients with CHF symptoms.

Iron deficiency is detected in about half of patients with CHF, leading to a deterioration in their functional status, quality of life, and increased mortality. The **CONFIRM-HF study (2014)** included 304 patients with CHF symptoms and LV EF ≤ 45%, elevated natriuretic peptide levels, and iron deficiency (ferritin < 100 ng/mL or 100-300 ng/mL if transferrin saturation < 20 %). After randomization, in addition to the recommended therapy for CHF, in half of the cases, intravenous iron carboxymaltose was repeatedly used, in the other half - placebo, with monitoring the results of treatment for 52 weeks. Iron supplementation significantly (by 33 ± 11 m; $p = 0.002$) lengthened 6-minute walking distance at 24 weeks (primary endpoint) compared with placebo, improved NYHA FC of CHF, quality of life, reduced symptoms, reduced the risk of hospitalization for CHF by 61% ($p = 0.009$). The frequency of adverse events in the groups did not differ significantly. Intravenous iron preparation is not yet recommended for the CHF treatment, but it is advisable when iron deficiency is detected.

Mineralocorticoid receptor antagonists spironolactone and eplerenone reduce morbidity and mortality in patients with CHF, but their use is limited by the risk of hyperkalemia. The drug finerenone is superior to spironolactone in selectivity, and eplerenone in terms of affinity for mineralocorticoid receptors. The **ARTS-HF study (2015)** included 1055 patients with type 2 diabetes and/or CKD who were hospitalized due to worsening systolic heart failure. Patients were randomized to six treatment groups with eplerenone, titrated from 25 mg every other day to 50 mg/day, or five groups of titration finerenone dose. (2.5 to 20 mg/day, trying to avoid hyperkalemia). Reductions in N-terminal brain natriuretic peptide precursor levels of 30% or more from baseline over 90 days of treatment (primary endpoint) occurred with similar frequency in the eplerenone group and the finerenone dose groups. At the same time, finerenon therapy was accompanied by a significant decrease in the frequency of hospitalization due to a cardiovascular cause ($p = 0.0229$), death from any cause ($p = 0.0262$) and death from a cardiovascular complication ($p = 0.0108$). The greatest reduction in the sum of adverse cardiovascular events was achieved with an initial dose of finerenone 10 mg/day with a possible increase to 20 mg/day (RR 0.56; $p = 0.0157$). An increase in plasma potassium levels up to 5.6 mmol/L or more was recorded only at a dose of finerenone 15-20 mg / day, and when prescribing the drug at 2.5-15 mg / day, it turned out to be safer than eplerenone.

Deficiency of the enzyme calcium ATPase of the sarcoplasmic reticulum is associated with the progression of CHF, so it was assumed that the correction of this disorder by gene transfer could improve heart function. In the **CUPID 2 study (2015)**, after randomization, patients underwent percutaneous intracoronary gene delivery with viruses (n = 121) or placebo (n = 122). During an average of 17.5 months of follow-up in the active therapy group, compared with the control group, it was not possible to reduce the number of hospitalizations or outpatient treatment for worsening CHF (RR 0.93; $p = 0.81$), the number of complications such as death, transplant heart or implantation of a mechanical circulatory support device (RR 1.27; $p = 0.40$). No safety concerns for gene therapy have been identified. Among the reasons for its ineffectiveness may be considered inadequate selection of the calcium ATPase of the sarcoplasmic reticulum as a target of treatment, insufficient intensity, or an unsuccessful method of applying gene therapy.

Central sleep apnea is associated with a poor prognosis in patients with CHF. The **SERVE-HF study (2015)** included 1325 CHF patients with an LV EF of 45% or less, 15 or more apnea/hypopnea events per hour, predominantly of central origin. After randomization, in first group non-invasive adaptive servoventilation maintaining positive airway pressure was added to the recommended CHF therapy, the second group was limited to pharmacotherapy (control). During the 12-month follow-up, the composite primary endpoint event rate (death from any cause, heart transplantation, implantation of an assistive

device to support LV function, resuscitation from sudden cardiac arrest/corresponding discharge of an implanted defibrillator, or unplanned hospitalization due to worsening CHF) did not significantly differ between the adaptive servoventilation and control groups (54.1% and 50.8%, respectively; RR 1.13; 95% CI 0.97 to 1.31; p = 0.10). Surprisingly, the adaptive servoventilation group had higher all-cause mortality (RR 1.28; 95% CI 1.06 to 1.55; p = 0.01) and cardiovascular mortality (RR 1.34; 95% CI 1.09 to 1.65; p = 0.006). In addition, patients in the adaptive servoventilation group showed no improvement in quality of life, distance in the 6-minute walk test, and a decrease in the severity of CHF symptoms. As a possible reason for the deterioration of the prognosis when using adaptive servoventilation, a violation of adaptive mechanisms in patients with systolic CHF can be considered.

In 271 patients with systolic CHF participating in the **CHART-1 study (2016)**, endomyocardial injections of autologous bone marrow stem cells were performed for the purpose of heart repair (n = 120) or imitation of this procedure (n = 151). At 39 weeks, all components of the primary endpoint (death from any cause, worsening CHF, MLHFQ total score, 6-minute walk distance, LV end-systolic volume, and LV EF) tended to improve, but even when they were summed, the difference did not reach statistical significance (RR 0.54; 95% CI 0.47 to 0.61; p = 0.27). Meanwhile, in the active therapy group, there was a decrease in the rate of sudden cardiac death/successful resuscitation (RR 0.16; p = 0.04). An additional analysis showed a significant decrease in the frequency of the primary end point (p = 0.015) with stem cell therapy in patients with an initial end-diastolic volume of the left ventricle of 200-370 ml (60% of the project participants) and who received less than 19 injections into the myocardium (p = 0.034), which should be considered in future research.

The study presented by **J. Butler (2016)** used mesenchymal stem cells (taken from healthy volunteers) which were grown under conditions of chronic hypoxia, which was supposed to improve their immunomodulatory properties. The authors of the work suggested the possibility of the anti-inflammatory action of stem cells, which can be realized without their intracardiac delivery. After randomization, 20 patients with non-ischemic systolic HF received a single intravenous injection of 1.5 million stem cells (n = 10) or placebo (n = 12). At 90 days after stem cell administration, there were no significant differences in hospitalization rates and adverse outcomes between the two groups. Cell therapy, compared with placebo, provided a statistically significant increase in distance on the 6-minute walk test (p = 0.02) and improved overall clinical status in the KCCQ score (p = 0.02), combined with a trend towards decrease in the volume of the left ventricle.

The **MARINER randomized, double-blind study (2018)** included 12,019 patients who were hospitalized for 3–10 days for heart failure with LV EF ≤ 45%, acute respiratory failure or exacerbation of chronic obstructive pulmonary disease,

acute ischemic stroke, acute infectious or inflammatory, including rheumatological disease, who had an increased risk of developing venous thromboembolism as assessed by IMPROVE (≥ 4 points or 2–3 points plus plasma D-dimer level more than twice the upper limit of normal according to the criteria local lab). At discharge, patients were randomized to receive rivaroxaban (n = 6007) or placebo (n = 6012) for 45 days. Rivaroxaban was administered at a dose of 10 mg (for creatinine clearance ≥ 50 ml/min) or 7.5 mg (for creatinine clearance ≥ 30 but < 50 ml/min) once daily. The primary efficacy endpoint of any symptomatic venous thromboembolism (deep vein thrombosis, pulmonary embolism, death from venous thromboembolism) occurred in 0.83% of patients in the rivaroxaban group and 1.10% in the placebo group (RR 0.76 at 95% CI from 0.52 to 1.09; p = 0.14), and symptomatic non-fatal deep vein thrombosis and non-fatal pulmonary embolism - in 0.18% and 0.42% (RR 0.44 at 95% CI from 0.22 to 0.89; p = 0.023) of patients, respectively. Separate evaluation of results according to baseline renal function showed equal efficacy of low dose anticoagulant (7.5 mg/day) and placebo (p = 0.994). Major bleeding occurred in 0.28% of patients treated with rivaroxaban and 0.15% with placebo (RR 1.88; 95% CI 0.84 to 4.23; P = 0.124), minor clinically significant bleeding also occurred more frequently. when treated with rivaroxaban (1.42% vs. 0.85%, RR 1.66; 95% CI 1.17 to 2.35; p = 0.004). The use of rivaroxaban in severely ill patients within 45 days of hospital discharge is not associated with a significant reduction in the risk of symptomatic and fatal venous thromboembolism compared with placebo.

The **MITRA.fr study (2018)** evaluated the hypothesis of a possible improvement in clinical outcomes in CHF with reduced LV EF of severe secondary mitral regurgitation because of percutaneous mitral valve clipping. Patients with severe secondary mitral regurgitation (regurgitation orifice area > 20 mm2 or regurgitation volume > 30 ml per beat), LV EF 15–40%, and symptoms of heart failure were randomized to percutaneous mitral valve clipping in addition to medical therapy (group intervention, n = 152) or drug treatment alone (control group, n = 152 patients). At 12 months of follow-up, the rates of the primary endpoint (death from any cause or unplanned hospitalization due to heart failure) were 54.6% and 51.3% (RR 1.16; 95% CI 0.73 to 1.84; p = 0.53), death from any cause — 24.3% and 22.4% (RR 1.11, 95% CI 0.69 to 1.77), unplanned hospitalization due to heart failure — 48, 7% and 47.4% (RR 1.13; 95% CI 0.81 to 1.56) in the intervention and control groups, respectively. Despite the neutral results of the work, it should be mentioned that later in the COAPT study in patients with even more severe secondary mitral regurgitation, it was possible to significantly reduce the incidence of hospitalization for heart failure and mortality of patients using percutaneous mitral valve clipping.

