INTRODUCTION
The cardiovascular diseases, as arterial hypertension (AH), determine the mortality and disability of the adult population. The number of the patients with AH increases with age, which is associated with a violation of the response to vasodilating factors, this problem leads to the development of vascular diseases, accompanied by pathological vascular remodeling, impaired tissue perfusion. An early predictor of atherosclerosis and complications of cardiovascular pathology is endothelial dysfunction. Vascular endothelium supports hemostasis, and endothelial dysfunction affects vascular tone, immune inflammation, and platelet activation [1, 2]. During the aging process of the endothelium, both structural and functional changes occur, in particular, angiogenesis, vascular wall tone are disrupted, and mitochondrial dysfunction occurs. In addition, endothelial disorders are affected by oxidative stress, hyperuricemia, activation of the renin-angiotensin system, and vascular inflammation [3-6].

The disorders of NO synthesis by endotheliocytes may be genetically determined. The replacement of guanine with thymine at 894 positions in exon 7 of the NOS3 gene leads to a change of the enzyme activity due to a change in the amino acid sequence (glutamine is replaced with arginine at 298 positions) [7-10]. The existing T allele in patients with AH and a high body mass index (BMI) is associated with an early (on average 4.5 years) development of the disease, which was found among 39-7% of patients.

The gene AGTR1 polymorphism is associated with high vascular stiffness [11] and endothelial dysfunction [12] and cardiovascular complications in pathology, which also affects the development and severity of hypertension [13-15]. Therefore, better understanding of the pathophysiology of cardiovascular diseases can be useful for optimizing prevention and treatment, and patients with AH will be provided optimal blood pressure (BP) control. Routine examinations of patients with AH can identify damage of the target-organs and determine the risks of complications, analyze the effectiveness of antihypertensive therapy, but the examinations do not show additional information on the personal treatment of such patients. A data variety about the contribution of the NOS3 and AGTR1 genes polymorphisms to the development of the disease and its complications, and the course of concomitant pathology,
in particular the 2nd type of the diabetes, obesity, hypercholesterolemia, chronic renal failure, are aimed to find a pharmacogenetic basis for the treatment choice strategy for patients with AH [16-24].

THE AIM
Objective of the research is to determine the effect of NOS3 and AGTR1 genotypes of patients with arterial hypertension and high body mass index in the course of the disease.

MATERIALS AND METHODS
58 patients (22 men and 36 women) with AH and high BMI were examined. The average age of the examined patients was 53.6±8.7 years. The analysis of rs1799983 polymorphisms of the NOS3 gene (localization 7q36.1; 7:150999023) and AGTR1 (type 1 receptor for angiotensin 2 1166 A>C) was performed using TaqMan assay (Thermo Fisher Scientific, USA) by real-time PCR (Applied Biosystems, USA) using TaqMan probe amplification products. Genomic DNA samples were isolated from stabilized blood using a Genomic DNA Mini Kit reagent (Invitrogen, USA). The Statistica 10 program (StatSoft Inc.) was used for statistical processing of the obtained data, USA). The independent samples were compared using the Mann-Whitney (U) criterion. In all cases of statistical evaluation, the reliability of differences was taken into account at a value of p<0.05.

RESULTS AND DISCUSSION
The Endothelial nitric oxide synthase (NOS3) is a dimeric enzyme, the activity and expression of which are regulated at the transcriptional, post-transcriptional, and post-translational levels. The gene encoding NOS3 includes polymorphic sites (single-nucleotide polymorphisms, tandem repeats, microsatellites, and inserts). Nitric oxide synthesis may be affected by some polymorphisms due to NOS3 activity or expression. NOS3 haplotypes can increase the risk of developing diseases [25] based on endothelial dysfunction, in particular ischemic heart disease (CHD), myocardial infarction, ischemic brain stroke, hypertension, and chronic kidney disease [26-31] (table. I).

The data of the research of gene polymorphism and the link between them with risks for patients with a Cardiovascular profile alter in different populations. Even on the territory of the same continent and the same country, depending on the region, the population may have different genotypes of the same gene, so it is not possible to extrapolate statistics on the polymorphism of a particular gene to the entire population of the country.

