KAPITEL 8 / *CHAPTER 8* [8]
ARTERIAL HYPERTENSION AND COMORBID CONDITIONS: TYPE 2 DIABETES MELLITUS AND OBESITY

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Arterial hypertension (AH) remains among the most common cardiovascular diseases (CVDs) worldwide and in Ukraine in particular, which results in its significant impact on public health indicators.

It's worth emphasizing that AH is an example of the relevance and importance of such a problem as comorbidities since it is almost impossible to find hypertension alone without concomitant metabolic disorders. Year by year, AH tends to rejuvenate progressively. According to several studies, AH is diagnosed in individuals aged 18 to 30 years, and its incidence is increasing annually [1,2]. AH is often called a "silent killer" for it may not cause symptoms for a long time, but remains a leading and independent risk factor for the development of coronary heart disease (CHD), stroke, kidney disease, peripheral artery disease, vascular cognitive impairment, and premature death in the world [3].

AH is characterized by a high level of comorbidity [4,5]. Patients with AH usually develop one or often several comorbidities. According to several investigations, from 10 to 43% of patients with AH have at least 2 comorbidities, from 3 to 18% - 3 or more. Based on an examination of 30,092 patients with high blood pressure, J. Noh et al. found that the most common comorbidities were obesity (60.1%), dyslipidemia (57.6%), and fasting hyperglycemia (45.1%) [6-8].

Currently, the worldwide prevalence of cardiovascular diseases is about 100 million. In turn, 70-80% of cardiovascular cases are reversible if treated with proven preventive measures. [3,9]

A rise in blood pressure (BP) significantly impairs patients' prognosis due to progressive damage to target organs and increases the risk of coronary heart disease (CHD), heart attack, stroke, acute and chronic heart failure, heart rhythm disturbances, and sudden death [3].

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Elevated BP tends to be a major cardiovascular risk factor in patients with diabetes mellitus (DM). The combination of high BP and DM dramatically raises the risk of damaging target organs (heart, brain, and kidneys) and results in a higher incidence of cardiovascular complications and death [10-12].

As of today, we are witnessing a steady climb in DM incidence, especially type 2, and a tendency to increase its development not only among the adult population but also among younger people. According to the International Diabetes Federation, there are 2.3 million people with DM in Ukraine, with 90% of these patients suffering from type 2 DM. In terms of AH, it is twice as common in patients with DM compared to the overall population and is diagnosed in about 80% of patients with type 2 DM. Moreover, patients with AH in combination with type 2 DM are 2 times more likely to develop acute cerebrovascular accident (CVA) and 3 times more likely to have coronary heart disease and heart failure [7,13-15].

Hence, according to the Framingham Heart Study, which has already become a classic reference, the presence of AH in DM patients was associated with a 57% higher incidence of cardiovascular accidents and a 72% higher risk of all-cause mortality [16].

Accordingly, patients with both type 2 DM and AH require effective BP-lowering measures and protection of target organs from damage, which can lower the risk of cardiovascular complications and premature death.

Obesity is another AH comorbidity. When compared with the last quarter of the past century, the number of overweight individuals worldwide has doubled and currently exceeds 1.9 billion adults, of whom about 500 million are considered obese [17].

AH is the most frequent disease associated with obesity, which appears both as a risk factor for its development and as a determinant of global CVR in patients with AH [18]. The place of high BMI values as a factor of CVR is determined by the findings of meta-analyses of multiple prospective studies demonstrating a J-shaped association of this variable with total and cardiovascular mortality with a minimum level of the latter in the range of 20.0 (22.5) kg/m^2 to 25 kg/m^2. Moreover, in the structure of overweight and obesity-related nosologic units, cardiovascular pathology is the leader.

More than two-thirds of the four million annual deaths worldwide associated with high BMI are attributed to cardiovascular deaths [19-21].

In most European countries, the actual prevalence of obesity is about 20% [22]. These figures have almost tripled since 1986, when the European Association for the Study of Obesity (EASO) was founded to address the emerging obesity challenge. According to the WHO, obesity is defined as "abnormal or excessive fat accumulation that presents a risk to health," especially its abdominal (visceral) formation. Contrary to the belief that obesity is only a risk factor for diseases, the World Obesity Federation (WOF) has declared obesity as a chronic recurrent progressive disease [23].

Nowadays, obesity remains one of the main public health concerns and reaches global epidemic levels. According to the WHO, the number of people suffering from obesity worldwide has more than tripled between 1975 and 2016. In 2016, well over 1.9 billion adults older than 18 were overweight, with about 650 million of them being obese. It is expected that by 2030, 1/2 (57.8%) of the world's adult population will have a BMI score of 25 kg/m² or more. Western Europe and the United States are traditionally considered to be the world leaders in obesity incidence, while the increase is also observed in developing countries. Annually, the number of people suffering from obesity increases by at least 1% in the population. In obesity epidemiology, a particularly alarming indicator is the percentage of overweight children and adolescents. It was 23.89% among boys and 22.6% among girls in developed countries in 2013. The study by Rao G. (2016) analyzed data from 40,780 American children and adolescents aged 2 to 19 years and showed that the prevalence of obesity was 17%, and 5.8% of children were severely obese [24]. By 2013, the percentage of overweight and obese children and adolescents in developing countries also increased from 8.1 to 12.9% among boys and from 8.4 to 13.4% among girls. Ukraine's obesity prevalence is also rising steadily. According to the first nationwide study on the prevalence of major risk factors for non-communicable diseases in Ukraine, which complies with the WHO-approved Epidemiological Surveillance, only 2/5 (39.6%) of Ukrainians had a normal weight in 2019, while almost 3/5 (59.1%) of the population were overweight, including a quarter of the population (24.8%) who were obese.