The angiotensin receptor and neprilysin inhibitor sacubitril/valsartan reduced the risk of hospitalization for CHF or death from cardiovascular causes in patients with CHF and reduced LV EF more than enalapril. The randomized **PARAGON-HF (2019)** trial compared the efficacy and safety of sacubitril/valsartan (target

dose 97/103 mg 2 times a day) and valsartan (target dose 160 mg 2 times a day) in 4822 patients with CHF II–IV FC according to the classification of the NYHA and the LV EF of 45%. At a median follow-up of 35 months, the combined primary endpoint (hospitalization for CHF or death from cardiovascular causes) was recorded at comparable rates in the sacubitril/valsartan and valsartan groups (RR 0.87; 95% CI 0.75 to 1 .01; p = 0.059), the frequency of its components did not differ: death from cardiovascular causes (RR 0.95 at 95% CI from 0.79 to 1.16) and hospitalization for CHF (RR 0.85 at 95% CI 0.72 to 1.00). Sacubitril/valsartan was more effective than valsartan in reducing CHF FC and improving quality of life after 8 months (KCCQ was used), worsening kidney function less frequently (RR 0.50, 95% CI 0.33 to 0.77). In the sacubitril/valsartan group, hypotension (15.8% versus 10.8% in the valsartan group) and angioedema (0.6% versus 0.2%, respectively) developed more frequently, and hyperkalemia was less common (13.2% versus 15. 3% respectively). A pre-planned analysis showed a significant superiority of sacubitril/valsartan in patients with lower EF (57% or less) and in women. Sacubitril/valsartan does not significantly reduce the total number of hospitalizations for CHF and death from cardiovascular causes among patients with CHF and an LV EF of 45% or higher. However, data have emerged on the benefits of its use in CHF with an EF of 45-57%, especially in women.

The **GALACTIC study (2019)** tested the hypothesis that in patients with acute heart failure, early, more intensive and long-term use of a complex of vasodilators, including renin-angiotensin system blockers, can improve outcomes compared with standard therapy by reducing pulmonary congestion and increased organ perfusion. Patients admitted to the emergency department with acute heart failure, symptoms of CHF III/IV FC according to the classification of the NYHA with elevated levels of natriuretic peptides and SBP ≥ 100 mm Hg randomized to standard care as recommended (n = 402) or treatment according to an early individualized intensive protocol (n = 386). The latter included high doses of commonly available vasodilators—transdermal and sublingual nitrates starting on day 1, oral hydralazine for 48 hours to prevent nitrate tolerance, then rapidly increasing ARB or ACE inhibitors. Other methods of treatment (aldosterone antagonists, BB, loop diuretics) were chosen at the discretion of the doctor and in accordance with the recommendations in both groups. The rate of rehospitalization for acute heart failure or death at 180 days was comparable with intensive care and standard care (30.6% vs. 27.8%, respectively; adjusted RR 1.07, 95% CI 0.83 to 1.39; p = 0.592). Until the 6th day of treatment, both groups experienced a similar reduction in dyspnea. Adverse events were significantly more common with more intensive treatment (82% vs. 75% of cases with standard care), as well as headache (26% vs. 10%) and systolic arterial hypotension (8% vs. 2%, respectively).
In a broad population of patients with acute heart failure, early intensive and prolonged vasodilation with nitrates, hydralazine, an ACE inhibitor, ARB, or individually adjusted doses of sacubitril/valsartan did not reduce the risk of hospitalization with acute heart failure or death. Pulmonary congestion, although a sign of acute heart failure, is not an ideal treatment goal. Efforts should be made to

prevent heart failure, its early diagnosis and treatment in order to avoid progression to acute heart failure. Due to the exclusion from randomized trials of patients with significant renal insufficiency, it is difficult to formulate sound conclusions about the selection of optimal treatment for CHF for patients with renal dysfunction.

In patients with type 2 diabetes, inhibitors of the sodium-glucose cotransporter type 2 reduce the risk of first hospitalization for CHF, apparently through mechanisms independent of the hypoglycemic effect. The hypothesis of the **DAPA-HF study (2019)** was the possibility of effective treatment of CHF with reduced LV EF in patients with type 2 diabetes and without diabetes. After randomization, patients with NYHA class II, III, or IV CHF and an LV EF of 40% or less received dapagliflozin 10 mg once daily (n = 2373) or placebo (n = 2371) in addition to recommended therapy. After a median of 18.2 months of follow-up, the dapagliflozin group experienced a significant reduction in the overall incidence of events that constituted the primary endpoint — hospitalization with CHF or urgent use of intravenous therapy for CHF, cardiovascular death (16.3% vs. 21.2% in the placebo group). RR 0.74, 95% CI 0.65 to 0.85, $p < 0.001$).
In the dapagliflozin group, both components of the primary endpoint were less frequently recorded - the first worsening of CHF (10.0% vs. 13.7% in the placebo group; RR 0.70 at 95% CI from 0.59 to 0.83; $p = 0.00001$) and death from cardiovascular causes (9.6% vs. 11.5% in the placebo group; RR 0.82; 95% CI 0.69 to 0.98; $p = 0.03$), as well as death from any cause (11.6% vs 13.9%; RR 0.83; 95% CI 0.71 to 0.97; $p = 0.022$). There was a decrease in symptoms of CHF (KCCQ) with dapagliflozin therapy compared with placebo. Since these drugs have a different mechanism of action the benefits of dapagliflozin were observed regardless of the use of sacubitril/valsartan. The frequency of adverse outcomes in patients with type 2 DM and without DM was similar. The frequency of adverse events associated with a decrease in circulating blood volume, as well as kidney dysfunction, severe hypoglycemia, amputation, and bone fractures, did not differ between treatment groups.
Among patients with CHF and a reduced LV EF, the risk of worsening CHF or death from cardiovascular causes is reduced when dapagliflozin is added to therapy compared with placebo, regardless of the presence of type 2 diabetes. Dapagliflozin, already successfully used for the treatment of type 2 diabetes and the prevention of CHF, can also be used in systolic CHF even in patients without type 2 diabetes.

The **BB-meta-HF study (2019)** evaluated the effect of BB on outcomes in patients with CHF and reduced LV EF, as well as kidney dysfunction, using a pool of data from 10 double-blind, randomized controlled trials of BB compared with placebo (n = 16 740). Renal dysfunction was a key marker of mortality in patients with CHF, which increased by 12% with a decrease in the calculated glomerular filtration rate for every 10 ml/min ($p < 0.001$). In sinus rhythm, the favorable prognostic effect of BB (the absolute reduction in the risk of death from any cause was 4.7% per year) extended to patients with moderate renal insufficiency - the

estimated glomerular filtration rate was 30–44 ml/min or more (but not less than 30 ml /min). BB treatment did not worsen kidney function, including its initial decrease. Patients with systolic CHF and concomitant AF had no prognostic benefit from the use of BB at any level of glomerular filtration rate.
Beta-blockers reduce mortality in CHF patients with reduced LV EF and sinus rhythm, even with moderate renal dysfunction at baseline. BB do not impair renal function and their presence should not prevent the prescription of drugs of this class with proven efficacy in patients with systolic CHF.

Of interest is the ability of ICDs to reduce mortality in a cohort of patients with systolic CHF receiving modern treatment. The work included data on patients from the **Swedish Heart Failure Registry (2019)** who met the ESC criteria for primary prevention of sudden cardiac death with an ICD. The association between ICD use and 1-year and 5-year total and cardiovascular mortality was assessed using Cox regression models and in predefined subgroups. Of the 16,702 patients eligible for ICD implantation, only 1,599 (10%) received it. ICD use was associated with reduced risk of all-cause mortality at 1 year (RR 0.73, 95% CI 0.60 to 0.90) and 5 years (RR 0.88, 95% CI 0.78 to 0.99). Similar results were observed in all subgroups, including patients with and without CAD, men and women, aged less than 75 years and 75 years and older, in patients with earlier and later registration in the Swedish Heart Failure Registry, in patients receiving and not receiving receiving cardiac resynchronization therapy.
In the modern population of patients with CHF with reduced LV EF, ICD is not used enough for primary prevention, despite a significant reduction in immediate and long-term mortality from all causes. ICD shows similar efficacy in all major clinical and demographic subgroups. These results support more active use of ICDs in systolic CHF.

Type 2 sodium-glucose cotransporter inhibitors reduce the risk of hospitalization for decompensated CHF, regardless of the presence or absence of type 2 diabetes. The presence of such an action distinguishes them from other hypoglycemic agents and requires further study to establish the mechanisms of the observed positive effect.
The **EMPEROR-Reduced (2020)** double-blind study included patients with CHF II, III, or IV NYHA FC and an LV EF of 40% or less who were randomized to receive empagliflozin (10 mg once daily). day, n = 1863) or placebo (n = 1867) in addition to the recommended therapy. During a median follow-up of 16 months, events for the combined primary endpoint (cardiovascular death or hospitalization for worsening CHF) occurred in 19.4% of patients in the empagliflozin group and in 24.7% of patients in the placebo group (RR 0 .75 at 95% CI 0.65 to 0.86, $p < 0.001$). The effect of empagliflozin on the risk of the primary endpoint was independent of the presence (in 50% of patients) or absence (in 50% of patients) of type 2 diabetes. The total number of hospitalizations for decompensation of CHF was significantly less in the empagliflozin group than in the placebo group (RR 0.70; 95% CI 0.58 to 0.85; $p < 0.001$). The annual decrease in estimated

glomerular filtration rate in the empagliflozin group was lower than in the placebo group (-0.55 vs. -2.28 ml/min/1.73 m2 of body surface area; p < 0.001). Uncomplicated genital tract infections more frequently observed with empagliflozin (1.7%) compared with placebo (0.6%).
The risk of death from CVD in the empagliflozin group was not significantly reduced (RR 0.92, 95% CI 0.75 to 1.12), while in a similar DAPA-HF study it was significantly reduced with dapagliflozin (RR 0.82 at 95% CI from 0.69 to 0.98). Whether this difference is due to the characteristics of the SGLT2 inhibitor molecules, the greater severity of CHF in EMPERORReduced participants with the inability to improve their survival, or is an accident remains unclear.

