

Health outcomes and economic consequences of using angiotensin-converting enzyme inhibitors in comparison with angiotensin receptor blockers in the treatment of arterial hypertension in the contemporary Polish setting

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Abstract

Background: Arterial hypertension (AH) represents a public health problem in Poland, firstly due to the huge, still growing population of patients (10.45 million patients based on NATPOL 2011 and PolSenior Surveys), and secondly because of the substantial cost of reimbursement from the National Health Fund (NHF). The most commonly used drugs in the treatment of AH include angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), the latter being associated with significantly higher unit reimbursement cost. Recent meta-analyses of randomised, controlled trials indicate that there is no medical reason to favour ARBs over ACEIs in AH treatment.

Aim: To assess the clinical benefit of using ACEIs instead of ARBs and to calculate the potential savings for the payer and patients associated with changing the treatment paradigm to preferential use of ACEIs.

Methods: The assessment of clinical consequences includes differences between ACEIs and ARBs in terms of average life expectancy and quality-adjusted life years (QALYs) gained. The impact of these drugs on general mortality was estimated based on the meta-analysis carried out by van Vark et al. in 2012. Patients' health-related quality of life was adjusted with Polish population utility norms derived for the EQ-5D-3L questionnaire and additionally for ACEI-induced cough-related utility decrease. Potential savings for the payer on a yearly basis were calculated for a hypothetical cohort of patients who are currently treated with ARBs and might be switched to ACEIs. The number of patients treated with ARBs and ACEIs was estimated based on NHF and IMS Health data.

Results: ACEIs were associated with a statistically significant 10% reduction in all-cause mortality, which results in extra life gained of 0.354 years (4.2 months) or an additional 0.201 QALY (2.4 months). Potential annual savings could amount to 112.0 million PLN (25.7 million EUR) and 10.5 million PLN (2.4 million EUR) for the public payer (NHF) and patients, respectively; and 1768 cardiovascular deaths per year could be prevented.

Conclusions: Preferential use of ACEIs in comparison with ARBs in the treatment of AH is associated with substantial extension of life (including quality-adjusted life), reduction of cardiovascular deaths, and savings for the NHF and patients.

Key words: arterial hypertension, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, National Health Fund, evidence-based prescribing, cost-consequence analysis

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INTRODUCTION

Arterial hypertension (AH) constitutes a health, social, and economic burden. AH is one of the primary risk factors of developing cardiovascular (CV) diseases and constitutes one of the most significant risk factors of premature death globally [1]. About 10.45 million people in Poland suffer from AH. The number of hypertensive subjects in Poland was calculated using demographic figures published yearly by the Central Statistical Office and data on the prevalence of AH from the national cross sectional NATPOL 2011 (for the age range 18–79 years) and PolSenior Surveys (age \geq 80) [2–5]. Recent data indicate an increasing prevalence of AH in Poland [1]. The economic burden on the National Health Fund (NHF) results from chronic drug use from disease diagnosis until death, and from management of disease complications. In 2010 the mean cost of annual treatment of AH was estimated at 3494 PLN per patient [6]. Antihypertensive drugs were associated with the highest reimbursement costs and constituted about 10% of the total NHF reimbursement budget in 2013 [7]. Renin–angiotensin–aldosterone system (RAAS) inhibitors play a crucial role in the treatment of AH in the Polish setting: according to recently published NHF sale data the share of RAAS inhibitors in the total volume of all antihypertensive agents is 66%.

The two most common of the five first-line antihypertensive drugs used in AH treatment are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). According to the recent guidelines on AH management issued by the Polish Society of Hypertension, ACEIs and ARBs are preferred for different patient subgroups [1]. Moreover, Polish guidelines refer to three significant meta-analyses published in 2012–2014 and focusing on different populations; all of them indicate additional benefit of using ACEIs over ARBs [8–10]. Reimbursement conditions of ACEIs and ARBs in Poland differ: ARBs are reimbursed with a 30% co-payment under limit group 45.0, and ACEIs are reimbursed with a lump sum co-payment under limit group 44.0 except for single-pill combination of ramipril + amlodipine reimbursed with a 30% co-payment under limit group 41.0. The average cost of reimbursement from public funds of a monthly ARB treatment is 4.6 times higher compared to ACEIs [11]. The number of hypertensive patients treated with ARBs is four times lower compared to ACEIs but constitutes almost 60% of the reimbursement spending for ACEIs and ARBs in total [11]. In 2014, Hermanowski et al. [11] showed possible annual savings for the NHF of 155 million PLN resulting from the creation of a common limit group for these drugs.

Because the unit ACEI reimbursement cost is lower than ARBs, and ACEIs are preferred for the majority of AH patients, we aimed to assess the long-term clinical consequences of preferential ACEI over ARB treatment and the related financial consequences for the payers (both public — NHF — and patient out of pocket spending).

METHODS

Clinical benefits — life expectancy and QALY associated with the use of ACEIs and ARBs

Patients' survival in the general population was estimated separately for men, women, and in total, based on life tables for 2014 according to data of the Central Statistical Office. The survival probability curves $S(t)$ were estimated, and subsequently cumulative hazard curves ($H_t = -\ln(S_t)$) where t = age of patients from the age at therapy initiation to 100) and mortality rates ($h_t = H_{t+1} - H_t$) were calculated. The mortality rates were adjusted for the appropriate health effects for ACEIs and ARBs in a chosen time horizon and then retransformed to survival curves.