Currently, chronic non-communicable diseases, including hypertension, type 2 DM, and obesity, have significantly escalated in our country. The main reasons for this are unfavorable social, economic, environmental, and migration circumstances for a particular person and unprecedented negative lifestyle patterns for a significant proportion of Ukrainians [25].

Multiple studies in different populations have shown an almost linear relationship between BMI and systolic and diastolic BP, whereas the prevalence of AH among obese patients exceeds 60%. However, the association between obesity and AH is defined by two main consequences: Higher morbidity and mortality from CVD, as well as an increase in the number of cases of treatment-resistant AH. Several authors have described the clinical features of obesity-associated AH, which include, in particular, systolic-diastolic AH at daytime and systolic AH at night, increased pulse pressure, and a violation of the daily BP profile with insufficient reduction of systolic BP at night.

There are many putative pathogenetic mechanisms behind obesity leading to AH. These include activation of the sympathetic nervous system, RAAS; imbalance of vasoconstrictor and vasodilator responses to stimuli; systemic inflammation; metabolic disorders (including hyperinsulinemia, adipokine imbalance, and increased cytokines). In overweight and obese individuals, the influence of adipokines may be one of the key processes involved in AH development. Numerous studies have concluded that the pattern of adipose tissue distribution, characterized by the predominance of VAT, is the most important factor in the increase in BP in overweight and obese individuals.

Effective BP lowering requires the following inseparable ingredients: the patient's desire to be treated; and the physician's desire to select the best treatment regimen for the patient. To achieve the target BP level in patients with DM, it is often advisable to prescribe combined therapy. According to current guidelines for AH treatment, most patients require 2 or more medications to achieve target BP levels.

The above findings were based on multiple clinical trials that demonstrated the need for combined therapy.

Nowadays, fixed combinations that significantly lower BP levels are the most

effective, promoting greater patient adherence to treatment. The combination of antihypertensive agents with a complementary effect increases efficacy and tolerability compared to high-dose monotherapy, reduces dose-related adverse reactions observed with high-dose monotherapy, and synergizes the pleiotropic effects of medications.

Treatment with a fixed combination should be started in patients with BP 20/10 mm Hg higher than the target.

These are the main requirements for a molecule in a fixed combination: all components must have a positive effect on cardiovascular prognosis, no frequent dosage adjustments are required, and they must have high tolerance.

Recent WHO guidelines on the frequency of AH assessment and treatment are highly relevant. These include the need for monthly monitoring after starting or changing antihypertensive drugs until patients reach the target value (provisory recommendation, lower-grade evidence). The WHO suggests that patients with low BP should be monitored every 3-6 months (provisory recommendation, lower-grade evidence). The WHO assumes that pharmacological treatment of hypertension should be ensured by professionals who have undergone proper independent training and are familiar with special treatment protocols [26].

We examined 56 patients with AH, type 2 DM, and obesity.

The mean age of the subjects was (64.4±1.1), of whom 24 (43%) were men and 32 (57%) were women. AH was diagnosed according to the recommendations of the International Society of Hypertension (ISH), 2020 [27]. Type 2 DM and obesity were diagnosed by clinical, instrumental, and biochemical criteria according to the WHO and European Society of Endocrinology expert recommendations. All patients were classified into several groups: Group 1 included 27 patients with AH, type 2 DM, and grade I obesity who received ramipril of 10 mg per day; Group 2 included 29 patients with AH, type 2 DM, and grade I obesity who received telmisartan of 40 mg per day. All patients also received standard therapy with a mean dose of 5 mg of bisoprolol and a mean dose of 1,000 mg of metformin. Patients were examined before starting therapy and 3 months after.

The examined comorbid patients with AH, type 2 DM, and concomitant obesity

belong to the group of high cardiovascular risk, in whom ACEIs reduce cardiovascular morbidity and mortality, and ARB have a similar effect. Nevertheless, comparing the effects of these two groups of drugs in a similar patient population is of particular interest.

Two groups of patients were examined and treated: Group 1 included 27 patients with AH, type 2 DM, and grade I obesity who received ramipril of 10 mg per day; Group 2 included 29 patients with AH, type 2 DM, and grade I obesity who received telmisartan of 40 mg per day. All patients also received standard therapy with a mean dose of 5 mg of bisoprolol and a mean dose of 1,000 mg of metformin. In addition to the prescribed treatment, patients were advised to follow non-drug treatment guidelines, namely, nutrition therapy aimed at correcting body weight and reducing BP to target levels. Patients were also urged to increase physical activity, mainly by walking at a fast or moderately fast pace for at least 45 minutes per day.