Half of patients with CHF have preserved (50% or more) or intermediate (40–49%) LV EF, but specific treatments have not been developed for them that can improve outcomes. According to the PARAGON-HF study, sacubitril/valsartan may be beneficial in patients with CHF and preserved LV EF. In the prospective study **PARALLAX (2020)** with active control in parallel groups, 2572 patients with CHF II or III FC according to the classification of the NYHA, LV EF > 40% and evidence of its diastolic dysfunction according to echocardiography, increased levels of N-terminal brain natriuretic peptide precursor treated with optimized treatment for comorbidities. Patients were randomized in a 1:1 ratio to receive sacubitril/valsartan or an individually tailored treatment that included 3 options. Thus, patients already taking ACE inhibitors were randomized to treatment with sacubitril/valsartan or enalapril, those already receiving ARB were randomized to receive sacubitril/valsartan or valsartan, and patients not receiving renin-angiotensin system blockers were randomized to receive sacubitril/valsartan or placebo.
After 12 weeks, there was a significant decrease in the primary endpoint, the level of the N-terminal precursor of the brain natriuretic peptide (by 16.4%; p < 0.0001) in the sacubitril/valsartan group compared with individualized drug therapy. At the same time, there were no significant differences in the other primary endpoint - change in the average distance in the 6-minute walk test after 24 weeks (an increase of 9.7 m with sacubitril / valsartan and 12.2 m with individualized drug therapy; mean difference –2.5 m at 95% CI –8.5 to 3.5, p = 0.79). Quality of life (according to the KCCQ) at 24 weeks of follow-up improved in both groups without statistically significant differences. Treatment with sacubitril / valsartan, compared with individually selected therapy, reduces the level of a prognostic marker of CHF, the N-terminal precursor of brain natriuretic peptide, but does not improve the functional status and quality of life of patients with CHF and LV EF > 40%.

The **GUIDE-HF (2021)** study included 1022 patients with NYHA FC II-IV CHF with any LV EF and with pulmonary artery pressure monitor and had either a recent hospitalization for CHF or an elevated natriuretic peptide level. After randomization, patients were assigned to either haemodynamic-guided heart failure management based on pulmonary artery pressure or a usual care control group. The

primary endpoint was a composite of all-cause mortality and total heart failure events (heart failure hospitalizations and urgent heart failure hospital visits) at 12 months and was recorded with a comparable frequency in groups with and without hemodynamic control (RR 0.88, 95% CI from 0 .74 to 1.05; p=0.16). In the pre-COVID-19, there was a reduced risk of primary endpoint events in the pulmonary artery pressure control group (RR 0.81; 95% CI 0.66 to 1.00; p = 0.049), but during COVID-19 pandemic this difference almost disappeared (RR 1.11; 95% CI 0.80 to 1.55; p=0.53). The cumulative incidence of heart failure events was not reduced by haemodynamic-guided management (0·85, 0·70-1·03; p=0·096) in the overall study analysis, however, the results of the study were influenced by the COVID-19 pandemic, when the number of hospitalizations for CHF sharply decreased.

Sodium-glucose cotransporter 2 inhibitors reduce the risk of hospitalization for CHF in patients with reduced LV EF, but their effects in patients with CHF and preserved LV EF have not been studied before. In a double-blind study, **EMPEROR-Preserved (2021)** 5988 patients with NYHA FC II-IV CHF with an EF of >40% were randomly assigned to double-blind treatment with placebo or empagliflozin (10 mg once daily), in addition to usual therapy, for a median of 26 months. The primary endpoint (a combination of cardiovascular death or hospitalization for CHF) was recorded in 13.8% of patients in the empagliflozin group and in 17.1% in the placebo group (HR 0.79 at 95% CI from 0.69 to 0.90; p<0.001). This effect was mainly due to a decrease in the risk of hospitalization for CHF in the empagliflozin group (HR 0.73 at 95% CI from 0.61 to 0.88; p<0.001), was observed in patients with type 2 DM and without it. Uncomplicated infections of the genitals and urinary tract and arterial hypotension were more often observed in the empagliflozin group. Consequently, empagliflozin reduces the combined risk of cardiovascular death or hospitalization due to CHF in patients with CHF and preserved LV EF, regardless of the presence of DM.

In the combined analysis of the **EMPEROR-Reduced and EMPEROR-Preserved (2021)** studies (9718 patients; 4860 in the empagliflozin group and 4858 – placebo), patients were grouped based on LV ejection fraction: <25% (n=999), 25-34% (n=2230), 35-44% (n=1272), 45-54% (n=2260), 55-64% (n=2092) and ≥65% (n=865). The decrease in the risk of cardiovascular death and hospitalization for CHF under the action of empagliflozin gradually decreased with an increase in the EF from <25% to ≥65%. Empagliflozin mainly reduced the risk of hospitalization for CHF: with LV EF <25% (HR 0.73 at 95% CI from 0.55 to 0.96); 25-34% (HR 0.63 at 95% CI 0.50 to 0.78); 35-44% (HR 0.72 at 95% CI 0.52 to 0.98); 45-54% (HR 0.66 at 95% CI 0.50 to 0.86); 55-64% (HR 0.70 at 95% CI 0.53 to 0.92); but not ≥65% (HR 1.05 at 95% CI from 0.70 to 1.58). A similar effect of empagliflozin was observed in relation to the quality of life of patients according to the KCCQ. As a result, empagliflozin significantly affected the course of CHF in patients with an ejection fraction from <25% to <65%, but its effect was not observed with an ejection fraction ≥65%.

Acetazolamide is a carbonic anhydrase inhibitor, which inhibits sodium and bicarbonate ion resorption in the renal proximal tubule. **ADVOR** study **(2022)** included 519 patients with acute decompensated heart failure and signs of volume overload (edema, pleural effusion or ascites), levels of the N–terminal precursor of the cerebral natriuretic peptide greater than 1000 pg/ml or cerebral natriuretic the peptide is more than 250 pg/ml. Patient were randomized in 1:1 fashion to IV bolus of acetazolamide (500 mg daily, n = 259) or matching placebo (n = 260). Oral loop diuretics were given (with first dose of loop diuretics) each day intravenously at double the oral maintenance dose over split doses. The primary endpoint, the successful elimination of stagnation, defined as the absence of signs of volume overload and indications for increased diuretic therapy 3 days after randomization, was achieved in 42.2% of patients in the acetazolamide group and in 30.5% in the placebo group (HR 1.46 at 95% CI from 1.17 to 1.82; p<0.001). Death from any cause or repeated hospitalization for heart failure during 3 months of follow–up was observed in 29.7% of patients in the acetazolamide group and 27.8% in the placebo group (HR 1.07 at 95% CI from 0.78 to 1.48). Acetazolamide treatment was associated with higher cumulative diuresis and natriuresis. The frequency of deterioration of renal function, hypokalemia, hypotension was similar in the compared groups. More active diuretic therapy provided a reduction in the length of hospital stay (8.8 vs. 9.9 days; p=0.016). The addition of acetazolamide to the treatment with loop diuretics in patients with acute decompensated heart failure increases the frequency of successful elimination of congestion, which indicates the importance of early aggressive therapy providing natriuresis.

In the **REVIVED-BCIS2** study **(2022)**, 700 patients with LV dysfunction (ejection fraction of 35% or less) caused by coronary stenoses amenable to PCI and proven myocardial viability after randomization underwent PCI in addition to optimal drug therapy (PCI group), or only optimal drug therapy (optimal drug therapy group). On average, over 41 months of follow–up, events of the combined primary endpoint (death from any cause or hospitalization for heart failure) were recorded in 37.2% of patients in the PCI group and in 38.0% in the optimal drug therapy group (HR 0.99 at 95% CI from 0.78 to 1.27; p=0.96). After 6 and 12 months, there were no differences in the average value of the LV ejection fraction in the two groups. Quality of life indicators at 6 and 12 months were better in the PCI group, but this difference was lost after 24 months of follow-up. Among patients with severe ischemic systolic LV dysfunction who received optimal drug therapy, myocardial revascularization with PCI did not lead to a reduction in the risk of mortality from any cause or hospitalization for heart failure, as well as an increase in LV ejection fraction and quality of life.

DELIVER study (2022) included 6263 patients with chronic heart failure and LV EF >40%, comparing the effect of dapagliflozin 10 mg once daily, vs. placebo, in addition to standard of care. The primary endpoint is time-to-first cardiovascular death or worsening heart failure event (heart failure hospitalization

or urgent heart failure visit) and will be assessed in dual primary analyses - the full population and in those with LV EF <60%. On average, over 2.3 years of follow–up, events of the primary endpoint - unplanned hospitalization for heart failure or an urgent visit for medical help due to heart failure, or cardiovascular death were observed in 16.4% of patients in the dapagliflozin group and in 19.5% - in the placebo group (HR 0.82 at 95% DI from 0.73 to 0.92; p<0.001), including aggravation of heart failure – in 11.8% vs. 14.5% (HR 0.79 at 95% CI 0.69 to 0.91) and cardiovascular death - in 7.4% vs. 8.3% (HR 0.88 at 95% CI 0.74 to 1.05) patients, respectively. In the dapagliflozin group, the severity of symptoms was significantly lower than in the placebo group. The results were similar in patients with LV ejection fraction of 60% or more, as well as less than 60%, with and without DM. The frequency of adverse events in the compared groups did not differ. Dapagliflozin reduces the combined risk of worsening heart failure or mortality from cardiovascular diseases among patients with heart failure and moderately reduced or preserved LV EF.

