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Effects of angiotensin-converting enzyme inhibitors beyond lowering blood pressure – are they important for doctors?

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Abstract:
Large clinical trials and experimental studies have indicated that not all of the beneficial properties of angiotensin-converting enzyme inhibitors (ACE-Is) can be attributed to the lowering of blood pressure. The aim of this study was to assess doctors' opinions about the importance of the cardioprotective effects of ACE-Is beyond lowering blood pressure.
The study participants (685 physicians) filled in a questionnaire testing doctors' knowledge of all of the therapeutic effects of ACE-Is not directly associated with lowering blood pressure and their clinical importance. In addition, each doctor filled in 20 questionnaires for subsequent patients treated with any ACE-I.
Fifty-nine percent of the investigated physicians were aware of most of the therapeutic effects of ACE-Is. The most important therapeutic effects for the respondents were the following: reduction of peripheral resistance, inhibition of left ventricle hypertrophy, inhibition of vascular remodeling and atherosclerotic plaque stabilization.
The most commonly prescribed ACE-Is were perindopril, lisinopril and chinalapril for inhibition of left ventricular hypertrophy and perindopril, ramipril and chinalapril for inhibition of arterial wall remodeling. The ACE-Is that were used to reduce peripheral vessel resistance included perindopril, lisinopril and trandolapril. Drugs used to stabilize the plaque included perindopril, lisinopril and cilazapril.
The therapeutic effects of ACE-Is beyond lowering blood pressure were considered to be valid and important in daily clinical practice for the prevention of cardiovascular diseases and diabetic complications. The attribution of the effects of a particular ACE-I was not always in accordance with evidence-based medicine. The obtained treatment outcomes were attributed to the entire group of ACE-Is.

Key words:
ACE-I, additional therapeutic effects

Introduction

Angiotensin converting enzyme (ACE), which is secreted by vascular endothelial cells in the lungs, converts angiotensin I into angiotensin II [31, 42]. It has been demonstrated that angiotensin II is also synthesized at a variety of sites, including the kidney, vascular endothelium, adrenal gland and brain [9, 22, 31, 51]. These extra-renal systems may account for the plasma levels of angiotensin II observed in anephric subjects [54]. The two major systemic effects of angiotensin II are vasoconstriction and sodium and water retention. The effects of angiotensin II are me-

diated by binding to specific angiotensin II receptors, AT_1 and AT_2. AT_1 receptors account for the vascular and renal tubular actions of angiotensin II. AT_2 receptors probably contribute to the tubular action of angiotensin II and to the regulation of cell proliferation in the arterial wall [16, 30, 36]. The pharmacological effects of angiotensin-converting enzyme inhibitors (ACE-I) are related to the reduction in the conversion of angiotensin I to angiotensin II. In the initial phase of ACE-I therapy, the reduction of either plasma angiotensin II or aldosterone levels is observed. Simultaneously, increased renin secretion and increased plasma levels of angiotensin I are found. During long-term therapy, angiotensin II and aldosterone serum levels rise slowly because of alternative chymase pathway activation, but this does not abolish the ACE-I effect [25]. Furthermore, inhibition of angiotensin-converting enzyme activity inhibits bradykinin degradation, which probably has a beneficial effect on the cardiovascular system and is the cause of cough in some patients [43]. Bradykinin may contribute to the hypotensive action of ACE-I by releasing nitric oxide from vascular endothelial cells; this was demonstrated by Hornig et al., who treated patients with an ACE inhibitor (quinaprilat), a bradykinin B_2 receptor antagonist (icatibant), or both [19]. ACE inhibition increased flow-dependent vasodilatation (determined by ultrasound of the radial artery), and the addition of the bradykinin B_2 receptor antagonist reversed this effect. A significant role for bradykinin in the induction of hypotension with ACE-I has also been found by Gainer et al. [15]. They observed that elevated plasma renin activity associated with ACE inhibition was reversed with a bradykinin B_2 receptor antagonist, suggesting that bradykinin was responsible for this effect.