It was found that complex antihypertensive treatment for three months resulted in a significant decrease in systolic blood pressure (SBP) (by 19.6%) $p<0.05$, diastolic blood pressure (DBP) (by 15%) $p<0.05$, and heart rate (HR) (by 9%) (Table 1).

Echocardiographic findings: decreased levels in EDV by 25.5% $p<0.05$, ESV by 17.3% $p<0.05$, EDD by 24.0% $p<0.05$, LVM by 8.3%; EF increased by 6% $p<0.05$ compared to the pretreatment parameters.

Conducted therapy of patients with comorbidities proved almost the same positive effect of ramipril and telmisartan on structural and functional parameters of LV and EF. Meanwhile, no significant differences were found between such parameters as fasting blood glucose, HbA1c, insulin, TC, TG, and HDL. However, a significant decrease in LDL levels and BMI $p<0.05$ was observed after treatment.

Based on the results, it's safe to say that telmisartan has the same efficacy as ramipril in patients with AH and concomitant type 2 DM and obesity, and this agent is less likely to cause angioedema. Choosing between telmisartan and ramipril depends on physicians' preferences and individual patient tolerance. The data obtained are consistent with global data on the beneficial effect of ACEIs. For instance, several international wide-scale trials (CONSENSUS I, SOLVD, SAVE, AIRE, TRACE, etc.)

Table 1 - Changes in parameters during complex treatment with ramipril or telmisartan in patients with AH and concomitant type 2 DM and obesity

Parameter	Before treatment n=56	After 3-month treatment	
		Group I n=27	Group II n=29
1	2	3	4
SBP, mm Hg	159.4±3.0	128.3±0.7*	127.2±0.7*
DBP, mm Hg	92.4±1.8	79.3±0.8*	79.3±0.8*
HR, bpm	76.8±2.1	70.1±1.0	68.9±1.4
EDV, ml	180.4±3.3	144.4±3.9*	135.8±1.4*
ESV, ml	82.8±1.6	69.5±2.9*	67.9±1.9*
EDD, cm	6.5±0.1	5.0±0.1	4.8±0.1
ESD, cm	3.2±0.1	2.8±0.1	2.8±0.1
EF, %	47.6±0.8	50.7±0.8*	50.6±0.83*
LVM, g	263.3±6.9	241.5±5.2*	240.8±6.9*
Insulin, μU/ml	29.3±0.5	28.9±0.4	28.8±0.4
Fasting glucose, mmol/l	7.5±0.4	7.3±0.1	7.1±0.1
HbA1c, %	7.8±0.6	7.6±0.1	7.7±0.1
TC, mmol/l	5.4±0.1	5.21±0.1	5.22±0.1
TG, mmol/l	1.9±0.1	1.8±0.1	1.81±0.1
HDL, mmol/l	0.9±0.03	0.93±0.02	1.0±0.01
LDL, mmol/l	3.1±0.1	2.8±0.1*	2.90±0.09*
VLDL, mmol/l	1.7±0.02	1.6±0.01	1.6±0.04
AC	3.4±0.1	3.1±0.1	3.1±0.1
BMI, kg/m^2	31.3±0.2	28.2±0.2*	29.3±0.3*

*Note. * - the difference in parameters compared to the control is reliable, p<0.05.*

have revealed both a significant clinical effect and an impact on hemodynamics and myocardial remodeling, as well as a marked improvement in the quality of life of patients [28-30]. Multiple clinical trials involving about 150,000 patients have convincingly demonstrated that ACEIs reduce mortality and prevent heart attack, stroke, and heart failure in patients with high cardiovascular risk.

Several studies have confirmed that prolonged ARB administration in comorbid patients was associated with a decrease in mortality or hospitalization in patients with low EF or those who could not tolerate ACEIs. Compared with ACEIs, ARB reduced the incidence of vascular complications in high-risk patients with AH, concomitant type 2 DM, and obesity [31-32]. This group of drugs is mainly known for its stable BP

control. Besides, several studies have shown additional organ-protective effects of sartans: cardioprotective (LIFE, JIKEI-HEART), nephroprotective (IRMA II, IDNT, MARVAL, RENAAL, DETAIL), neuroprotective (MOSES, ACCESS), as well as a positive effect on glycemic control (VALUE, LIFE, ALPINE, NAVIGATOR) [33].

Therefore, the world is currently experiencing high rates of growth in such chronic diseases as arterial hypertension (AH), type 2 diabetes mellitus (type 2 DM), and obesity. The combination of AH and type 2 DM literally multiplies the risk of developing fatal cardiovascular complications. A reduction in systolic blood pressure (SBP) by every 10 mm Hg proved to reduce mortality by 15% in the UKPDS study (1998).

An individual approach based on the complications or their risk with the relevant differentiated tactics is the most up-to-date treatment strategy for comorbid patients. The first step for those at high risk of developing vascular complications is to normalize BP. The current tactic consists of taking antihypertensive drugs that are effective for a particular patient and do not cause adverse effects.