There was a meta-analysis of data from the **DAPA-HF trial** (participant LV EF ≤40%), and **DELIVER** trial (participant LVEF >40%) **(2022)**, to assess the effects of randomized treatment on cause-specific mortality. The trials assigned patients with chronic HF, NYHA class II-IV symptoms, and elevated natriuretic peptides to treatment with dapagliflozin (10 mg, once daily) or placebo. The primary outcome for each study was a composite of worsening HF events (hospitalization or urgent heart failure visits) or CV death. The study included 11,007 participants with an average LV ejection fraction of 44%. Treatment with dapagliflozin was associated with lower rates of CV death (hazard ratio [HR], 0.86; 95% CI, 0.75-0.98; P = .02), principally due to lower rates of sudden death (HR, 0.84; 95% CI, 0.70-1.01; P = .07) and HF death (HR, 0.88; 95% CI, 0.70-1.11; P = .30), with little difference in rates of death from stroke or MI.

In a meta-analysis of patients with HF in the DAPA-HF and DELIVER randomized clinical trials, across the full spectrum of LVEF, dapagliflozin significantly reduced risks of CV death with contributions from lower rates of sudden death and death from progressive HF.

After a preliminary meta-analysis of the **DELIVER** and **EMPEROR-Preserved studies (2022)** in patients with CHF and a preserved or moderately reduced LV EF, further investigation included the results of treatment of CHF with a reduced LV EF (DAPA-HF and EMPEROR-Reduced), as well as those hospitalized with worsening heart failure, regardless of the LV EF (SOLOIST-WHF). Among 12,251 participants in the DELIVER and EMPEROR-Preserved studies, sodium-glucose cotransporter type 2 inhibitors reduced the total risk of death from cardiovascular diseases or first hospitalization for heart failure (HR 0.80 at 95% CI 0.73 to 0.87) with a simultaneous reduction in the risk of both components of this primary endpoint (cardiovascular death – HR 0.88 at 95% CI from 0.77 to 1.00; first hospitalization for heart failure – HR 0.74 at 95% CI from 0.67 to 0.83). The results of 5 studies (21,947 patients) showed that sodium-

glucose cotransporter type 2 inhibitors reduced the risk of cardiovascular death or hospitalization for heart failure (HR 0.77 at 95% CI 0.72 to 0.82), cardiovascular death (HR 0.87 at 95% CI 0.79 to 0.95), the first hospitalization for heart failure (HR 0.72 at 95% CI 0.67 to 0.78) and death from all causes (HR 0.92 at 95% CI 0.86 to 0.99). For each of the endpoints, the effects of sodium-glucose cotransporter type 2 inhibitors treatment were consistently observed both in studies of heart failure with a moderately reduced or preserved LV EF, and in all 5 studies selected for meta-analysis. The effect of treatment on the events of the primary endpoint was generally the same in all 14 subgroups studied. Sodium-glucose cotransporter type 2 inhibitors reduce the risk of cardiovascular death and hospitalization for heart failure in a wide range of patients with heart failure, supporting the role of these drugs as a basic therapy for heart failure, regardless of LV EF or treatment conditions.

VALVULAR HEART DISEASE

The follow-up of 1038 participants in the **SOURCE REGISTRY TAVI project (2010)**, in which transapical or transfemoral aortic valve bioprosthesis implantation was performed, was continued up to 1 year. Survival after the interventions did not differ significantly - 72.1% and 81.1%, respectively. The causes of death in 49.2% of cases were non-cardiac causes - respiratory, renal failure, cancer, stroke, diseases of the gastrointestinal tract.

The **EVOLUTION study (2010)** included 72 patients with dilated cardiomyopathy or CAD who had mitral regurgitation from 2+ to 4+. In 59 cases, patients were implanted with the MONARC system to correct this disorder. After 3 years, in 83% of cases there was a decrease in the FC of CHF according to the classification of the NYHA, in 64% of cases cardiovascular complications did not develop.

The European CRT survey (2011) included 2438 patients with CHF from 13 European countries who underwent resynchronization therapy. During the year, 81% of patients reported improvement, 4% worsening, and 16% no improvement. Mortality during this time was 9.8% and its predictors were more severe CHF and its ischemic etiology, AF. Better survival was observed in women and in patients who were implanted with devices for resynchronization therapy with defibrillator function.

The first results of the **German GARY registry (2012)** included in-hospital outcomes of operations for aortic valve stenosis in 13860 patients. In 6523 cases, valve replacement surgery was performed, in 3462 patients it was supplemented by coronary bypass grafting, and in 2694 and 1181 cases, respectively, transvascular or transapical catheter intervention on the aortic valve was performed. The average age of those who received traditional surgical treatment was 68.3 years, while those who underwent catheter intervention were 81.0 and 80.3 years, respectively. Hospital mortality in the group of surgical valve replacement, its combination with coronary artery bypass grafting, transvascular and transapical catheter intervention

was 2.1%, 4.5%, 5.1% and 7.7%, respectively, cerebrovascular complications in the hospital - 2.2% in surgical operations versus 3.7 and 3.5% in catheter interventions. Transfusion of more than 2 packs of red blood cells was required in 29.4% of patients after conventional surgery, 25.4% after transapical and only 11.5% after transfemoral catheter intervention. Meanwhile, the rate of new pacemaker implantation was 23.7% in the transfemoral group, 9.9% in the transapical group, and 4.6% in the conventional group.

The phase I study **ACCESS-EUROPE (2012)** prospectively followed up the results of using American MitraClip system in Europe in 567 patients in order to obtain evidence of its safety and effectiveness. At inclusion in the study, the mean age of patients was 74 years, 63% of them had CAD, 42% had moderate to severe CKD, 85% had CHF III/IV FC according to the classification of the NYHA, 98% had mitral regurgitation 3+ and more, 53% - LV EF less than 40%. A year later, 82% of patients survived, the proportion of patients with mitral regurgitation less than 2 + was 79%, surgical operation on the mitral valve was not required in 94% of cases, CHF I / II FC according to NYHA was in 72% of patients, and the distance of a 6-minute walk lengthened by an average of 60.5 m from the initial level. The MLHFQ showed a significant improvement in quality of life.

The EORP TCVT registry (2012) included 4571 patients (mean age 81.4 ± 7.1 years) who underwent transcatheter aortic valve implantation in 137 centers in 10 European countries in 2011-2012. Most often (74.2%), the transfemoral method of introducing an artificial valve was used, less often - transapical (16.4%) or another (9.4%), usually subclavian. Mortality was lower with transfemoral (5.9%, $p < 0.01$) than with transapical (12.8%) and other (9.7%) approaches. In-hospital mortality did not differ significantly between CoreValve (6.7%) or SapienXT (7.9%, $p = 0.15$), however, implantation of a permanent pacemaker was more often required in the first case (23.4% vs. 6.0%, $p < 0.01$). According to echocardiography, grade 2 aortic regurgitation was detected in 7.7%, grade 3 — in 1.3% of patients, more often after the use of the CoreValve valve ($p < 0.01$).

The FRANCE 2 registry (2012) included 3933 patients (mean age 82.8 ± 7 years) who underwent transcatheter implantation of SAPIEN (67%) or CoreValve (33%) artificial aortic valves in 34 French centers in 2010–2011. The transfemoral approach was used in 73%, the transapical approach was used in 18% of cases, and less commonly, other routes of prosthetic valve insertion were used. The procedure was successful in 97% of patients. Mortality at 30 days, 6 months, and 1 year was 9.5%, 18%, and 24.1%, respectively, independent of the valve model. However, the need for pacemaker implantation arose in 12% of cases after the introduction of the SAPIEN valve and 24% after the CoreValve.

Patients with Marfan syndrome have an increased risk of dangerous aortic dilation and dissection. In the open-label **COMPARE study (2013)**, after randomization for 3 years, losartan 100 mg/day (n = 116) or treatment without

losartan (n = 117) were used in operated and non-operated adult patients with Marfan syndrome. According to MRI during controlled therapy, the mean aortic root dilatation was 0.77 versus 1.35 mm (p = 0.014) in non-operated patients and 0.50 versus 1.01 mm (p = 0.033) in previously operated patients. However, the overall incidence of complications (aortic dissection, aortic surgery, cardiovascular death) did not differ significantly between the compared groups.

After cardiac surgery, pericardial effusion is detected in 50–85% of patients, and 1–2% develop pericardial tamponade. In the **POPE 2 randomized trial (2014)**, patients undergoing coronary artery bypass grafting, heart valve surgery, or aortic surgery received colchicine 1 mg/day (n = 98) or placebo (n = 99) for 14 days, evaluating the incidence of exudative pericarditis (primary endpoint) within 30 days. Colchicine, comparable to placebo, affected the severity of pleural effusion according to echocardiography (p = 0.23), the frequency of pericardial tamponade (p = 0.80) and the need for drainage of its cavity, that is, it did not have the desired therapeutic effect.

Postpericardiotomy syndrome, postoperative AF worsen morbidity rates and increase the cost of treating patients who have undergone coronary artery bypass grafting or heart valve surgery. These patients in sinus rhythm in the **COPPS-2 project (2014)** after randomization were assigned colchicine (n = 180) at 0.5 mg 2 times a day or 0.5 mg 1 time per day with a body weight < 70 kg for 48 -72 hours before surgery and within 1 month after surgery or placebo (n = 180). Postpericardiotomy syndrome (primary endpoint) was recorded in 19.4% of patients treated with colchicine and in 29.4% of placebo. However, the incidence of postoperative AF and significant pericardial effusion did not differ significantly between the compared groups. The observed gastrointestinal side effects of colchicine limit its potential benefits when used in cardiac surgery.