The effect of ACEIs and ARBs on general mortality was based on the van Vark et al. meta-analysis [8], which is currently the most comprehensive analysis, reflecting clinical heterogeneity of real world AH patients, which showed a statistically significant difference in favour of ACEIs over ARBs. According to results from the van Vark et al. study [8], the use of ACEIs was associated with a statistically significant 10% general mortality decrease: Hazard ratio (HR) = 0.90 (95% confidence interval [CI] 0.84–0.97, $p = 0.004$). In patients treated with ARBs the treatment effect on the mortality outcome was neither statistically nor clinically significant: HR = 0.99 (95% CI 0.94–1.04, $p = 0.683$).

Two hypotheses were analysed in parallel. The first analysed the treatment effect from the age of 48 years (50 years for women, 46 years for men — NATPOL 2011 Survey database) until the end of the patient's life, and the second one, which was more conservative, analysed patients starting treatment at the age of 67 years and continuing it for four years (based on van Vark et al. [8]). Due to the fact that AH is a chronic disease, the base case analysis assumed that the treatment effect on mortality (i.e. 0.90 in the ACEIs group and 0.99 in the ARBs group) would be maintained from the start of treatment to the end of the patient's life.

Data on the average age at which hypertensive subjects are started on treatment in Poland were calculated from the NATPOL 2011 Survey database. The NATPOL 2011 Survey (full Polish title: *Nadciśnienie tętnicze oraz inne czynniki ryzyka chorób serca i naczyń w Polsce*) was a cross-sectional observational study aimed at assessing the prevalence and control of CV disease risk factors in Poland, performed in a representative sample of 2413 adults — 1168 men and 1245 women aged 18–79 years. Age distribution was as follows: 974 subjects aged 18–39 years, 879 subjects aged 40–59 years, and 590 subjects aged 60–79 years. The detailed description of a three-stage sample selection procedure, examination methods used for assessment of existing risk factors, and the diagnostic procedures were all described in detail in an earlier paper [2]. In short, the participation rate was 66.5%. Blood pressure measurements (three during each visit) were performed by nurses during two separate visits with the participant in a seated position, on the

right upper arm, after at least 5 min of rest and at 1-min intervals. Blood pressure readings were taken using fully automatic oscillometric blood pressure measuring devices (A&D UA 767). Before the first measurement, the nurse measured the circumference of the patient's right arm. If the patient's arm circumference was ≥ 32 cm, the readings were performed using a wider cuff. AH was diagnosed in line with 2013 ESH/ESC Guidelines for the Management of Arterial Hypertension [12] and 2015 Polish Society of Hypertension Guidelines for the management of hypertension [1]: if average blood pressure values from two measurements during each of two visits were equal to or higher than 140 mm Hg (systolic blood pressure) and/or 90 mm Hg (diastolic blood pressure), or if the patient was taking hypotensive drugs over the past two weeks due to an earlier diagnosis of AH.

The mean age of patients in clinical trials included in the van Vark et al. study [8] and the overall mean follow-up duration were, respectively, 67 years and 4 years. Therefore, in the sensitivity analysis a conservative approach was tested, where $h(t)$ was adjusted for treatment effects only in ages 67–70 years.

In order to adjust the length of life for the quality of patients' life utility, values dedicated to the Polish population according to the EQ-5D-3L questionnaire based on the Golicki and Niewada study [13] were used. Life years were adjusted for utility values in different age ranges separately for men and for women, and for both sexes combined. A utility decrement was introduced in the ACEI group due to decreased quality of life in patients who experienced persistent dry cough — a characteristic adverse event of ACEIs. For this purpose the percentage of patients treated with ACEIs who experienced cough was assumed at 10.6% in each year according to the Bangalore et al. [14] meta-analysis of 125 studies, which included a total of 198,130 patients. Disutility in the case of cough was assumed to be 0.05 based on the Adarkwah et al. [15] cost-effectiveness analysis of ACEIs versus no treatment, in patients with advanced renal disease in the Netherlands, which we found in the utility literature review. Disutilities due to cough in the ACEI group were included for the same period as the therapeutic effect. In the Adarkwah et al. study [15] disutility due to adverse events was adopted only in sensitivity analysis (base case analysis adopted no utility decrement); therefore, utility adjustment for cough (in the ACEI group) represents a conservative assumption in our calculations.

The results were discounted at the discount rate for health effects recommended by the Agency for Health Technology Assessment and Tariff System, i.e. 3.5%.