Mutations in the Nos3 gene can become predictors of the 2nd type diabetes mellitus (DM) [32, 33], although the dominant AG genotype of the NOS3 rs1800779 and T2D polymorphisms is protective [34], while the GT polymorphism of the NOS3 gene is associated with the development of arterial hypertension in Brazilian women [35]. The presented meta-analysis data in the European population according to Mendelian randomization indicate an association of exon polymorphism in NOS3 (rs1799983, p.Glu298Asp) and in intron COL4A1 (rs9521634) and near DYRK1A (rs720470) with ischemic brain stroke due to changes in blood pressure levels [36]. In patients in the Antalya population, the NOS3 GT and TC polymorphism (rs2070744) is associated with hypertension [37].

Also, a prospective study shows the role of nos3 gene polymorphism in the formation of cerebral artery aneurysms, their rupture or the development of vasospasm, and the existing polymorphism can be considered a risk factor for the development of vascular complications along with smoking, hypertension, and diabetes [38]. The RS2070744 NOS3 polymorphism may be considered a factor of genetic predisposition in Sudan to hypertension [39].

A high risk of CHD was shown in Caucasians, South Asian populations, and Middle Eastern people with the existing TT and GT nos3 polymorphism. TT polymorphism significantly increases the risk (odds ratio >2) of developing ASF in 10 countries (Ukraine, Brazil, Great Britain, Egypt, India, Iran, Chile, South Korea, Morocco, Japan, etc.) [40]. A strong correlation exists in the TG Enos and AG polymorphism in Morocco [41]. Conflicting data on NOS3 polymorphism and the risk of myocardial infarction. A meta-analysis revealed an association of TC polymorphism in the NOS3 gene with the risk of myocardial infarction in Asian and European populations [42]. In patients with CHD from Pakistan, the Glu298Asp variant of the NOS3 gene showed no association with hypertension and dyslipidemia, but had a strong correlation with systolic blood pressure [43]. NOS3 polymorphism in Iranian patients is associated with the development of multiple sclerosis [44], GT, TC, and 4a/4b polymorphisms were not associated with the risk of CHD in residents of northern Iran [45]. Patients with CHD are more likely to have the rs1799983 t and rs2070744 G alleles than the GG genotype, and diastolic blood pressure increases with increasing BMI [46].

Among the examined patients, the wild allele of the NOS3 gene was found inside 35 (60.3%) individuals, the GT genotype - inside 20 (34.5%) patients, and the TT genotype – inside 3 (5.2%) subjects. It is known that the TT polymorphism increases the risk of hypertension by 2.3 times: the no level is lower in patients with hypertension and diabetes with GT and TT polymorphism [47, 48].

The early development of CHD with a gt gene polymorphism was found [49-51], although among the Tunisian population, the GT polymorphism is not associated with the development of CHD [52].

The pathogenesis contribution arguable data of cardiovascular diseases are presented in numerous literature reviews of the polymorphism of the AGTR1 gene. Thus, GT (rs275652) and AG (rs275653) polymorphisms are associated with severe atherosclerotic vascular damage among patients in the Mexican population [53, 54] (table. II).

Also, polymorphism of the AGTR1 gene causes sodium reabsorption in the distal tubules and the development of vascular stiffness, regardless of the level of blood pressure [55, 56]. The activation of renin-angiotensin of the aldoste-
The renin-angiotensin-aldosterone system (RAAS) is connected with AH. The results of a meta-analysis of the genetic association between RAAS genes and chronic kidney disease indicated a reduced risk of kidney damage in the presence of the AGT rs699-T allele and the AGTR1 rs5186-a allele [57], which also depends on the population [58]. The genetic polymorphism of AGTR1 in many researches is not associated with the development of hypertension [59, 60], although the CC genotype of this gene is associated with high level of renin, which contributes to the development of hypertension, at least in some populations [61-65] and negatively affects the course of concomitant diseases [66-69].