Slowing aortic dilatation in Marfan syndrome is an important treatment goal achieved with BB, ACE inhibitors, and ARB. The **AIMS study (2018)** included patients aged 6 to 40 years who received BB, provided they were well tolerated (more than half of the cases). Patients were randomized to receive irbesartan once a day at 150-300 mg depending on body weight (n = 104) or placebo (n = 88). On 5-year annual follow-up transthoracic echocardiography, the aorta continued to dilate in both groups, but the rate of dilation was slower in the irbesartan group compared with the placebo group (0.53 mm vs. 0.74 mm per year, respectively; p = 0.030). The frequency of adverse events, the need for surgical prosthetics of the aortic root in the compared groups did not differ significantly. Irbesartan was well tolerated even in childhood, which makes it possible to use it to delay the need for elective surgical intervention.

The **MITRA-FR study (2019)** included patients with mitral regurgitation and symptoms of CHF on the background of drug therapy, who were hospitalized at least once during the last 12 months. After randomization, percutaneous mitral

valve repair was performed using the MitraClip device (intervention group, n = 152) or medical treatment alone was continued (control group, n = 152). At 24 months, death from all causes or unplanned hospitalization for CHF (combined primary endpoint) was recorded in 63.8% of patients in the intervention group and 67.1% in the control group (RR 1.01; 95% CI of 0, 77 to 1.34). All-cause mortality was 34.9% versus 34.2% (RR 1.02, 95% CI 0.70 to 1.50), and unplanned hospitalization for CHF was 55.9% versus 61.8 % of cases in the intervention and control groups (RR 0.97; 95% CI 0.72 to 1.30), respectively.

In patients with severe secondary mitral regurgitation, percutaneous valve repair in addition to medical treatment does not significantly reduce the risk of death or hospitalization for CHF at 2 years compared with medical treatment alone. In contrast, a similar **COAPT study (2019)** showed a benefit of mitral valve repair with the MitraClip device in reducing the rate of hospitalization for CHF over 24 months. Patient mortality was significantly different in MITRA-FR and COAPT (34% and 46% over 2 years, respectively), which may be due to both the greater severity of cardiac pathology in COAPT participants and more intensive pharmacotherapy in MITRA-FR. It is believed that patients with severe secondary mitral regurgitation without excessive LV dilatation and persistent symptoms despite maximally tolerated medical therapy may benefit from MitraClip. The COAPT and MITRA-FR investigators plan to continue follow-up of patients up to 5 years.

The effect of antiplatelet monotherapy versus dual antiplatelet therapy on the risk of bleeding and thromboembolism after transcatheter aortic valve implantation in patients not eligible for long-term anticoagulant therapy has not been well studied. In the **POPular TAVI (2020)** controlled trial, patients with severe aortic stenosis who were undergoing transcatheter aortic valve implantation and were not eligible for long-term anticoagulation were randomized to receive aspirin 80–100 mg daily (n = 331) or aspirin 80 –100 mg daily and clopidogrel 75 mg daily for 3 months (n = 334).

Over a 12-month treatment period, one primary endpoint, all bleeding (including minor, major, and life-threatening or disabling bleeding), was reported less frequently in the aspirin group than in the aspirin plus clopidogrel group (RR 0.57; 95% CI of 0.42 to 0.77; p = 0.001), as well as the other primary endpoint, bleeding not associated with the transcatheter aortic valve implantation procedure (RR 0.61; 95% CI 0.44 to 0.83; p = 0.005) . The combination of events (cardiovascular death, non-procedure bleeding, stroke, or MI) was less common in aspirin-only users (RR 0.74; 95% CI 0.57 to 0.95; p < 0.001 for no less effective, p = 0.04 for superiority), and another combination of complications (death from cardiovascular causes, ischemic stroke or MI) with a comparable frequency (RR 0.98; 95% CI 0.62 to 1.55 ; p = 0.004 for non-inferiority, p = 0.93 for superiority) compared with those treated with aspirin and clopidogrel. During the study, 13.3% and 9.6% of patients in the mono- and dual antiplatelet therapy groups received oral anticoagulants, respectively.

Among patients undergoing transcatheter aortic valve implantation who did not have an indication for oral anticoagulation, the incidence of bleeding and the totality of bleeding or thromboembolic events at 1 year of treatment was significantly less with aspirin than with aspirin plus clopidogrel used for 3 months. In the authors' opinion, in patients after transcatheter aortic valve implantation who are not receiving oral anticoagulants and have not recently undergone coronary stenting, aspirin monotherapy should be used.

In the treatment of Marfan syndrome ARB and BB are widely used to try to reduce the rate of progressive aortic root enlargement characteristic of this condition, but their separate and joint effects are uncertain. The meta-analysis of **The Marfan Treatment Trialists' Collaboration (2022)** included 10 randomized comparisons of ARB with control or ARB with BAB in patients with Marfan syndrome who had not previously had surgery on the aorta (n=1442). The primary endpoint was the annual rate of change of body surface area-adjusted aortic root dimension Z score, measured at the Valsalva sinuses. With a median follow-up of 3 years, the appointment of ARB approximately halved the annual rate of change in the value of the aortic root Z-criterion (an average annual increase of 0.07 in the ARB group versus 0.13 in the control; p=0.012). A predetermined analysis in subgroups showed that the effects of ARB were especially significant in patients with pathogenic variants of fibrillin-1 compared with those without them, and there was no reason to assume that the effect of ARB varied depending on the use of BB (p=0.54 for heterogeneity). In three studies (n=766), suitable participants were compared with ARB. With a median follow-up of 3 years, the annual changes in the value of the aortic root Z-test were the same in the compared groups (0.08 in the ARB group compared to 0.11 in the BB group; p=0.48), while the difference in the annual change in the aortic root Z-test between the BB group and the control was 0.09 (p=0.042). In people with Marfan syndrome and without previous operations on the aorta, ARB reduce the rate of increase in the Z-criterion of the aortic root by about half, including among women who took it. The positive effects of BB and ARB are comparable, and the use of their combination would provide even greater reductions in the rate of aortic enlargement than either treatment alone, which, if maintained over a number of years, would be expected to lead to a delay in the need for aortic surgery.

ENDOCARDITIS AND PERICARDITIS

COPPS (2010) is the first randomized trial of colchicine in the prevention of postpericardiotomy syndrome, which occurs in 10–45% of patients after cardiac surgery. Of the 360 patients, 77% underwent coronary bypass surgery. Treatment with colchicine or placebo lasted 1 month and after 1-year postpericardiotomy syndrome occurred in 8.9% vs. 21.1% of patients, respectively ($p = 0.002$). Colchicine also reduced the overall rate of hospitalizations, cardiac tamponade, constrictive pericarditis, and recurrent disease ($p = 0.024$). The frequency of side effects, mainly gastrointestinal, did not differ significantly between colchicine and placebo (8.8% vs. 5.0%, $p = 0.213$).

The efficacy and safety of colchicine in the prevention of recurrent pericarditis has been proven in the **CORP study (2011).** A total of 120 patients were randomized to treatment with colchicine (1.0–2.0 mg in 2 divided doses on the first day, then 0.5–1.0 mg/day in 2 divided doses, $n = 60$) or placebo ($n = 60$) in within 6 months. During the follow-up period of 18 months, pericarditis recurrence was observed in 24% of cases in those who received colchicine and in 55% ($p < 0.001$) in those who did not receive colchicine. Symptoms of the disease in the first 72 hours of treatment persisted in 23.3% and 53.3% of patients, respectively. Treatment tolerance was similar between the colchicine and placebo groups.

Tuberculous pericarditis is associated with high morbidity and mortality, even with anti-tuberculosis therapy. The **IMPI study (2014)** assessed the effects of adjuvant 6-week prednisolone therapy (starting at 120 mg/day, tapered to 5 mg/day) and immunotherapy with Mycobacterium indicus pranii (5 injections over 3 months) using a 2 x 2-factor design in 1400 patients with tuberculous pericarditis. Two-thirds of the study participants had the human immunodeficiency virus. The primary endpoint (death, pericardial tamponade, or pericardial stenosing) was not significantly different between patients treated with prednisolone or placebo (23.8% vs. 24.5%; $P = 0.66$) and those treated with immunotherapy or placebo (25 .0% versus 24.3%, $p = 0.81$).
Prednisolone, compared with placebo, significantly reduced the incidence of constrictive pericarditis (4.4% vs. 7.8%; $p = 0.009$). Both prednisone and

immunotherapy significantly increased cancer incidence compared to placebo (1.8% vs. 0.6%; p = 0.03, and 1.8% vs. 0.5%; p = 0.03, respectively), which was explained by the influence of human immunodeficiency virus infection.

The **POET study (2018)** included clinically stable patients with infective endocarditis with mitral and/or aortic valve disease caused by streptococcus, Enterococcus faecalis, Staphylococcus aureus, or coagulase-negative staphylococci who received intravenous antibiotics for at least 10 days. Patients with signs of a stable condition (no fever, normal C-reactive protein, no abscess, or other reason for surgery on transesophageal echocardiography) were randomized to further IV therapy in the hospital (n = 199) with a median duration of 19 days (interquartile interval, 14–25) or oral antibiotics (n=201) in 80% of cases on an outpatient basis, with a median duration of 17 days (interquartile range 14 to 25). Patients treated with oral antibiotics on an outpatient basis were examined every 3–4 days to assess their condition and determine plasma drug levels. Between randomization and 6 months after completion of antibiotic therapy, the primary endpoint (all-cause death, unplanned cardiac surgery, embolic complication, or recurrence of bacteremia with the underlying pathogen) was observed in 12.1% of patients in the intravenous group, and in 9.0% of those in the oral therapy group (p = 0.40), which met the criteria for assessing “not worse”.
Switching to oral antibiotics in stable patients with infective endocarditis can significantly shorten hospital stay and reduce the risk of new nosocomial infections. Reproducing the results of POET in practice will require strict adherence to the criteria used in the study for selecting patients and monitoring them.