Savings for the payer associated with using ACEIs instead of ARBs

To estimate the maximal potential savings for the payer associated with using ACEIs instead of ARBs, the size of the

hypothetical target population was estimated. The number of all patients treated with ACEIs and ARBs was established based on defined daily doses (DDD) of currently reimbursed preparations of ACEIs and ARBs (the number of reimbursed packages was adopted from sales data of the NHF for 2014 and DDDs for the respective substances according to the World Health Organisation [WHO]) divided by the number of days in a year (365.25). The total number of patients treated with either ACEIs or ARBs was estimated at 8.5 million (74% were treated with ACEIs and 26% with ARBs). The sales data of the NHF do not differentiate indications. Based on IMS Health data (dedicated analysis of the Medical Index study data), AH was assumed to be diagnosed in 79% and 87% of all patients treated with ACEIs and ARBs, respectively. Therefore, the size of the target AH population was estimated at 6.9 million patients, including 4.9 million patients treated with ACEIs and 2.0 million patients treated with ARBs. Preferential use of ACEIs in comparison with ARBs was assumed in the treatment of AH (i.e. introducing limitations in the use of ARBs, e.g. only in cases of ACEI intolerance) and treatment switch from ARBs to ACEIs. We assumed that all patients, except for patients experiencing persistent cough (10.6% based on the results of a meta-analysis of randomised controlled trials from the Bangalore et al. study [14]), could be treated with ACEIs, i.e. 6.1 million with ACEIs and 0.7 million with ARBs (Fig. 1).

The CV mortality benefit of ACEIs over ARBs was based on the van Vark et al. study [8] and was adjusted for average effect in the control group. According to the results of the van Vark et al. study [8], among patients treated with ACEIs, in comparison with controls, there were 9.1 vs. 11.2 CV deaths per 1000 patient-years and 8.8 vs. 9.2 CV deaths per 1000 patient-years treated with ARBs vs. the control group, respectively. Based on the relative effect of the ACEI group and the ARB group in relation to the control group, and the average effect in the control group (10.2 deaths per 1000 patient-years), the effect in the ACEI group and ARB group was adjusted for the average effect in the control group. The estimated adjusted incidence rate was 8.29 and 9.76 CV deaths per 1000 patient-years for ACEIs and ARBs, respectively. The clinical benefit of 1.47 fewer CV deaths in the ACEI group was translated into reduced cost of care for patients treated with ACEIs in comparison with ARBs.

The cost of fatal CV events was estimated based on published statistics of Diagnosis-Related Groups for 2014 corresponding with such CV events as stroke, acute myocardial infarction, and heart failure. The average percentage of fatal CV hospitalisations was estimated at 7.3%. Therefore, it was assumed that 7.3% of all CV deaths are associated with the average cost of CV hospitalisation (weighted number of hospitalisations), i.e. 5917.31 PLN, and the remaining 92.7% of CV deaths are not assigned any additional costs, so the average cost of a fatal CV event was estimated at 430.01 PLN.

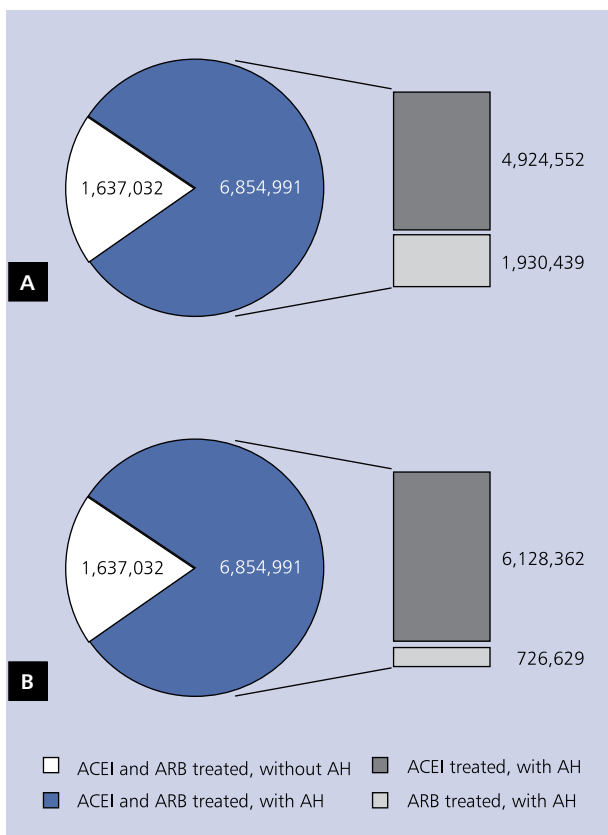


Figure 1. Target population; **A.** Existing scenario; **B.** New scenario; ACEI — angiotensin-converting enzyme inhibitors; AH — arterial hypertension; ARB — angiotensin receptor blockers

The average cost of ACEIs and ARBs was estimated based on the latest announcement of the Minister of Health and the market shares in volume (WHO DDDs) obtained from the sales data of the NHF for 2014.

RESULTS

Clinical benefits

For a patient aged 48 years the expected remaining length of life is 31.64 years, corresponding to 17.69 discounted years (the base case in our analysis). If this patient had been treated from 48 years of age to the end of life with ACEIs or ARBs, the remaining discounted life expectancy would be 18.05 years and 17.73 years, respectively (the treatment effect has been assigned throughout the whole treatment period).

In relation to the general population ACEIs prolong life (discounted values) by 4.2 months (0.354 life years gained [LYG]) and 2.4 months of life in perfect health (0.201 quality-adjusted life years [QALY]), and ARBs by 0.4 months (0.034 LYG) and 0.3 months (0.029 QALY), respectively. In both groups these benefits are higher for men due to higher general mortality associated with a larger effect in this group (Table 1; for the results of sensitivity analysis see Table 2).