The primary pharmacological effect of ACE-I is vasodilatation, which reduces peripheral vascular resistance and leads to decreased blood pressure. Reduced peripheral resistance, which decreases left ventricular afterload, is followed by inhibition or even regression of left ventricular hypertrophy in patients with hypertension [10]. Not all beneficial effects of ACE-Is may be explained by the lowering of blood pressure, the reduction of vascular tonus, and peripheral resistance or by the decreased left ventricle afterload. In large clinical trials, it has been shown that at least some of ACE-Is (ramipril, perindopril) decreased the incidence of cardiovascular events (myocardial infarction, stroke) and improved survival in patients with stable angina without accompanying left ventricular dysfunction [14, 17]. Even a small reduction in systolic blood pressure (3 mm Hg), as observed during ramipril therapy in HOPE (Heart Outcomes Prevention Evaluation) study, resulted in a 22% reduction of risk of death from cardiovascular causes [20]. Similarly, in the EUROPA (European trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) study, the lowering of systolic blood pressure by 5 mm Hg with perindopril therapy was associated with a 20% reduction of cardiovascular risk in patients with stable angina [14]. The most probable explanation of these beneficial effects was that ACE-I improved endothelial function, decreased the severity of inflammation (reduced the secretion of proinflammatory cytokines by monocytes), slowed the progression of atherosclerosis (stabilized plaque, reduced the production of free radicals by inhibiting xanthine oxidase and reducing LDL oxidation) and remodeling of blood vessels (decreased proliferation of vascular myocytes) [11, 41]. In addition, ACE-Is have exhibited anticoagulant (inhibition of platelet aggregation) and fibrinolytic (increased secretion of PAI-1 (plasminogen activator inhibitor-1)) properties [3, 13].

It has been demonstrated that ACE-Is combined with amiodarone are more effective than amiodarone alone in maintaining sinus rhythm [48]. However, prospective trials did not confirm the prevention of new-onset atrial fibrillation in patients treated with ramipril [24, 38]. ACE-Is can also reduce the activity of the sympathetic nervous system and increase baroreceptor excitability [29]. Until recently, ACE-Is were thought to increase insulin sensitivity. However, the DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) study, in which diabetes was the "end point", did not confirm a significant influence of ramipril on risk reduction of diabetes incidence in patients with pre-diabetes (elevated fasting glucose level or impaired glucose tolerance) [46]. Ramipril therapy did not decrease the incidence of diabetes, but only resulted in a reduction of fasting glucose level [46].

ACE-Is were also used in both the prevention and therapy of diabetic nephropathy in patients with type 1 diabetes. Their beneficial effect is thought to be related to the reduction of intraglomerular pressure as well as non-hemodynamic effects [53]. Additionally, ACE-Is were shown to decrease the lower limb edema caused by vasodilators, such as dihydropyridine-like calcium channel blockers [12].

ACE-Is are less effective in stroke risk reduction than calcium channels blockers and antagonists of the type 1 receptor for angiotensin II in patients with hypertension [50].

The beneficial effects of ACE-Is are frequently discussed during conferences and congresses on cardiology, hypertension, diabetes and nephrology. However, we do not know how the pieces of information learned from the courses influence the practitioners and their choice of specific ACE-Is.

Therefore, the purpose of the present study was to assess the doctors' opinions concerning the importance of the cardioprotective effects of ACE-Is other than blood pressure reduction. Secondly, we addressed the question of which pleiotropic effects of ACE-Is are important for practitioners when they decide which ACE-I to choose for a specific therapeutic indication. In this portion, we included their "class effect", which is often negated.

Patients and methods

Six hundred eighty-five physicians working in primary health care, private medical practices and specialist ambulatory clinics throughout the country participated in this questionnaire study.

The questionnaire consisted of two sections. The first section gathered data on place of employment (primary ambulatory clinic, specialized ambulatory clinic, individual medical practice), specialization, names of the most commonly used ACE-Is and the three most important indications for their use. Participants were also asked to select the three most important effects from a list of therapeutic effects of ACE-Is not directly associated with lowering blood pressure. The last part of the first section included questions about the level of knowledge of the effects of ACE-Is not directly related to blood pressure lowering (all, most, about half, some or none). Each physician was also provided with the second section of a survey covering 20 attachments completed individually for subsequent patients treated with any ACE-I. This part of the questionnaire included patient demographic data (gender, age, residence, education and professional activity), the indication for the treatment with ACE-I (all registered indications included), the international name of the drug (all registered names in Poland) and a question about the importance of pleiotropic effects that could influence a doctor's decision. The inclusion criterion in the present study was previous treatment with any ACE-I.

All selected questionnaires (685 forms of section one and 9995 forms of section two) were subjected to statistical analysis. This analysis included a list of applied medications, indications and therapeutic effects of ACE-I (not directly related to blood pressure lowering) and awareness of these effects. The characteristics of the study group are presented in Table 1. A separate analysis was performed for data obtained from the second section of the questionnaire, including the classification of indications and drugs.

All data are expressed as the mean ± standard deviation. Analyses were performed using the STATISTICA 8.0 PL (StatSoft Polska, Kraków, Poland) software. The χ^2 test was used to compare distribution between groups. Logistic regression analysis was applied for the establishment of the order of priority of ACE-I therapeutic effects not directly related to blood pressure lowering in different ACE-I indications; p values < 0.05 were considered to be statistically significant.