CARDIOMYOPATHIES

Chagas disease, common in South America, is caused by trypanosoma. In a prospective **BENEFIT study (2015)**, patients with diagnosed Chagas cardiomyopathy after randomization were prescribed benznidazole (n = 1431) or placebo (n = 1423) for up to 80 days, followed by an average follow-up period of 5.4 years. The composite primary endpoint (death, cardiac arrest resuscitation, sustained ventricular tachycardia, implantation of an electrocardiostimulator or defibrillator, heart transplantation, CHF, stroke, or other thromboembolic complications) was recorded in 27.5% of cases in the benznidazole group and in 29.1% in the placebo group (HR 0.93 at 95% CI from 0.81 to 1.07; p = 0.31). Initially, polymerase chain reaction confirmed the presence of Trypanosoma cruzi in blood samples in 60.5% of patients. By the end of treatment, a negative result of this test was observed in 66.2% of patients in the benznidazole group and 33.5% of the placebo group at the end of treatment, after 2 years — in 55.4% and 35.3% of cases, after 5 years or more — in 46.7% and 33.1% of cases, respectively ($p < 0.001$ for all comparisons). The effect of benznidazole treatment significantly depended on the geographical region. Meanwhile, elimination of Trypanosoma cruzi did not have a slowing effect on the progression and clinical outcomes of Chagas disease (p = 0.16 for interaction).

Excessive contractility of cardiomyocytes is a key pathophysiological mechanism for the development of hypertrophic cardiomyopathy and the main factor in dynamic obstruction of the LV outflow tract. Mavacamten is the first in its class small molecular weight selective allosteric inhibitor of cardiac myosin adenosine triphosphatase, which reduces the formation of cross bridges between actin and myosin.

The double-blind, placebo-controlled study **EXPLORER-HCM (2020)** included patients with hypertrophic cardiomyopathy, an LV outflow tract pressure gradient of 50 mmHg. or higher and CHF II or III NYHA FC who were randomized to receive mavacamten (starting at 5 mg) or placebo in addition to treatment with BB or calcium channel blockers. The primary endpoint was an increase in peak oxygen consumption of 1.5 ml/kg/minute or more with a decrease in the severity of CHF symptoms by at least one NYHA FC or an increase in peak oxygen consumption of

3.0 ml/kg/minute or more without degrading the NYHA FC. Secondary endpoints were changes in LV outflow tract pressure gradient after exercise, peak oxygen consumption, NYHA class, KCCQ total score, and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscale score.
Within 30 weeks, the mavacamten group (n = 123) compared with the placebo group (n = 128) significantly more often reached the primary endpoint (37% vs. 17% of cases; p = 0.0005), the pressure gradient in the efferent LV tract after exercise (–47 vs. –10 mmHg; p < 0.0001), peak oxygen consumption increased more (+ 1.4 vs.) and improved symptom scores on questionnaires (p < 0.0001). Significantly more patients in the mavacamten group (65% versus 31% in the placebo group) showed an improvement in CHF symptoms by at least one NYHA class (p < 0.00001). The safety and tolerability of mavacamten was similar to placebo.
The use of mavacamten opens the possibility of effective treatment of hypertrophic cardiomyopathy by influencing the pathophysiology of this disease.

NON-CARDIOVASCULAR COMORBIDITIES

Chronic kidney disease

Patients with CKD have a high risk of adverse renal outcomes and cardiovascular events, which indicates the relevance of finding means to prevent them.

The **DAPA-CKD study (2020)** included 4304 patients with CKD, 67.5% of them had type 2 diabetes, with an estimated glomerular filtration rate of 25-75 ml / min / 1.73 m², urinary albumin / creatinine ratio 200–5000 mg/g who are already receiving the maximum tolerated dose of an ACE inhibitor or ARB as background therapy. Patients were randomized to receive the sodium glucose cotransporter type 2 inhibitor dapagliflozin 10 mg once daily or placebo.

With a mean follow-up of 2.4 years, the event rate of the combined primary endpoint (impaired kidney function, defined as a persistent decrease in estimated glomerular filtration rate of ≥ 50% or development of end-stage kidney disease, death from kidney disease, or CVD) in the dapagliflozin group was 39% less than the placebo group (RR 0.61; 95% CI 0.51 to 0.72; p = 0.000000028) without regard to the presence or absence of DM (RR 0.64 and 0 .50 respectively, p = 0.24 for interaction). Dapagliflozin reduced the overall risk of worsening kidney function or death from renal failure (RR 0.56; 95% CI 0.45 to 0.68; P < 0.0001), the overall risk of hospitalization for heart failure, or death from CVD (RR 0.71; 95% CI 0.55 to 0.92; p = 0.0089) and all-cause mortality (RR 0.69; 95% CI 0.53 to 0.88; p = 0 .0035) compared with placebo. In the dapagliflozin and placebo groups, there was a similar proportion of patients who discontinued participation in the study due to an adverse event (5.5% and 5.7%, respectively) or experienced a serious adverse event (29.5% and 33.9%, respectively). Diabetic ketoacidosis developed only in the placebo group in two patients. Neither diabetic ketoacidosis nor severe hypoglycemia has been observed in patients without type 2 diabetes.

The ability of the sodium glucose cotransporter type 2 inhibitor dapagliflozin to significantly reduce, compared with placebo, the risk of renal failure, CVD death or hospitalization due to CHF decompensation, as well as all-cause mortality in patients with CKD, both type 2 diabetes and without it, allows us to consider this drug as a new effective treatment for this category of patients.

Chronic obstructive pulmonary disease

The impact of the presence of chronic obstructive pulmonary disease on the incidence of major diseases (2011) was estimated in 7.4 million people in Denmark. Patients with this pathology of the respiratory system more often developed MI (1.26 times), lung cancer (2.05 times), hip fracture (2.12 times), depression (1.74 times) and diabetes (1.21 times). However, these mean numbers varied significantly before and after the first hospitalization for chronic obstructive pulmonary disease. The authors of the study believe that genetic factors, lifestyle, and unfavorable environment may have a greater negative impact on the occurrence of socially significant diseases than chronic obstructive disease.
lung by itself.

Amyloidosis

THAOS (2012) is an international registry of cases of amyloidosis, initiated to study differences in the course of the disease, the geographical distribution of patient groups, and to evaluate the effectiveness and safety of treatment methods. As of June 2012, 1366 people from 19 countries, predominantly Portugal, USA, Italy, France, Brazil and Japan, were included in THAOS. The mutations of Val30Met (75%), byVal122Ile (4.4%) and Gln89Glu (2.1%) were most frequently detected in the examined patients. In symptomatic patients, the following phenotypes were noted - "mainly neurological" (49.7%), "mainly cardiac" (25.5%) and "mixed" (24.8%).
The cardiac phenotype had a heterogeneous genotype and included symmetric LV hypertrophy without its dilatation, but with a moderate decrease in EF, usually found in men over 60 years of age. Cardiac amyloidosis can mimic hypertrophic cardiomyopathy because it is accompanied by LV hypertrophy of unknown origin.

The **ATTR-ACT study (2018)** evaluated the efficacy and safety in transthyretin-associated cardiomyopathy of a new non-steroidal anti-inflammatory drug tafamidis, which can inhibit amyloidogenesis.
The work involved 441 patients with familial amyloidosis caused by the inheritance of a mutant gene, as well as with wild-type transthyretin amyloid cardiomyopathy and typical echocardiographic findings, detection of transthyretin amyloid during tissue biopsy, and the level of the N-terminal precursor of brain natriuretic peptide in plasma ≥ 600 pg/ml, distance in the test with a 6-minute walk > 100 m. After randomization in a ratio of 2:1:2, patients were prescribed tafamidis 80 mg 1 time per day, tafamidis 20 mg 1 time per day, or placebo for a period of 30 months. During follow-up, the pooled incidence of all-cause death and cardiovascular-related hospitalizations (primary endpoint) was significantly lower in 264 patients treated with tafamidis compared to 177 patients treated with placebo ($p < 0.001$). Tafamidis significantly reduced both overall mortality (29.5% vs. 42.9% placebo - RR 0.70, 95% CI 0.51 to 0.96; $p = 0.0259$) and hospital admissions for CVD (RR 0.68; 95% CI 0.56 to 0.81; $p < 0.0001$). Treatment with tafamidis slowed down the decrease in distance in the 6-minute walk test ($p < 0.001$) and the Kansas Cardiomyopathy QoL score ($p < 0.001$). The frequency and

types of side effects in the tafamidis and placebo groups did not differ significantly. The benefits of tafamidis did not depend on the etiology of amyloidosis (hereditary or wild type) and the dose of the drug (20 or 80 mg) but appeared only in the reversible stage of the disease with CHF FC I or II of NYHA.

Rheumatoid arthritis

The **SCOT study (2015)** included 7297 patients without CVD who received the selective cyclooxygenase-2 inhibitor celecoxib or non-selective non-steroidal anti-inflammatory drugs (diclofenac, ibuprofen) for the treatment of osteoarthritis or rheumatoid arthritis. The composite primary endpoint included hospitalization for non-fatal ACS with elevated levels of biomarkers of myocardial necrosis, non-fatal stroke, death from cardiovascular causes and was recorded over a median of 3.2 years in 1.8% and 2.2% of cases in groups treated with celecoxib or other non-steroidal anti-inflammatory drugs, respectively (RR 1.12; p = 0.50). Differences in the frequency of serious adverse reactions were also not significant (5.2% in the celecoxib group versus 5.8% in the group of other non-steroidal anti-inflammatory drugs). However, the total number of side effects was higher in those treated with celecoxib (22% vs 16.1% of cases; p < 0.001), and its withdrawal was also noted more often than other non-steroidal anti-inflammatory drugs (50.9% vs 30.2%; p < 0). ,0001). In general, in patients without serious CVD, the use of non-steroidal anti-inflammatory drugs was associated with a low risk of cardiovascular complications.