Savings for the payer and for the patients

Angiotensin converting enzyme inhibitor treatment is cheaper by 0.26 PLN/DDD than treatment with ARBs from an NHF perspective (0.08 PLN/DDD and 0.34 PLN/DDD, respectively) and cheaper by 0.02 PLN/DDD from the patient’s perspective (0.20 PLN/DDD and 0.22 PLN/DDD, respectively).

Table 1. Clinical benefits associated with use of ACEIs instead of ARBs related with decrease in general mortality — discounted (undiscounted) results of the base case

Difference	Life years gained			Quality-adjusted life years		
	Male (M)	Female (F)	M + F	Male (M)	Female (F)	M + F
ACEIs vs. control*	0.382 (1.051)	0.307 (0.890)	0.354 (0.998)	0.233 (0.752)	0.158 (0.587)	0.201 (0.689)
ARBs vs. control*	0.037 (0.100)	0.030 (0.085)	0.034 (0.095)	0.031 (0.086)	0.025 (0.073)	0.029 (0.081)
ACEIs vs. ARBs	0.345 (0.951)	0.278 (0.805)	0.320 (0.902)	0.201 (0.666)	0.133 (0.515)	0.173 (0.608)

*Control treatment (placebo, active control, or usual care) [8]; ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers

Table 2. Clinical benefits associated with use of ACEIs instead of ARBs related with decrease of general mortality — discounted (undiscounted) results of the sensitivity analysis

Difference	Life years gained			Quality-adjusted life years,		
	Male (M)	Female (F)	M + F	Male (M)	Female (F)	M + F
ACEIs vs. control*	0.081 (0.112)	0.055 (0.079)	0.071 (0.100)	0.054 (0.080)	0.028 (0.047)	0.043 (0.067)
ARBs vs. control*	0.008 (0.011)	0.006 (0.008)	0.007 (0.010)	0.007 (0.009)	0.004 (0.007)	0.006 (0.008)
ACEIs vs. ARBs	0.073 (0.101)	0.050 (0.072)	0.064 (0.090)	0.047 (0.071)	0.023 (0.041)	0.037 (0.059)

*Control treatment (placebo, active control, or usual care) [8]; ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers

Table 3. Estimated annual savings for the National Health Fund and patients associated with preferential use of ACEIs instead of ARBs

	Existing scenario	New scenario	Difference (negative values indicate savings)
Number of cardiovascular deaths	59,647	57,878	-1768
Costs for the public payer (NHF)			
Cost of fatal CV events, thousands PLN (EUR)	25,649 (5883)	24,888 (5708)	-760 (-174)
Costs of drugs, thousands PLN (EUR)	369,743 (84,803)	258,470 (59,282)	-111,273 (-26,521)
Total costs, thousands PLN (EUR)	395,391 (90,686)	283,358 (64,990)	-112,033 (-25,696)
Costs for the patients			
Cost of drugs, thousands PLN* (EUR)	516,983 (118,574)	506,525 (116,175)	-10,458 (-2399)
Health outcomes, QALY (LYG)	4,924,706 (6,042,584)	4,925,536 (6,043,602)	830 (1018)**

*No costs of fatal CV events for patients was assumed; **In favour of the new scenario (changing treatment from ARBs to ACEIs); exchange rate 1 EUR = 4.36 PLN; ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; CV — cardiovascular; LYG — life years gained; QALYs — quality-adjusted life years

Use of ACEIs instead of ARBs is associated with a decreased number of CV deaths [8] and therefore lower costs of fatal CV events and lower cost of therapy (Table 3). It was estimated that the annual savings for the NHF, if all patients, except for patients experiencing cough, were treated with ACEIs, would amount to 112.0 million PLN (25.7 million EUR), resulting mainly from the lower cost of drug treatment in the case of ACEIs. Preferential use of ACEIs would reduce patients' annual expenditure on drugs by 10.5 million PLN (2.4 million EUR). The number of CV deaths in the target population would decrease by 1768 deaths per year. Assuming the average age of a treated patient with AH is 59 years (NATPOL 2011 Survey database), i.e. patient with relatively low risk of death, the annual gain from the change of treatment from ARBs to ACEIs would be 830 QALY and 1018 LYG.

DISCUSSION

Our cost-consequence analysis confirms the medical and economic benefits of preferring ACEI treatment instead of use of ARBs as a first-line therapy. ACEIs prolong the patient's life and overall quality of life. Due to the lower unit cost of ACEI treatment the cost of drug reimbursement borne by the NHF, as well as the patients' spending, might be substantially reduced. According to the reported expenditure of the NHF on the whole pharmacy reimbursement and on AH drug reimbursement, the projected savings for the public payer resulting from treatment with ACEIs, which are cheaper than ARBs, would amount to 1.5% and 15.1% of these expenses, respectively. Additionally, a reduction in the number of CV deaths is expected.

In our analysis we assumed preferential use of ACEIs in AH, for example through modification of reimbursement indications in both therapeutic groups, i.e. ARBs could be used in second-line treatment after ACEIs.

Angiotensin converting enzyme inhibitor treatment is cheaper than treatment with ARBs both from the NHF perspective and from the patient's perspective, thus savings associated with using ACEIs instead of ARBs were observed for both perspectives. Another way of generating savings for the public payer in the annual horizon, besides the change of reimbursement indication, is the potential creation of a common limit group for ACEIs and ARBs, which was analysed by Hermanowski et al. in 2014 [11] and amounted to 155 million PLN. Analysis of savings for both the public payer and for the patients concerns a limited one-year horizon. In terms of direct impact on the payer's budget it is important to present the most likely scenario involving clinical practice and cumulative savings associated with ACEI use in the subsequent years.