Results

Of the interviewed physicians, 82.9% were specialists (internal medicine – 37.0%, family medicine – 28.9%, cardiology – 17.0%), 13.0% had not completed specialization (family medicine – 5.3%, internal medicine – 5.8%, cardiology – 1.9%) and 4.1% had not started their training yet. The majority of doctors (55.6%) were practicing in primary ambulatory clinics, 30.8% in private practice and 13.6% in specialist ambulatory clinics.

Declared and real administration of ACE-Is in clinical practice

The analyzed group of doctors reported that they use all available types of ACE-Is, but the most commonly used drugs were perindopril (98.5%), ramipril (88.0%), lisinopril (47.5%), enalapril (45.2%), cilazapril (34.8%) and chinalapril (33.8%). A complete list of ACE-Is is presented in Table 2. The doctors reported that they used four ACE-Is on average. Most physicians (64%) prescribed from 2 to 5 drugs from the ACE-Is; 36%

Tab. 1. Characteristics of patients treated with ACE inhibitors

Age (years)	59 ± 11
65 years (%)	70.3
> 65 years (%)	29.7
Sex M/F (%)	50.9/49.1
Place of residence (%)	
Country and village (10,000 residents)	25.5
Town (10,000–50,000 residents)	12.9
Town (51,000–100,000 residents)	14.5
Town > 100,000 residents	47.1
Education (%)	
Basic	12.1
Vocational	27.3
Secondary	43.1
Higher	17.5
Professional activity (%)	
Professionally active	37.6
Unemployed	3.7
Not working	10.7
Pensioner	11.2
Retired	36.8
Indications for ACE-I therapy* (%)	
Hypertension	86.6
Diabetes mellitus	29.3
Stabile angina	22.2
Heart failure	20.2
Past myocardial infarction	19.9
Stroke	6.4
Diabetic nephropathy	4.8
Non-diabetic nephropathy	1.5

* More than one indication in selected patients

prescribed 2–3 and 28% prescribed 3–5 drugs ACE-Is. Only 9% of physicians declared the prescription of a single ACE-I.

The analysis of the frequency with which the ACE-Is were prescribed differs significantly from that stated in the questionnaire and was dominated by perindopril (73.4%). Other frequently used drugs were ramipril (12.8%), lisinopril (4.2%), enalapril (3.4%) and chinalapril (2.3%). The rate of administration of other drugs did not exceed 2% (Tab. 1).

Tab. 2. The use of ACE-Is by surveyed physicians

	The percentage of physicians using	The percentage of patients treated with
Benazepril	10.3	0.2
Chinapril	33.8	2.3
Cilazapril	34.8	1.6
Enalapril	45.3	3.4
Fosinopril	0.5	0.1
Imidapril	3.3	0.2
Captopril	25.0	0.4
Lisinopril	47.5	4.2
Moexipil	0.5	0.1
Perindopril	98.5	73.4
Ramipril	88.0	12.8
Trandolapril	29.0	1.3

Declared and real list of indications for ACE-I therapy

The most important declared medical indication for the use of ACE-I was hypertension (67.7%, Fig. 1). The second was heart failure, including that occurring after myocardial infarction (62.8%). Diabetes (with or without nephropathy) (28.2%) and stable angina pectoris (21.8%) were ranked third.

The analysis of medical indications for ACE-I therapy, based on individual patients' questionnaires, confirmed that the most common indication was hypertension (86.6% of patients). The second most common indication was diabetes mellitus (29.3% of patients), but not heart failure, which was ranked third (20.2%). Other indications are shown in Figure 2. Most patients (60.6%) had more than one indication for ACE-I treatment.

ACE-I effects not directly related to blood pressure lowering

The most commonly mentioned therapeutic effects of ACE-Is included inhibition of left ventricular hypertrophy (79.5%), inhibition of vascular wall remodeling (71.5%), decreased peripheral vascular resistance (56.0%) and atherosclerotic plaque stabilization (42.0%). The frequency of selected ACE-Is therapeutic effects is summarized in Figure 3. The most important therapeutic effects for the respondents were reduction of peripheral vascular resistance (32.8%), in-