### Table I. Association of NOS3 gene polymorphisms with the development of pathological conditions

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Result</th>
<th>Reference</th>
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<tbody>
<tr>
<td>TT polymorphism of the NOS3 gene</td>
<td>AH</td>
<td>Abel Barbosa Lira Neto et al., 2019; Sanaa Nassereddine et al., 2018; Boqian Zhu et al., 2017; Khalil Mahmoodi et al., 2016; Sherif Arafa et al., 2018;</td>
</tr>
<tr>
<td>GT polymorphism of the NOS3 gene</td>
<td>AH; the early development of IXC</td>
<td></td>
</tr>
<tr>
<td>Alleles rs1799983 T and rs2070744 G of the NOS3 gene</td>
<td>Increased diastolic blood pressure among patients with high BMI</td>
<td>G L Zhao and et al., 2016;</td>
</tr>
<tr>
<td>NOS3 haplotypes G894T/T-786C</td>
<td>Reduced NO level among patients with hypertension and diabetes; CHD; myocardial infarction; ischemic cerebral stroke; hypertension; chronic kidney disease</td>
<td>Robin Johns et al., 2018; Omneya Moguib et al., 2017; Jelita Siregar et al., 2020; Cecilia Vecoli, 2014; Alejandro Marin Medina et al., 2018; E A Trifonova et al., 2019; N Yu et al., 2019; Beata Soltész et al.; Gustavo H Oliveira-Paula et al., 2016; Xiang-Zhen Kong et al., 2017; Dalia El-Lebedy et al., 2018; Süleyman Ömer Anliaçık et al., 2019; Sahar Gamil et al., 2017; Rainer Malik et al., 2018;</td>
</tr>
<tr>
<td>AG polymorphism NOS3 rs1800779 and T2D</td>
<td>High systolic blood pressure</td>
<td>Saleem Ullah Shahid et al., 2017;</td>
</tr>
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</table>

### Table II. Association of agtr1 gene polymorphisms with the development of pathological conditions

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Result</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>AGTR1 gene polymorphism</td>
<td>Increased vascular stiffness; Hypoxia resistance</td>
<td>Marcin Cwynar et al., 2016; Tatyana I Baranova et al., 2017;</td>
</tr>
<tr>
<td>Agtr1 GT (rs275652) and agtr1 AG (rs275653) polymorphisms</td>
<td>Systemic atherosclerosis</td>
<td>Tatiana S Rodriguez-Reyna et al., 2016; Zhongping Shi ta in, 2021;</td>
</tr>
<tr>
<td>genotype CC AGTR1</td>
<td>High renin levels; Complications of concomitant diseases</td>
<td>Tatyana Mulerova et al., 2020; Ana Célia Sousa et al., 2018; Keping Chen et al., 2021; Samantha Kohli et al., 2016; Sandrini Simonyte et al., 2017; Benjamin Goldstein et al., 2016; Sudhir Jain et al., 2018; Elena V Zholdybayeva et al., 2016; Roseline Wai Kuan Yap et al., 2017; Hsien-Feng Chang et al., 2018;</td>
</tr>
<tr>
<td>AC polymorphism of the AGTR1 gene</td>
<td>Liver damage; Insulin resistance; Endothelial dysfunction; Adipokine activation; Diabetic nephropathy; Hypertriglyceridemia; Increased low-density lipoproteins</td>
<td>Giovanni Musso et al, 2019; Dana de Gracia Hahn et al, 2019; Yan Zhuang et al, 2018; H-L Xu et al, 2020; Xun Li et al, 2016;</td>
</tr>
<tr>
<td>Alel C in rs5186 of the AGTR1 gene</td>
<td>High mortality and cardiovascular complications among patients with end-stage kidney disease</td>
<td>Sharon M Moe et al, 2019.</td>
</tr>
</tbody>
</table>
The collected data result for the dominant type of AA homozygote of the AGTR1 gene was detected inside 39 (67.2%) patients, and the heterozygous AC polymorphism was detected inside 19 (37.8%) of the examined patients.