For the purpose of this analysis, the meta-analysis by van Vark et al. in 2012 [8], which included 20 randomised controlled trials involving 158,998 patients, was chosen as the source of clinical benefits [8]. The van Vark et al. study [8] was selected due to inclusion criteria of clinical studies in the meta-analysis — each study had to include at least 2/3 of patients with diagnosed AH — and population heterogeneity similar to clinical practice. As a result of the inclusion criteria a large study indicating the benefits of using ramipril in patients with high risk of CV events (HOPE study), in which less than half of the participants had AH, was excluded from the publication [16]. However, the treatment effect estimated from the HOPE trial is consistent and numerically even more extreme than the pooled result reported in the van Vark et al. paper [8] for the ACEI group; this implies that the relative effectiveness of ACEIs vs. ARBs would be augmented if the meta-analysis had included the HOPE trial. It should be emphasised that meta-analyses regarding subpopulations other than patients with AH (patients without heart failure and patients with diabetes — both publications included the

HOPE study) also demonstrated no benefit in favour of ARBs [9, 10]. According to clinical guidelines on management in AH, ACEIs should be preferred in patients with AH and with high CV risk (i.e. concomitant CV and metabolic complications) [1], with the exception of telmisartan, which belongs to first-line drugs in high-risk patients due to the outcomes of the ONTARGET study, which demonstrated non-inferiority of telmisartan compared to ramipril in this group of patients [17]. It has to be emphasised, however, that even in this case, the financial part of our argumentation holds and supports use of ARBs as second-line therapy, in cases when patients cannot be treated with ACEIs.

This analysis considers the relative reduction of total mortality as a result of using ACEIs in line with the results of the meta-analysis by van Vark et al. in 2012 [8]. In another publication the authors of this meta-analysis presented the benefits of using ACEIs with regard to mortality also in the form of the number of patients who had to be treated in a particular period of time in order to avoid one death — number needed to treat — NNT [18]. According to the results of this publication the number of patients (median) who had to be treated with ACEIs in a 4.3-year horizon in order to avoid one all-cause death or one CV death was 67 and 116, respectively. In the case of ARBs a much larger group of patients should be treated to avoid one all-cause death or one CV death — 335 and 409, respectively. Also, the results of other publications confirm the impact of ACEIs on mortality decrease [19].

Epidemiological data on the number of AH patients are limited, and to provide the most reliable number of patients treated with ACEIs and ARBs the estimates were based on NHF published sales data. Basing calculations on DDD, which does not always correspond to the real doses used in clinical practice in Poland (e.g. ramipril is more often used in 5-mg or 10-mg tablets than in DDD, i.e. 2.5 mg), is a limitation. On the other hand, this approach is consistent with the approach of the public payer and structure of the Polish reimbursement system. In order to estimate maximal annual savings for the payer it was hypothetically assumed that all patients, except for patients experiencing cough, would be treated with ACEIs instead of ARBs. However, the occurrence of cough does not always lead to permanent ACEI treatment discontinuation — according to the results of Sato and Fukuda [20], the percentage of patients treated with ACEIs, who discontinued treatment due to cough, was much lower than the total percentage of patients with cough (5.1% and 19.9%, respectively). Therefore, in real-world conditions, ARBs are administered only in a small proportion of patients due to ACEI intolerance [21]. However, due to the subjective nature of a bothersome cough, the conservative assumption was adopted that 10.6% patients treated with ACEIs terminate therapy due to dry cough. The cough proportion, based on Bangalore et al. [14], was also used to adjust the estimated average patient survival for quality of life in the ACEI group. Adopting such

an adjustment only in the ACEI group is a conservative approach because cough is also reported in 0–13% of patients treated with ARBs [22].

A limitation to this study is utilisation of a non-specific life table for AH patients — a conservative approach. Because AH is an accepted risk of death, life tables for the general population lead to overestimation of life expectancy regardless of the treatment regimen.

The annual gain attributable to treatment change from ARBs to ACEIs was estimated for an AH patient at an average age of 59 years based on the NATPOL 2011 Survey. This approach is conservative for the following reasons: 59 years is an unbiased estimate of the average age in the younger cohort of AH patients covered by the NATPOL 2011 sample (i.e. age distribution cut at 79 years), disregarding the population of patients aged ≥ 80 years. More importantly, the treatment effect calculated for a patient at an average age underestimates the actual average benefit expected in the population, because assumption of constant relative treatment effect implies the expected absolute effect will be augmented at older ages in line with increasing baseline risk. Therefore, incorporating the actual age distribution of AH patients reflecting higher risk in older patients, would result in higher LYG and QALY gains vs. our conservative estimates reported in Table 3.

Finally, it was assumed that the treatment effect based on van Vark et al. [8] for patients from the included clinical trials is constant over time and life-long, which needs to be confirmed in further studies. On the other hand, this assumption is consistent with life-long treatment of AH as recommended in the clinical guidelines, and also most clinical trials show the growing benefit of ACEIs vs. comparators over time. It should therefore be emphasised that our findings should be interpreted in relation to the adopted assumptions.