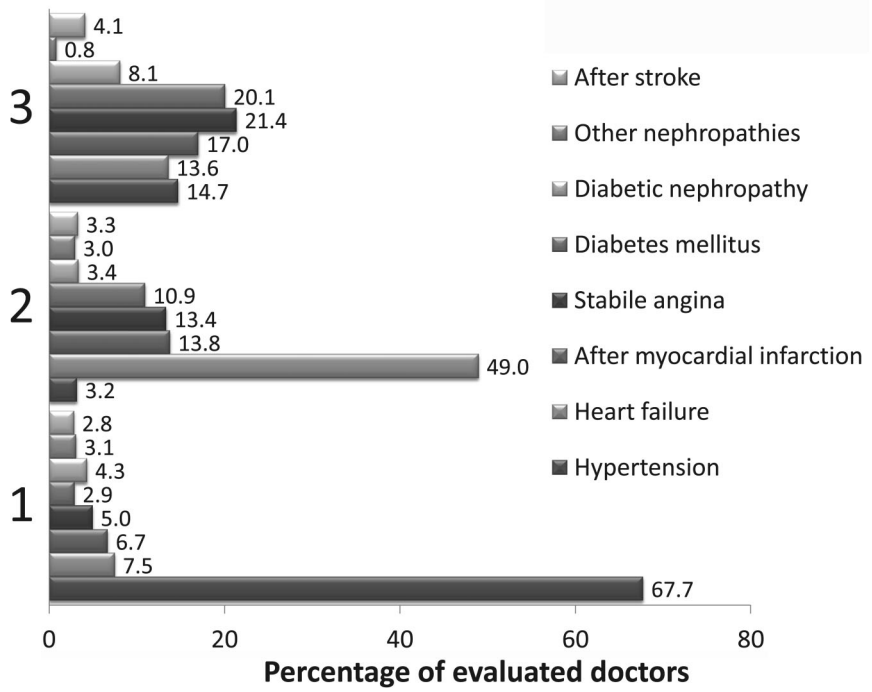

Fig. 1. Three most important indications for ACE-I therapy declared by the surveyed doctors

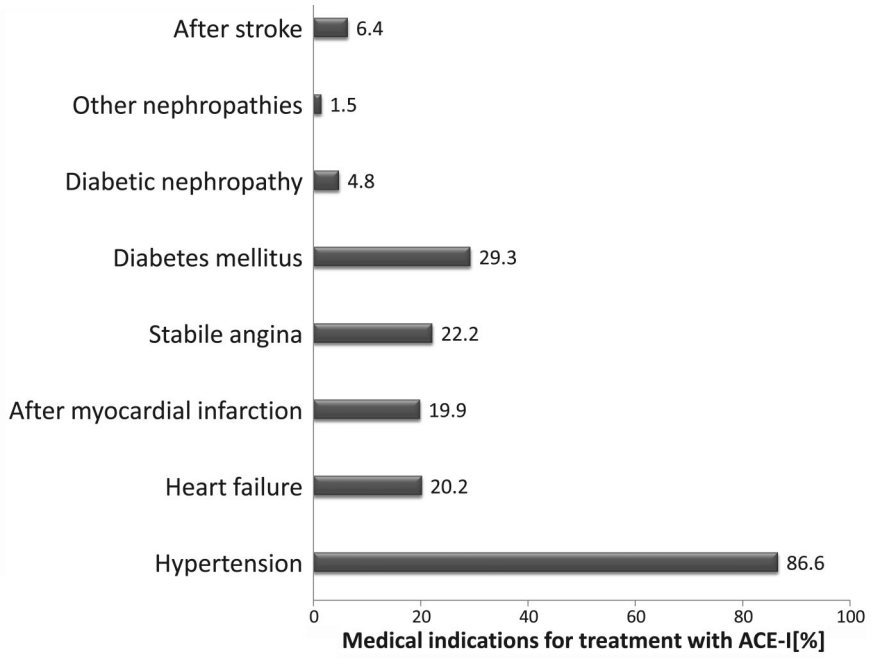

Fig. 2. List of indications for ACE-I treatment (an average 1.9 indication per patient)

hibition of left ventricular hypertrophy (26.0%) and inhibition of vascular remodeling (23.0%). Inhibition of vascular remodeling (33.3%) and inhibition of left ventricular hypertrophy (27.8%) were ranked second in terms of validity. Inhibition of left ventricular hypertrophy (25.8%) and plaque stabilization (21.0%) were ranked third. One in four doctors (with or without specialization) was aware of all of the therapeutic effects of ACE-Is. Physicians without specialization did not have complete knowledge of this issue (Tab. 3).