A number of researches have shown no association between AGTR1 gene polymorphism and insulin resistance [70], although another study found the effect of AGTR1 AC polymorphism on liver damage, the development of insulin resistance and endothelial dysfunction, the effect on the activation of adipokines, chemokines and pro-inflammatory cells in response to fat consumption [71, 72], which is important while choosing drugs. The AGTR1 gene mutation is associated with the development of diabetic nephropathy among the Asian population [73]. The research result linked the existing polymorphism to high levels of triglycerides and low-density lipoproteins [74, 75]. The C allele in rs5186 of the AGTR1 gene is associated with high mortality and cardiovascular complications in patients with end-stage kidney disease, both in the European and African populations [76]. Also, according to other authors, polymorphism of the AGTR1 gene can cause resistance to hypoxia [77].

It is known about the link of myocardial remodeling with AH, which is determined among patients with hypertension to determine the stage and control the course of the disease, namely, the relative thickness of the left ventricle (VTS LV), left ventricular myocardial mass (MMLSH), and the left ventricular myocardial mass index (MMLSH) [78, 79]. Hypercholesterolemia is also a risk factor for hypertension and requires pharmacological correction in overweight patients, even at normal blood pressure values [80-82]. Hyperuricemia increases the risk of developing complications of hypertension, and it is advisable to determine the level of uric acid (uric acid) in all patients with increased blood pressure [83-85]. Both hypertension and obesity are associated with increased immune inflammation, which promotes remodeling of the vascular wall and increases its stiffness [86-88]. Obese patients have a high risk of developing insulin resistance and diabetes of the 2nd type [89-91].

According to the results of the analysis of indicators obtained during the examination of patients with AH, the heart rate (HR) has a likely relationship with the prediction of the existing polymorphism of the NOS3 and AGTR1 genes.

As a result of performing logistic regression to model the differentiation of existing polymorphism by NOS3 or AGTR1 genes separately, no statistically significant results were found. However, with the simultaneous polymorphism of these genes, we obtained strong correlations with the given risk factors for the course of hypertension. We created a mathematical equation according to which the probability of genetic mutations for two genes (NOS3 and AGTR1) can be predicted with a probability of 95%:

\[
Y = 38.8 \times BLP \; HD + 21.8 \times BLP \; LD + 0.75 \times FBG + 5.6 \times AI - 0.009 \times ILVMM - 0.069 \times LVMM + 0.86 \times N + 0.009 \times \text{urinary capacity} + 0.21 \times \text{HD AH} - 1.84 \times \text{TC} + 2.8 \times FBG + 0.006 \times HR - 122.1
\]

Where:
- Y is the theoretical probability of mutations;
- BLP HD - high-density beta-lipoproteins;
- BLP LD - low-density beta-lipoproteins;
- AI - atherogenicity index;
- N - neutrophil count;
- HD AH - hypertension-duration of arterial hypertension;
- TC - total cholesterol;
- FBG - fasting blood glucose;
- HR - heart rate;
- LVMM - left ventricular myocardial mass;
- ILVMM - left ventricular myocardial mass index;
- The inclusion in the formula of the indicator – the duration of the disease, can become a criterion for an early prognosis of the AH development in this category of patients.

The definition of gene polymorphism is associated not only with the risk of developing the disease, in particular, certain gene mutations can be protective in nature. Information about the gene polymorphism helps in choosing pharmacogenetic treatment for patients with the high risk of developing cardiovascular complications.

Since these indicators can be determined while examining a patient at the primary level and do not require high economic costs, this formula will help identify individuals with the likely presence of polymorphism for two genes (NOS3 and AGTR1) and, if need, send them for additional genetic examination to correct the treatment.

CONCLUSIONS

1. Polymorphism of the NOS3 and AGTR1 genes is associated with early development and complicated course of cardiovascular pathology.
2. The combination of NOS3 and AGTR1 gene polymorphism in patients with the high body mass index increases the risk of complications in hypertension.
3. Using a mathematical model to predict the probability (95%) of genetic mutations in two genes (NOS3 and AGTR1) increases the effectiveness of diagnosis for patients with the high risk of developing cardiovascular complications.

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