Last but not least, in this paper we analyse the health outcomes and economic consequences of using ACEIs and ARBs in the Polish setting in the treatment of AH only. Although AH is by far the most prevalent indication for both classes, they are also routinely used in clinical practice in other indications, i.e. coronary artery disease and heart failure. In these indications, ARBs are explicitly positioned by clinical guidelines [23, 24] as second-line in the case of intolerance or contraindications for the ACEIs, which implies that existing clinical evidence supports the preference of ACEIs. On the other hand, current financing of both classes from public funds does not discriminate between indications, i.e. the NHF unit cost of ARB treatment is more than four times higher than the cost of ACEIs.

Precise estimation of potential health and economic gains to be generated in coronary artery disease and heart failure (on top of the results presented for AH) warrants further research; nevertheless, the direction of inference is clear from the assumptions outlined above, i.e. the additional results in coronary artery disease and heart failure would strengthen

our conclusions because ARBs are dominated by ACEIs also in these indications.

CONCLUSIONS

Preferential use of ACEIs in comparison to ARBs in the treatment of AH is associated with projected extension of patients' lives, including quality-adjusted life, reduction of the number of CV deaths, and savings for the public payer (NHF) and patients. Introducing systemic changes, such as modifications of reimbursement indications for these groups of drugs, is possible and will bring benefits to patients as well as the public payer, which has been proven by the experiences of other European countries [25]. In terms of direct impact on the payer's budget it is essential to present the most likely scenario, which includes clinical practice and cumulative savings associated with ACEI use in consecutive years. In terms of public health and limited public funds our paper might indicate directions for decision makers (both for the prescribing physicians and decision makers) to improve current AH treatment from both a clinical and an economic point of view. By using fewer funds the NHF could offer better treatment for millions of Polish AH patients. The demonstrated clinical and economic unit gains combined with the huge epidemiological burden of AH in the Polish setting suggest substantial expected benefits, both in terms of improved health outcomes and significant financial savings for the NHF and patients.

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References

1. Tykarski A, Narkiewicz K, Gaciong Z et al. Zasady postępowania w nadciśnieniu tętniczym, 2015 rok. *Nadciśn Tętn w Prakt*, 2015; 1: 1–70.
2. Zdrojewski T, Rutkowski M, Bandosz P et al. Prevalence and control of cardiovascular risk factors in Poland. Assumptions and objectives of the NATPOL 2011 Survey. *Kardiologia Pol*, 2013; 71: 381–392.
3. Zdrojewski T, Bandosz P, Rutkowski M et al. Rozpowszechnienie, wykrywanie i skuteczność leczenia nadciśnienia tętniczego w Polsce: wyniki badania NATPOL 2011. *Nadciśn Tętn*, 2014; 18: 116–117.
4. Zdrojewski T, Więcek A, Grodzicki T et al. Rozpowszechnianie, świadomość i skuteczność leczenia nadciśnienia tętniczego u osób powyżej 65. roku życia w Polsce. In: Mossakowska M, Więcek A, Błądowski P eds. *Aspekty medyczne, psychologiczne, socjologiczne i ekonomiczne starzenia się ludzi w Polsce*. Termedia, Wydawnictwa Medyczne, Poznań 2012; 155–168.
5. Błądowski P, Mossakowska M, Chudek J et al. Medical, psychological and socioeconomic aspects of aging in Poland. Assumptions and objectives of the PolSenior project. *Exp Gerontol*, 2011; 46: 1003–1009.
6. Paczkowska A, Bryl W, Hoffmann K et al. Analiza kosztów leczenia nadciśnienia tętniczego w Polsce. *Now Lek*, 2012; 81: 145–151.
7. Bogusławski S, Smaga A, Falkiewicz B et al. Wpływ ustawy o refundacji leków na dostęp pacjenta do farmakoterapii, budżet NFZ oraz branżę farmaceutyczną. Ocena skutków regulacji. *Infarma*, Warszawa, październik 2014. Available from: http://infarma.pl/fileadmin/templates/infarma_v1.0/design/gfx/Raport_Wplyw_ustawy_o_refundacji_lekow.pdf [accessed: 28 July 2015].
8. Van Vark L, Bertrand M, Akkerhuis K et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158 998 patients. *Eur Heart J*, 2012; 33: 2088–2097. doi: [10.1093/eurheartj/ehs075](https://doi.org/10.1093/eurheartj/ehs075).
9. Savarese G, Costanzo P, Cleland J et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. *J Am Coll Cardiol*, 2013; 61: 131–142. doi: [10.1016/j.jacc.2012.10.011](https://doi.org/10.1016/j.jacc.2012.10.011).
10. Cheng J, Zhang W, Zhang X et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis. *JAMA Intern Med*, 2014; 174: 773–785. doi: [10.1001/jamainternmed.2014.348](https://doi.org/10.1001/jamainternmed.2014.348).
11. Hermanowski T, Borowiec Ł, Faluta T. How to optimize public spending on antihypertensive treatment in Poland: an example of rationalization analysis. *JHPOR*, 2014; 2: 78–87. doi: [10.7365/JHPOR.2013.4.9](https://doi.org/10.7365/JHPOR.2013.4.9).
12. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*, 2013; 31: 1281–1357. doi: [10.1093/eurheartj/ehs151](https://doi.org/10.1093/eurheartj/ehs151).
13. Golicki D, Niewada M. General population reference values for 3-level EQ-5D (EQ-5D-3L) questionnaire in Poland. *Pol Arch Med Wewn*, 2015; 125: 18–26.
14. Bangalore S, Kumar S, Messerli F. Angiotensin-converting enzyme inhibitor associated cough: deceptive information from the Physicians' Desk Reference. *Am J Med*, 2010; 123: 1016–1030. doi: [10.1016/j.amjmed.2010.06.014](https://doi.org/10.1016/j.amjmed.2010.06.014).
15. Adarkwah C, Gandjour A, Akkerman M, Evers S. To treat or not to treat? Cost-effectiveness of ace inhibitors in non-diabetic advanced renal disease - a Dutch perspective. *Kidney Blood Press Res*, 2013; 37: 168–180. doi: [10.1159/000350142](https://doi.org/10.1159/000350142).
16. Yusuf S, Sleight P, Pogue J et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*, 2000; 342: 145–153. doi: [10.1056/NEJM200001203420301](https://doi.org/10.1056/NEJM200001203420301).
17. Yusuf S, Teo K, Pogue J et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*, 2008; 358: 1547–1559. doi: [10.1056/NEJMoa0801317](https://doi.org/10.1056/NEJMoa0801317).
18. Brugts J, van Vark L, Akkerhuis M et al. Impact of renin-angiotensin system inhibitors on mortality and major cardiovascular endpoints in hypertension: A number-needed-to-treat analysis. *Int J Cardiol*, 2015; 181: 425–429. doi: [10.1016/j.ijcard.2014.11.179](https://doi.org/10.1016/j.ijcard.2014.11.179).
19. Buch P, Rasmussen S, Abildstrom S et al. The long-term impact of the angiotensin-converting enzyme inhibitor trandolapril on mortality and hospital admissions in patients with left ventricular dysfunction after a myocardial infarction: follow-up to 12 years. *Eur Heart J*, 2005; 26: 145–152. doi: [10.1093/eurheartj/ehi021](https://doi.org/10.1093/eurheartj/ehi021).
20. Sato A, Fukuda S. A prospective study of frequency and characteristics of cough during ACE inhibitor treatment. *Clin Exp Hypertens*, 2015; 37: 563–568. doi: [10.3109/10641963.2015.1026040](https://doi.org/10.3109/10641963.2015.1026040).
21. Formoso G, Magrini N, Marata A. Choosing ACE-inhibitors instead of sartans: Encouraging results of an evidence-based policy in Emilia-Romagna, Italy. *Eur J Intern Med*, 2015; 26: e21–e22. doi: [10.1016/j.ejim.2015.04.006](https://doi.org/10.1016/j.ejim.2015.04.006).