Tab. 3. The awareness of the effects of ACE-Is not directly related to lowering blood pressure among surveyed physicians

	Whole group	Without specialization	During training	Specialists
All (%)	24.5	6.3	26.9	25.1
Most (%)	59.0	56.2	51.9	60.2
About half (%)	10.3	18.8	13.5	9.2
Several (%)	6.2	18.7	7.7	5.5
None (%)	0	0	0	0

Selection of drug based on ACE-I therapeutic effects

In 81.2% of patients with hypertension, effects other than lowering blood pressure were taken into account when making the choice of ACE-I (Fig. 3). According to the respondents, the most important effects of these drugs were inhibition of myocardial hypertrophy of the left ventricle (63.9%), reduction of peripheral vascular resistance (58.3%), inhibition of arterial remodeling (51.5%) and stabilization of atherosclerotic plaque (33.2%). However, the logistic regression analysis showed that decreases in peripheral vascular resistance, antioxidant activity and inhibition of left ventricular hypertrophy were the most specific for this indication (Tab. 4).

Additional therapeutic effects of ACE-Is were considered in 78.2% of patients with heart failure. In the analyzed group, heart failure coexisted with hypertension in 73.8% of cases. The inhibition of left ventricular hypertrophy was recognized as the most important additional effect of ACE-Is (64.4%), rather than the reduction of peripheral resistance (40.2%). Other frequently selected activities included inhibition of arterial remodeling (28.7%), improvement of electrical stability of the heart (27.6%) and stabilization of atherosclerotic plaque. Surprisingly, the logistic regression revealed that the reduction of fluid retention was mentioned by physicians more than the inhibition of the left ventricular hypertrophy effect of ACE-I therapy (Tab. 4).

In patients who had past a myocardial infarction, additional therapeutic effects of ACE-Is were considered in 93.3% of cases. Hypertension occurred in 74.9% of patients. The influence of ACE-Is on left ventricular hypertrophy was considered to be important for 77.8% of patients. The reduction of peripheral vascular resistance was second (56.7%). The following effects were also considered to be important: inhibition of arterial remodeling (54.4%), stabilization of atherosclerotic plaques (48.9%), reduction in platelet activity and aggregation (35.6%), improvement of the electrical stability of the heart (35.6%) and reduction of fluid retention (32.2%). According to the logistic regression analysis, the most specific ACE-I effects ascribed to this indication were the stabilization of

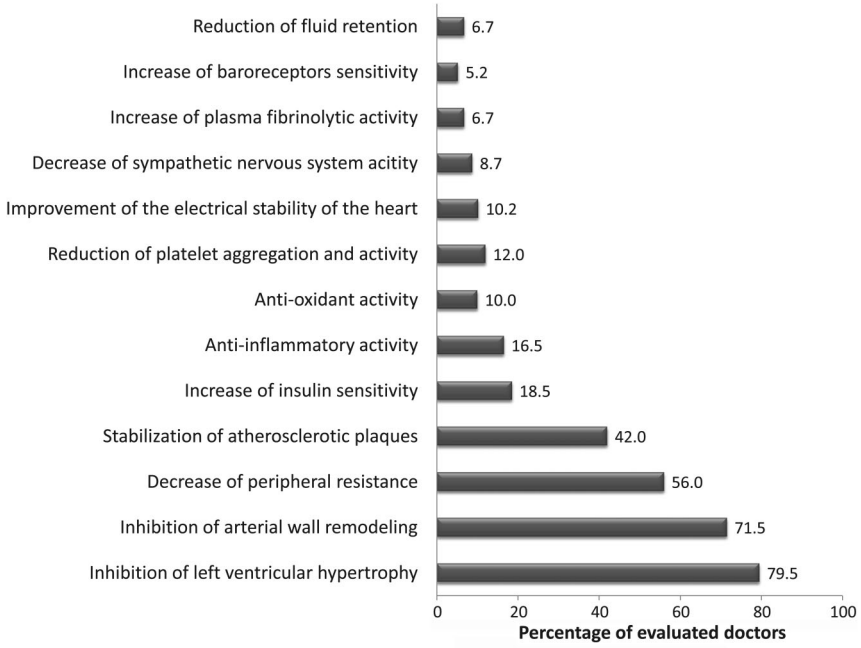

Fig. 3. Characteristics of ACE-I therapeutic effects not directly related to lowering blood pressure that were important for the surveyed physicians

Tab. 4. The results of logistic regression analysis on the importance of ACE-I therapeutic effects not directly related to lowering blood pressure in different indications