In the **PRECISION-ABPM project (2017)**, 444 patients with osteoarthritis (92%) or rheumatoid arthritis (8%) were treated double-blindly with the selective COX-2 inhibitor celecoxib 100–200 mg twice daily (n = 146) or non-selective ibuprofen 600-800 mg 3 times a day (n = 151), as well as naproxen 375-500 mg 2 times a day (n = 147). After 4 months of therapy, according to 24-hour outpatient monitoring, the average daily SBP decreased by 0.3 mm Hg. those taking celecoxib increased by 3.7 (p = 0.0009) and 1.6 mm Hg. in those receiving ibuprofen or naproxen, respectively. Among those surveyed with initially normal blood pressure, the development of arterial hypertension (mean daily SBP ≥ 130 and/or DBP ≥ 80 mm Hg) was observed in 23.2% of those receiving ibuprofen, 19.0% of naproxen and 10.3% of celecoxib (RR 0.39 vs ibuprofen; p = 0.004 and RR 0.49 vs naproxen; p = 0.03). Arthritis treatment with ibuprofen is associated with a significant increase in SBP and more frequent development of arterial hypertension compared with celecoxib therapy.

Obstructive sleep apnea syndrome

Obstructive sleep apnea, which affects 40–60% of patients with CVD, is associated with an increased risk of vascular complications. The ability to reduce this risk with continuous positive airway pressure (CPAP) therapy has not yet been proven. In the **SAVE randomized trial (2016)**, 2717 patients with moderate/severe obstructive sleep apnea but no significant daytime sleepiness and

CAD or cerebrovascular disease were treated as usual with or without CPAP (n = 1346) (n = 1341). In the CPAP group, the average duration per day was only 3.3 hours, but the average apnea-hypopnea index decreased from 29.0 to 3.7 events per hour. At a median follow-up, the primary composite endpoint (cardiovascular death, MI, stroke, hospitalization for unstable angina, heart failure, or transient ischemic attack) occurred in 17.0% of patients in the CPAP group and 15.4% % in the usual treatment group (RR 1.10; 95% CI 0.91 to 1.32; p = 0.34). There was no significant effect of CPAP therapy on any single complication as part of the primary endpoint. At the same time, CPAP therapy significantly reduced snoring, daytime sleepiness, the number of days of temporary disability, the risk of depression, and improved the quality of life of patients. According to the results of this study, CPAP therapy does not prevent cardiovascular complications in patients with moderate/severe obstructive sleep apnea and diagnosed CVD.

COVID-19

Since the beginning of the rapid worldwide spread of the SARSCoV-2, conflicting observational data have accumulated, forming points of view both about the dangers and about the benefits of inhibitors of the renin-angiotensin-aldosterone system during the COVID-19 pandemic. The arguments in the discussion were, on the one hand, the theoretical risk that ACE inhibitors and ARB can increase the expression on cell membranes of ACE 2, which the SARS-CoV-2 binds to, increasing its penetration into cells with worse outcomes; on the other hand, the possibility of reducing acute damage and inflammation of the lungs, mediated by angiotensin II, in the treatment of ACE inhibitors and ARB. Given the widespread use of ACE inhibitors and ARB in clinical practice, strong evidence is needed to rule out potential negative effects of their use in patients hospitalized with COVID-19.

The **BRACE CORONA study (2020)** is the first randomized trial conducted in 659 patients on chronic ACE inhibitors or ARB who were hospitalized with COVID-19 in 29 centers in Brazil. Patients who were hospitalized in the last 12 months due to CHF decompensation, who were taking more than three antihypertensive drugs or sacubitril/valsartan and were admitted with unstable hemodynamics, were not included in the study.
Patients were randomized to temporarily stop ACE inhibitor/ARB for 30 days or continue ACE inhibitor/ARB.

The primary endpoint (mean number of days patients were alive and out of the hospital during 30 days of follow-up) was similar in the ACE inhibitor/ARB treatment stop-and-go group, 21.9 ± 8.0 vs. 22.9 ± 7 .1, respectively (RR 0.95; 95% CI 0.90 to 1.01; p = 0.09), as well as the proportion of survivors and hospital discharges by day 30 (91.8% vs. 95.0%, respectively) and the death rate at 30 days was 2.7% versus 2.8%, respectively (RR 0.97, 95% CI 0.38 to 2.52).

The lack of evidence of clinical benefit from discontinuing regular ACE inhibitor/ARB treatment for 30 days in hospitalized patients with mild to moderate COVID-19 indicates that it is safe and reasonable to continue taking them when indicated.

The efficacy and safety of prophylactic full-dose anticoagulation and antiplatelet therapy in critically ill COVID-19 patients remain uncertain. Multicenter, 2×2 factorial, open-label, randomized-controlled trial **COVID-PACT (2022)** included patients with COVID-19, those were randomly assigned to a strategy of full-dose anticoagulation or standard-dose prophylactic anticoagulation. Absent an indication for antiplatelet therapy, patients were additionally randomly assigned to either clopidogrel or no antiplatelet therapy. The primary endpoint of efficacy (a combination of death associated with venous or arterial thrombosis, pulmonary embolism, clinically apparent deep vein thrombosis, type 1 MI, ischemic stroke, systemic embolism or acute limb ischemia, as well as clinically asymptomatic deep vein thrombosis before hospital discharge or 28 days) was observed less frequently in the full dose group anticoagulants compared to the standard dose – 9.9% vs. 15.2% of cases (HR 0.56 at 95% CI from 0.32 to 0.99; p= 0.046). The primary safety endpoint – fatal or life–threatening bleeding occurred in 2.1% of patients receiving the full dose and in 0.5% - the standard dose of anticoagulants (p=0.19); the secondary safety endpoint (moderate/severe bleeding) was observed in 7.9% and 0.5% of patients (p=0.002), respectively. There were no differences in mortality from all causes between the groups of full and standard doses of anticoagulants (HR 0.91 at 95% CI from 0.56 to 1.48; p=0.70). There were no differences in the primary efficacy or safety end points with clopidogrel versus no antiplatelet therapy. In critically ill patients with COVID-19, full-dose anticoagulation, but not clopidogrel, reduced thrombotic complications with an increase in bleeding, driven primarily by transfusions in hemodynamically stable patients, and no apparent excess in mortality. Recruitment was stopped early in March 2022 (≈50% planned recruitment) because of waning intensive care unit-level COVID-19 rates.

COVID-19 disease is accompanied by a dysregulated immune response and hypercoagulability. The randomised, controlled, open-label, 2 × 2 factorial inpatient **trial ACT (2022)**, included patients with symptomatic, laboratory confirmed COVID-19, who were randomly assigned (1:1) to receive colchicine 1.2 mg followed by 0.6 mg 2 h later and then 0.6 mg twice daily for 28 days versus usual care; and in a second (1:1) randomisation, to the combination of rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily for 28 days(n=1304) versus usual care (n=1307). For the second time, patients were randomized (1:1) to use antithrombotic therapy with a combination of rivaroxaban 2.5 mg 2 times a day and aspirin 100 mg 1 time a day for 28 days (n=1063) or routine management (n=1056). After 45 days of follow–up, events of the primary endpoint (the need for high-flow oxygen therapy, mechanical ventilation or death) were recorded in 28.2% of patients in the colchicine group versus 27.2% in the control group (HR

1.04 at 95% CI from 0.90 to 1.21; p=0.58), and the other primary endpoint (MI, stroke, acute limb ischemia or pulmonary embolism) – in 26.4% of patients in the rivaroxaban + aspirin group versus 28.4% in the control group (HR 0.92 at 95% CI from 0.78 to 1.09; p=0.32). The results obtained were confirmed by analysis in subgroups, did not depend on the status of vaccination, the initial severity of the disease and the period of randomization from the onset of symptoms. Adverse reactions, mostly gastrointestinal, led to discontinuation of the study drug, were observed in 0.61% of patients in the colchicine group. Bleeding was observed in 1.6% of patients in the rivaroxaban and aspirin combination group versus 0.66% in the control group (p=0.042), but the frequency of major bleeding did not differ significantly – 0.19% versus 0.57% of cases, respectively (p=0.18). In addition, no patients assigned to rivaroxaban and aspirin had serious adverse events that led to discontinuation of study drug. Among patients hospitalised with COVID-19, neither colchicine nor the combination of rivaroxaban and aspirin prevent disease progression or death.

The open controlled **study ACT (2022)** with factorial design 2×2 involved 3917 outpatient patients from 48 centers in 11 countries with symptoms of laboratory-confirmed COVID-19 with a high risk of disease progression, who were randomized (1:1) for anti-inflammatory therapy with colchicine 0.6 mg 2 times a day for up to 7 days from diagnosis for 3 days, and then 0.6 mg once a day for 25 days (n=1939) or usual treatment (n=1942); For the second time, patients were randomized (1:1) for the use of antithrombotic therapy with aspirin 100 mg once a day for 28 days (n=1945) or routine management (n=1936). After 45 days of follow–up, the events of the primary endpoint (hospitalization or death) occurred in 3.4% of patients in the colchicine group and in 3.3% in the control group (HR 1.02 at 95% CI 0.72 to 1.43; p=0.93), and the other primary endpoint (major thrombosis, hospitalization or death) – in 3.0% of patients from the aspirin group and in 3.8% of the control group (HR 0.80 at 95% CI from 0.57 to 1.13; p= 0.21). The results obtained were consistent in all predefined subgroups, including independent of the vaccination status, the timing of randomization from the onset of symptoms and the timing of registration in accordance with the phase of the pandemic. Serious side effects developed in 1.8% of patients in the colchicine group versus 1.4% in the control group and in 1.6% of patients in the aspirin group versus 1.6% in the control group, but none in either group that led to discontinuation of study interventions. The results provide no support for the use of colchicine or aspirin to prevent disease progression or death in outpatients with COVID-19.