22. Matchar D, McCrory D, Orlando L et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med*, 2008; 148: 16–29. doi: [10.7326/0003-4819-148-1-200801010-00189](https://doi.org/10.7326/0003-4819-148-1-200801010-00189).
23. Montalescot G, Sechtem U, Achenbach S et al. Wytyczne ESC dotyczące postępowania w stabilnej chorobie wieńcowej w 2013 roku. *Kardiologia Pol*, 2013; 71 (suppl. X): 243–318. doi: [10.5603/KP.2013.0280](https://doi.org/10.5603/KP.2013.0280).
24. McMurray J, Adamopoulos S, Anker S et al. Wytyczne ESC dotyczące rozpoznania oraz leczenia ostrej i przewlekłej niewydolności serca na 2012 rok. *Kardiologia Pol*, 2012; 70 (suppl. II): 101–176.
25. Wettermark B, Godman B, Neovius M et al. Initial effects of a reimbursement restriction to improve the cost-effectiveness of antihypertensive treatment. *Health Policy*, 2010; 94: 221–229. doi: [10.1016/j.healthpol.2009.09.014](https://doi.org/10.1016/j.healthpol.2009.09.014).

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Efekty zdrowotne i konsekwencje ekonomiczne stosowania inhibitorów konwertazy angiotensyny w porównaniu z antagonistami receptora angiotensyny w leczeniu nadciśnienia tętniczego w warunkach polskich

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Streszczenie

Wstęp: Nadciśnienie tętnicze (AH) stanowi istotny problem zdrowia publicznego w Polsce, po pierwsze z powodu ogromnej, wciąż rosnącej populacji pacjentów z AH, szacowanej na podstawie danych z badań NATPOL 2011 i PolSenior na 10,45 mln chorych, a po drugie z powodu dużych obciążeń refundacyjnych generowanych dla Narodowego Funduszu Zdrowia (NFZ). Do najczęściej stosowanych leków w terapii AH należą inhibitory konwertazy angiotensyny (ACEI) i antagoniści receptora angiotensyny (ARB), z których te drugie wiążą się z większą jednostkową wysokością refundacji. Najnowsze metaanalizy randomizowanych badań klinicznych wskazują na brak podstaw do faworyzowania ARB w stosunku do ACEI w leczeniu AH.