	OR	p
Hypertension		
Decrease of peripheral resistance	5.16 (3.02–8.82)	< 0.001
Antioxidant activity	1.88 (1.04–3.42)	0.037
Inhibition of left ventricular hypertrophy	1.63 (1.01–2.63)	0.044
Heart failure		
Reduction of fluid retention	3.27 (2.20–4.87)	< 0.001
Inhibition of left ventricular hypertrophy	1.53 (1.01–2.33)	0.048
Past myocardial infarction		
Stabilization of atherosclerotic plaques	2.87 (1.96–4.22)	< 0.001
Improvement of the electrical stability of the heart	1.94 (1.26–2.99)	0.003
Inhibition of left ventricular hypertrophy	1.63 (1.04–2.54)	0.032
Stabile angina		
Stabilization of atherosclerotic plaques	2.89 (1.99–4.19)	< 0.001
Decrease of the sympathetic nervous system activity	1.87 (1.20–2.91)	0.006
Inhibition of left ventricular hypertrophy	1.63 (1.07–2.48)	0.023
Diabetes mellitus		
Increase of insulin sensitivity	90.22 (50.93–159.82)	< 0.001
Reduction of platelet aggregation and activity	2.16 (1.23–3.80)	0.007
Decrease of peripheral resistance	1.98 (1.18–3.31)	0.01
Diabetic nephropathy		
Increase of insulin sensitivity	11.18 (5.58–22.41)	< 0.001
Decrease of the sympathetic nervous system activity	2.64 (1.20–5.81)	0.016
Non-diabetic nephropathy		
Decrease of the sympathetic nervous system activity	7.77 (2.19–27.56)	0.002
Stroke		
Stabilization of atherosclerotic plaques	3.25 (1.64–6.45)	< 0.001
Inhibition of arterial wall remodeling	3.89 (1.82–8.31)	< 0.001
Increase plasma fibrinolytic activity	2.76 (1.23–6.19)	0.014

atherosclerotic plaques, the improvement of the electrical stability of the heart and the inhibition of left ventricular hyperthrophy (Tab. 4).

In patients with stable angina, additional therapeutic effects of ACE-I were considered in 85.6% of cases. In 80.2% of patients, stable angina coexisted with hypertension. As with the previous group, the inhibition of ventricular hypertrophy (70.3%) was considered to be the most important therapeutic action of ACE-I in this group of patients. The less important actions included inhibition of arterial remodeling (54.1%), stabilization of atherosclerotic plaques (52.3%), reduction of peripheral resistance (51.4%), reduction of activity and platelet aggregation (32.4%) and improvement of the electrical stability of the heart (26.1%). The logistic regression indicated that the stabilization of atherosclerotic plaques, the reduction in activity of the sympathetic nervous system and the inhibition of left ventricular hypertrophy were the ACE-I effects most attributed to stable angina therapy (Tab. 4).

In the case of diabetic patients (concomitant hypertension – 90.4%), additional therapeutic effects of ACE-Is were taken into account in 83.0% of the cases. In this group of patients, the inhibition of left ventricle hypertrophy (63.7%) was found to be the most important additional therapeutic effect of ACE-Is

less frequently than in other diseases. Additional advantages of ACE-Is included reduction of peripheral vascular resistance (62.6%), increased insulin sensitivity (62.6%), inhibition of arterial remodeling (54.4%), reduced platelet aggregation and activity (38.6%), stabilization of atherosclerotic plaque (33.9%), increased antioxidant activity (30.4%) and lower fluid retention (30.4%). Regression analysis found that increased insulin sensitivity was the most specific ACE-I effect considered by physicians in diabetic patients (OR = 90.22) (Tab. 4).

In patients with nephropathies, including diabetic nephropathy, the additional therapeutic effects of ACE-Is were particularly important (100% and 87.5%). In patients with diabetic nephropathy, the greatest importance was assigned to the improvement of insulin sensitivity (50.0%), the stabilization of atherosclerotic plaque (50.0%) and the inhibition of arterial remodeling (37.5%). In other nephropathies (the smallest group of patients), the most important therapeutic actions of ACE-I included reduction of peripheral resistance (63.7%), inhibition of left ventricle hypertrophy (66.7%), increased insulin sensitivity (33.4 %), inhibition of arterial remodeling (33.3%), reduction of platelet activity and aggregation (33.3%), increased anti-inflammatory (33.3%) and antioxidant (33.3%) effects, and a lower activity of the sympathetic nervous system (33.3%). The list of important activities of ACE-Is did not include their effect on fluid retention. Logistic regression revealed that the reduction of sympathetic nervous system activity is frequently considered an ACE-I effect in both diabetic and non-diabetic nephropathies (Tab. 4).

After suffering strokes, 79.7% of stroke patients were treated for hypertension. The additional therapeutic effects of ACE-Is were particularly essential in 92.9% of these patients. Inhibition of arterial wall remodeling (78.6%), stabilization of atherosclerotic plaques (60.7%), decreased peripheral resistance (57.1%), inhibition of left ventricular hypertrophy (50.0%), reduced platelet activity and aggregation (42.9%), increased antioxidant activity (35.7%), reduced fluid retention (35.7%), increased plasma fibrinolytic activity (32.1%), anti-inflammatory activity (28.6%) and decreased activity of the sympathetic nervous system (28.6%) were found to be important in that group of patients. According to the regression analysis, the stabilization of atherosclerotic plaques, the inhibition of arterial wall remodeling and the increased plasma fibrinolytic activity were more frequently cited by physicians as important therapeutic effects in stroke patients than in other groups of patients (Tab. 4).