Flu vaccine

Observational and small randomized studies show that the flu vaccine can reduce the frequency of future cardiovascular events in patients with CVD. The **IAMI study (2021)** compared the effect of an inactivated influenza vaccine (n=1290) with placebo (n=1281) administered shortly after MI (99.7% of patients)

or with stable high-risk CAD (0.3%). During 12 months of follow-up, the primary endpoint (a combination of death from all causes, MI or stent thrombosis) was observed in 5.3% of participants in the vaccine administration group and in 7.2% in the placebo group (HR 0.72 at 95% CI 0.52 to 0.99; p=0.040). The incidence of death from all causes was 2.9% and 4.9% (HR 0.59 at 95% CI from 0.39 to 0.89; p=0.010), cardiovascular death - 2.7% and 4.5% (HR 0.59 at 95% CI from 0.39 to 0.90; p=0.014), MI – 2.0% and 2.4% of cases (HR 0.86 at 95% CI 0.50 to 1.46, p=0.57) in the influenza vaccine and placebo groups, respectively. Vaccination against influenza early after MI or with high-risk CAD in the next 12 months reduces the risk of death from all causes and from CVD, MI and stent thrombosis compared with placebo.

Prostate cancer

In international, multicenter, prospective, randomized, open-label trial **PRONOUNCE (2021)**, 545 men with prostate cancer and concomitant atherosclerotic cardiovascular disease were randomly assigned 1:1 to receive the gonadotropin-releasing hormone antagonist degarelix or the gonadotropin-releasing hormone agonist leuprolide for 12 months. The median age was 73 years, 49.8% had localized prostate cancer; 26.3% had locally advanced disease, and 20.4% had metastatic disease. A major adverse cardiovascular event occurred in 15 (5.5%) patients assigned to degarelix and 11 (4.1%) patients assigned to leuprolide (hazard ratio, 1.28 [95% CI, 0.59-2.79]; *P*=0.53). The study was terminated prematurely because of the smaller than planned number of participants and events, and no difference in major adverse cardiovascular events at 1 year between patients assigned to degarelix or leuprolide was observed. The relative cardiovascular safety of GnRH antagonists and agonists remains unresolved.

When performing manual chest compressions, technique-impairing fatigue and defibrillation pauses can contribute to the failure of resuscitation efforts. In the **LINC study (2013)**, 2589 patients with out-of-hospital cardiac arrest were randomized to mechanical chest compressions and defibrillation without stopping compressions using a LUCAS device (n = 1300) or conventional cardiopulmonary resuscitation (n = 1289). The proportion of survivors after 4 hours was 23.6% and 23.7% (p = 1.00) with mechanical and manual resuscitation, survivors with a good neurological outcome at discharge from the hospital were 8.3% versus 7.8% (p = 0.61), after a month - 8.1% vs. 7.3% (p = 0.46), after 6 months - 8.5% vs. 7.6% (p = 0.43), respectively. Apparently, differences in survival and neurological outcome could not be obtained due to effective work during manual resuscitation.

The prospective controlled study **CAAM (2017)** included patients with sudden out-of-hospital cardiac arrest who, after randomization, underwent resuscitation with mechanical ventilation using a mask method (n = 1018) or using tracheal intubation (n = 1022). The primary endpoint (survival to 28 days with a good neurological outcome) was observed in 4.2% of cases with mask ventilation versus 4.3% (p = 0.11) of cases with tracheal intubation. Meanwhile, lung ventilation was ineffective in 6.3% of patients in the mask method and only in 2.5% of cases in the tracheal intubation group (p < 0.0001), and gastric regurgitation/aspiration occurred in 14.9% and 7 .7% (p < 0.0001) of cases, respectively. According to the authors of the work, despite the simplicity of mask ventilation, it should not be recommended as a standard method during cardiopulmonary resuscitation in out-of-hospital cardiac arrest.

Treatment of patients with pulmonary embolism and a low risk of adverse outcome is possible outside the hospital with an appropriate outpatient care, including anticoagulant therapy. To determine the safety of outpatient treatment of pulmonary embolism, experts from the ESC recommend using an assessment of the risk of death from all causes using a simplified PESI score, and experts from the American College of Cardiology do not recommend a predefined scoring

system and suggest using a list of pragmatic criteria - the HESTIA (Home Evaluation of Stroke Induced Aid Read) rule.
The **HOME-PE (2020)** controlled trial of 1974 patients with pulmonary embolism admitted to hospital within 24 hours of diagnosis compared two outpatient triage strategies with blinded endpoint evaluation. Patients were randomized to triage based on the HESTIA rule (contains 11 criteria, with 0 criteria the patient is eligible for treatment at home) or the PESI strategy (contains 6 criteria, with 0 points the patient is eligible for outpatient treatment). The study evaluated the assumption that the HESTIA-based strategy is no worse than the PESI-based strategy in terms of the risk of events of the combined primary endpoint (recurrent venous thromboembolism, major bleeding or death), which was demonstrated (3.8% of cases for the HESTIA group versus 3.6% for the PESI group, respectively; p = 0.005 for not worse). The HESTIA score was less likely to allow outpatient treatment for pulmonary embolism compared to the PESI score (39% vs. 48% of low-risk patients). In the HESTIA triage group, there were fewer deviations in early discharge from the attending physician compared to the PESI group (3% versus 29% of cases, respectively). As a result, similar proportions of patients in both groups (38% of the total HESTIA group and 37% of the PESI group) were discharged for outpatient treatment within 24 hours. According to the authors of the work, the triage strategy for patients with pulmonary embolism based on the HESTIA pragmatic rule is noninferior to the strategy based on the PESI risk assessment scale, and the choice of outpatient treatment can be safe in both cases, with the obligatory consideration of the opinion of the attending physician.

Antithrombotic therapy used to treat MI increases the risk of bleeding, anemia that occurs in 5–10% of patients and can lead to increased mortality. However, the optimal strategy for blood transfusion in these patients remains unclear. Blood transfusion is expensive, comes with side effects, and is logistically difficult. The **REALITY study (2020)** recruited 668 patients with acute MI and anemia (hemoglobin 7–10 g/dl) at any time during hospitalization in 35 hospitals in France and Spain. Patients were randomized to a restrictive or liberal transfusion strategy with a follow-up of 30 days. With a restrictive strategy, blood transfusion was stopped if the hemoglobin level did not fall to 8 g/dl. According to the liberal strategy, blood transfusion was performed as soon as the hemoglobin level decreased to 10 g/dl or less. The frequency of events of the combined primary endpoint (death from all causes, MI, stroke and emergency PCI due to myocardial ischemia) for 30 days was 11.0% in the restrictive group and 14.0% in the liberal strategy group — HR 0.79 (difference -3.0% at 95% CI from -8.4% to + 2.4%). With a restrictive blood transfusion strategy, compared with the liberal one, a smaller proportion of patients received donor red blood cells (35.7% vs. 86.7%, respectively; p < 0.0001), they had lower minimum hemoglobin levels during hospital stay (8.3 vs. 8.8 g/dl, respectively; p < 0.0001) and at discharge (9.7 vs. 11.1 g/dl, respectively; p < 0.0001). Cost-effectiveness analysis showed that the restrictive strategy reduced treatment costs by 84%. In patients included in the

group of restrictive hemotransfusion strategy, there was a decrease in the likelihood of infection (0.0% vs. 1.5%, respectively; p = 0.03) or acute lung injury (0.3% vs. 2.2%, respectively; p = 0.03) compared with patients from the liberal strategy group. The restrictive hemotransfusion strategy for anemia in patients with MI is no worse than the liberal one with respect to the 30-day frequency of severe ischemic complications and is more cost-effective compared to the liberal strategy.

The **BOX** study **(2022)** included with a 2-by-2 factorial design, randomly assigned comatose adults with out-of-hospital cardiac arrest in a 1:1 ratio to either a restrictive oxygen target of a partial pressure of arterial oxygen (Pao_2) of 9 to 10 kPa (68 to 75 mm Hg) or a liberal oxygen target of a Pao_2 of 13 to 14 kPa (98 to 105 mm Hg) and vasopressant/inotropic therapy to achieve an average blood pressure of 63 mmHg or with 77 mmHg. The primary endpoint – death from any cause or discharge from the hospital with severe disability/coma was observed in 32.0% versus 33.9% of patients in groups with a lower or higher target level of partial oxygen pressure in arterial blood (HR 0.95 at 95% CI from 0.75 to 1.21; p=0.69), as well as in 34% versus 32% of patients in groups with a lower or higher target level of mean blood pressure (HR 1.08 at 95% CI from 0.84 to 1.37; p=0.56), respectively. The compared variants of the intensity of oxygen therapy and the use of vasopressor/inotropic therapy did not reveal significant differences in outcomes (death from any cause or discharge from hospital with severe disability/coma) within 90 days after successful resuscitation in out-of-hospital cardiac arrest.

CARDIAC REHABILITATION

The randomized **OPTICARE trial (2016)** included 914 patients who underwent ACS and, in more than 90% of cases, myocardial revascularization. Cardiological rehabilitation was started after 6 weeks and was carried out in the form of three options: 1) standard (group counseling on lifestyle correction 2 times a week for 3 months, 90 minutes in total) (n = 306); 2) standard + 3 face-to-face consultations on physical activity for 9 months (n = 309); 3) standard + 5-6 sessions of telephone lifestyle counseling within 9 months (n = 299). On average, 83% of patients in each of the three groups completed the standard program, but only 61% of patients fully completed face—to-face and 57% completed telephone consultations. As a result, the primary endpoint (risk of death according to SCORE) after 18 months did not differ significantly with three methods of rehabilitation. Both more intensive rehabilitation programs led to a decrease in the proportion of smokers ($p < 0.05$) and a decrease in the level of total cholesterol in the blood ($p < 0.001$), but did not change the average blood pressure, waist circumference. In patients who underwent an extended full-time rehabilitation program, the level of anxiety decreased, the quality of life improved, and the number of steps taken per day increased compared to the standard rehabilitation group. Both more intensive rehabilitation programs, probably due to low compliance, did not improve clinical outcomes (death, repeated hospitalization with ACS, repeated myocardial revascularization).

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