Cel: Celem niniejszej pracy było oszacowanie korzyści klinicznych ze stosowania ACEI zamiast ARB oraz oszacowanie potencjalnych oszczędności dla płatnika i pacjentów związanych ze zmianą paradygmatu leczenia na preferencyjne stosowanie ACEI.

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Metody: Ocenę konsekwencji klinicznych przeprowadzono w odniesieniu do różnic w średniej długości życia, w tym skorygowanej o jakość (QALY), w przypadku stosowania ACEI i ARB. W tym celu uwzględniono wpływ tych leków na umieralność ogólną na podstawie wyników metaanalizy van Vark i wsp. (2012) — ryzyko względne (HR) = 0,90 w grupie ACEI i HR = 0,99 w grupie ARB. Jakość życia chorych skorygowano zgodnie z polskimi normami populacyjnymi dla kwestionariusza EQ-5D-3L oraz dodatkowo o zmniejszenie użyteczności z powodu kaszlu w grupie ACEI. Analizowano dwie sytuacje — w analizie podstawowej efekt leczniczy na podstawie wyniku metaanalizy van Vark i wsp. (2012) przypisano pacjentom od początku leczenia, tj. od 48. rż. (średni wiek rozpoczęcia terapii AH zgodnie z badaniem NATPOL 2011) do końca życia, a w analizie dodatkowej, bardziej konserwatywnej, od 67. rż. przez 4 lata na podstawie średniego wieku populacji objętej analizą van Vark i wsp. (2012). Wyniki zdrowotne dyskontowano (stopa 3,5%). Potencjalne oszczędności dla płatnika w horyzoncie rocznym oszacowano dla hipotetycznej kohorty chorych leczonych obecnie ARB i mogących zmienić terapię na ACEI. Liczbę chorych leczonych ARB i ACEI oszacowano na podstawie opublikowanych danych NFZ oraz badania IMS „indeks medyczny”, a liczbę zdefiniowanych dawek dobowych dla poszczególnych preparatów wg Światowej Organizacji Zdrowia, odpowiednio na 2,0 mln i 4,8 mln chorych (sytuacja obecna). W przypadku preferencyjnego stosowania ACEI założono, że wszyscy ci pacjenci, z wyjątkiem 10,6% osób z kaszlem, będą leczeni ACEI, tj. 6,1 mln chorych leczonych ACEI i 0,7 mln stosujących ARB. Dla tych scenariuszy oszacowano różnice w liczbie zgonów sercowo-naczyniowych i kosztów z nimi związanych (na podstawie statystyk Jednorodnych Grup Pacjentów) oraz różnice kosztów rocznej farmakoterapii ACEI i ARB (koszty leków przypisano na podstawie Obwieszczenia Ministra Zdrowia i danych sprzedażowych NFZ).

Wyniki: Na podstawie danych klinicznych stosowanie ACEI wiąże się z istotnym statystycznie 10-procentowym zmniejszeniem umieralności ogólnej. Tym samym, w przeprowadzonej analizie podstawowej, stosowanie ACEI wydłuża życie chorego średnio o 0,354 roku (4,2 miesiąca) lub 0,201 roku (2,4 miesiąca) w pełnym zdrowiu, tj. skorygowanego o jakość, podczas gdy stosowanie ARB wydłuża życie chorego o 0,034 roku (0,4 miesiąca) lub 0,029 roku (0,3 miesiąca) w pełnym zdrowiu. W scenariuszu konserwatywnym wyniki te wynoszą odpowiednio 0,071 roku i 0,043 roku w pełnym zdrowiu dla ACEI oraz 0,007 roku i 0,006 roku w pełnym zdrowiu dla ARB. W przypadku preferencyjnego stosowania ACEI w analizowanej hipotetycznej sytuacji oszczędności roczne dla NFZ wyniosłyby 112,0 mln PLN (25,7 mln EUR; w tym większość oszczędności wynika z mniejszego kosztu jednostkowego terapii ACEI), a pacjenci wydaliby na terapię o 10,5 mln PLN (2,4 mln EUR) mniej niż obecnie. Liczba zgonów sercowo-naczyniowych zmniejszyłaby się o 1768 rocznie.

Wnioski: Wprowadzenie zmian systemowych mających na celu preferencyjne stosowanie ACEI w porównaniu z ARB w leczeniu AH wiąże się z przedłużeniem życia, w tym skorygowanego o jakość, redukcją liczby zgonów sercowo-naczyniowych i oszczędnościami dla NFZ oraz pacjentów. Przedstawione oszacowania jednostkowych korzyści w połączeniu z dużym obciążeniem epidemiologicznym, jakie stanowi AH w Polsce, wskazują na możliwość wygenerowania istotnych korzyści zarówno w postaci dodatkowych efektów zdrowotnych, jak i znaczących oszczędności finansowych. Pod kątem bezpośredniego wpływu na budżet płatnika istotne jest pokazanie najbardziej prawdopodobnego scenariusza uwzględniającego praktykę kliniczną i kumulujące się oszczędności związane ze stosowaniem ACEI w kolejnych latach, co będzie przedmiotem następnych analiz.

Słowa kluczowe: nadciśnienie tętnicze, inhibitory konwertazy angiotensyny, antagoniści receptora angiotensyny, Narodowy Fundusz Zdrowia, preskrypcja oparta na dowodach naukowych, analiza konsekwencji kosztów

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