Therapeutic effects of ACE-I not directly related to blood pressure lowering attributed to the specific drug

The analysis was performed for the seven most commonly used ACE-Is, prescribed at a rate of at least 0.5% (Tab. 2). Based on the reported additional effects of ACE-Is not directly related to lowering blood pressure, but affecting drug selection in an individual patient, it can be concluded that the drugs most frequently considered to inhibit ventricle hypertrophy included perindopril, lisinopril, and chinalapril. The same drugs were also considered to inhibit arterial wall remodeling. Perindopril, lisinopril and trandolapril were most commonly referred to as drugs that decrease peripheral vascular resistance. Drugs whose function is to stabilize the atherosclerotic plaque and have an antioxidant effect included perindopril, lisinopril, and cilazapril. Increased insulin sensitivity and anti-inflammatory activity was linked with the use of trandolapril, perindopril and cilazapril. The list of drugs that reduced platelet activity and aggregation included perindopril, chinalapril and trandolapril. Increased plasma fibrinolytic activity was assigned to trandolapril, perindopril and ramipril.

An effect on cardiac electrical activity was associated with the use of perindopril, ramipril and lisinopril. Decreased activity of the autonomic nervous system was associated with the use of chinalapril, perindopril and ramipril. Perindopril, ramipril and trandolapril were expected to increase the baroreflex sensitivity. Treatment with perindopril, lisinopril and cilazapril was expected to reduce peripheral edema.

Interestingly, the list of additional therapeutic effects of ACE-I was not attributed to enalapril, which is still commonly used in clinical practice.

Discussion

The present study found that one in four doctors (during the course of training or specialists) had knowledge of all of the cardioprotective effects of ACE-Is, and 59% of them knew of most of the cardioprotective effects. As expected, physicians with specializa-

tion or during their training were better trained than physicians without specialization.

For clinicians, the most important effects of ACE inhibitors beyond lowering blood pressure were the inhibition of left ventricle hypertrophy and vascular remodeling, the reduction of peripheral vascular resistance and atherosclerotic plaque stabilization. Undoubtedly, the effects mentioned above are the best documented and most clinically important. Inhibition of left ventricular hypertrophy (high possibility of reduction of the existing hypertrophy in patients with hypertension) was confirmed by meta-analysis carried out in the 1990s [6, 40] and made ACE-Is widely recommended in the therapy of hypertension in young people. Similarly, the use of ACE-Is was found to be effective in inhibiting left ventricle remodeling in patients after myocardial infarction [1]. This therapy is already a standard in cardiac care units and is supposed to prevent the occurrence of left ventricular failure.

Initially, the beneficial properties of ACE-Is were confirmed for the now rarely used captopril (ISIS-4 study – Fourth International Study of Infarct Survival) [21], lisinopril (GISSI-3 study – Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico) [17], trandolapril (TRACE study – Trandolapril Cardiac Evaluation Study) [25] and ramipril (AIRE – Acute Infarction Ramipril Efficacy study) [44]. However, according to the practitioners' opinions, inhibition of left ventricular hypertrophy was mainly attributed to the use of perindopril and chinalapril. Lisinopril was the third drug mentioned by the evaluated physicians, and only 29.4% of them remembered that the influence of enalapril on the heart is quite similar.

Decreased peripheral vascular resistance following treatment with ACE-Is, described in the late 1980s, was a milestone in the philosophy of heart failure therapy associated with left ventricular insufficiency, including post myocardial dysfunction. Two large clinical trials (performed in 1980) with captopril (SAVE study – Survival and Ventricular Enlargement trial) [37] and enalapril (SOLVD – Studies of Left Ventricular Dysfunction and CONSENSUS – Cooperative North Scandinavian enalapril survival study) [45, 47] provided evidence that the use of these drugs reduces the risk of development of symptomatic heart failure and mortality by up to 40%. Opposite to EBM, practitioners attributed this effect mostly to the actions of perindopril, lisinopril and trandolapril (enalapril was not mentioned).

One of the most important actions of ACE-Is is the prevention of vascular wall remodeling. This could be attributed to inhibition of smooth vascular muscle hypertrophy in medium-sized arteries and to the inhibition of the replacement of elastin fibers by collagen fibers in large arteries (as it is in the case of hypertension and the process of aging) [5]. Moreover, ACE-Is may enhance the release of endogenous substances (such as endothelial prostacyclin), that directly influence cardiovascular system [18]. Such a beneficial effect, not directly related to blood pressure lowering, was demonstrated for perindopril and cilazapril [39]. However, because of technical problems (the need for minimally invasive and indirect assessment of vascular wall remodeling, mainly aortic elasticity) and the slow nature of the process, the strength of that evidence is limited. Another method that allows the evaluation of vascular sclerosis is the measurement of the intima media thickness (IMT). In the SECURE study (Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E), treatment with 10 mg of ramipril resulted in the reduction of IMT [27]. Slow-progressing changes in IMT require several measurements in order to reduce errors associated with measurement accuracy and a long follow up. Our uncertainties concerning slower progression of IMT were not reduced by a meta-analysis [52]. Opposite to the randomized controlled trials mentioned above, the practitioners attribute the vascular protection to perindopril, chinalapril and ramipril.

Progression of atherosclerosis and plaque instability is another significant vascular pathology that could be modified by pharmacological blockade of the RAA (Renin Angiotensin Aldosterone) system [41]. The efficacy of ACE-Is in increasing the stability of atherosclerotic plaque was confirmed indirectly by large clinical trials. Treatment with ACE-Is resulted in a reduction of the incidence of fatal and non-fatal cardiovascular events, both in primary and secondary prevention [14, 38]. The aforementioned beneficial effects of ACE-Is may also be a consequence of an inhibition of platelet aggregation and an increased plasma fibrinolytic activity. The best documented anti-atherosclerotic action of ACE-Is was demonstrated for ramipril (HOPE study) [26] and perindopril (EUROPA and ADVANCE studies) [14, 33]. However, according to practitioners, this effect can not only be attributed to perindopril, but also to chinalapril and lisinopril.

It is also worth mentioning that the insulin-sensitizing properties of ACE-I appear in the practitioners' opinions. Such a hypothesis was discussed on

the basis of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study results, in which the lowest incidence of type 2 diabetes was reported for patients treated with lisinopril (8.1%) [2]. The incidence was even lower than in patients treated with calcium channel blockers that are believed to be metabolically neutral. A few years later, the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study confirmed a 32% lower incidence of type 2 diabetes in patients treated with perindopril and amlodipine than in hypertensive patients treated with atenolol and a thiazide diuretic (bendroflumetiazid). The development of diabetes was not the designated "end point" in these studies [7]. On the other hand, in the DREAM study, new incidence of diabetes was the "end point", although treatment with ramipril did not significantly reduce the occurrence of diabetes in patients with pre-diabetes (elevated fasting glucose or impaired glucose tolerance) [46]. Such a therapy did not reduce the incidence of diabetes, but only resulted in a reduction in fasting glucose levels. Surprisingly, the practitioners still believed in the anti-diabetic properties of ACE-Is, which are especially emphasized in patients with diabetes and diabetic nephropathy (50.0–62.6%).

The results of recently published studies like ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) raised the question as to whether blocking the angiotensin system had special cardiovascular protective effects. It also must be mentioned that contrary data regarding a possible benefit of ACE-I treatment in reducing exercise-induced ischemia were published. Van den Heuvel and colleagues observed that exercise time to ST segment depression was significantly increased in patients at twelve weeks on enalapril (10 mg twice daily), compared to the placebo group [49]. However, in the QUASAR (Quinapril Anti-Ischemia and Symptoms of Angina Reduction) study, Pepine et al. observed no improvement in the exercise time to 1 mm ST segment depression at eight weeks in patients treated with 40 mg daily of quinalapril [34].

Another issue that should be noted is that ACE-I therapy is not the only medication reducing the risk of cardiovascular events in CAD patients [32, 35]. Published meta-analyses revealed that aspirin offered the most pronounced benefit. In CAD patients who were non-adherent to aspirin therapy, the risk of major adverse cardiac events was 1.82 (1.52–2.18, 95% CI) [4]. Moreover, the severely criticized ALLHAT study showed no differences in outcomes among patients with hypertension and coronary artery disease treated with ACE-Is, calcium antagonists and diuretics [28].

Finally, statin, ACE-I therapy and β-blockers resulted in a similar 17% reduction of cardiovascular events [8, 23].

Conclusions

1. The therapeutic effects of ACE-Is beyond lowering blood pressure are considered to be valid and important in daily clinical practice for the prevention of cardiovascular diseases and diabetic complications.
2. The attribution of effects of the particular ACE-I is not always in accordance with evidence-based medicine. The obtained treatment outcomes are attributed to the entire group of ACE-Is.

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