

ORIGINAL ARTICLE

Anthracycline-induced cardiotoxicity prevention with angiotensin-converting enzyme inhibitor ramipril in women with low-risk breast cancer: results of a prospective randomized study

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KEY WORDS

anthracyclines, breast cancer, cardiotoxicity prevention, ramipril

ABSTRACT

BACKGROUND Anthracycline-induced cardiotoxicity (AIC) remains the main long-term irreversible side effect in malignancy survivors. Cardiotoxicity prevention is one of the most reasonable approaches.

AIMS In this prospective randomized open-label study, we aimed to verify whether ramipril protects from early-onset AIC in women with breast cancer (BC).

METHODS We analyzed data from 96 women (median age, 47 years) with BC after breast surgery, without significant cardiovascular diseases, who were eligible for adjuvant anthracyclines. They were randomized to a ramipril or control arm. Cardiotoxicity was estimated with repeat echocardiography and the measurement of troponin I and N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) levels over 1-year follow-up. Anthracycline-induced cardiotoxicity was defined as a decrease in left ventricular ejection fraction (LVEF), elevated biomarker levels, and/or occurrence of heart failure (HF) or cardiac death.

RESULTS A decrease in LVEF above 10-percent points occurred in 6.3% of ramipril patients and 18.5% of controls ($P=0.15$). No cases of HF, cardiac death, or LVEF decline below 50% were reported. The percentage of patients with elevated NT-proBNP levels increased with time in controls ($P=0.003$) and remained unchanged in the ramipril arm. At the end of follow-up, an increase in NT-proBNP levels was more common and decline was less common in the control than ramipril arm ($P=0.01$). No significant differences in troponin levels were found between the study arms. Ramipril was well tolerated in normotensive women.

CONCLUSIONS In relatively young women with BC without serious comorbidities, who received anthracyclines, 1-year treatment with ramipril exerts potentially protective effects on cardiotoxicity assessed with NT-proBNP levels.

INTRODUCTION Breast cancer (BC) is the most common malignancy in women worldwide.^{1,2} The use of potentially cardiotoxic anthracyclines, cytostatic agents introduced many years ago, still remains the cornerstone of BC therapy.³⁻⁵ Most sources distinguish between acute (throughout anthracycline treatment)

and chronic forms of anthracycline-induced cardiotoxicity (AIC), which is classified into early-onset (first year) and late-onset cardiotoxicity.⁶ Chronic AIC typically presents as irreversible myocardial dysfunction and heart failure (HF). The estimated incidence of HF ranges from 6.6% to 26%.^{7,8} An asymptomatic

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WHAT'S NEW?

In women with breast cancer (BC) referred for cardiotoxic chemotherapy, a prophylactic intervention with an angiotensin-converting enzyme inhibitor is not supported by sufficient data. In our prospective study, treatment with ramipril was introduced shortly before chemotherapy in relatively young women with BC without significant cardiovascular disorders. At baseline and during and after chemotherapy with adjuvant anthracyclines, participants underwent repeated diagnostic workup with echocardiography as well as the measurement of NT-proBNP and troponin levels during a 1-year follow-up. Ramipril showed potentially protective effects on cardiotoxicity, as assessed by NT-proBNP levels.

decline in left ventricular ejection fraction (LVEF) is observed in 9% to 50% of cases, moderately corresponding to the adopted definition of cardiotoxicity.⁸⁻¹⁰

The risk factors for AIC include young age or age above 65 years, anthracycline cumulative dose (doxorubicin dose ≥ 250 mg/m²), use of other cardiotoxic drugs, previous or current chest radiotherapy, and history of cardiovascular comorbidities.¹¹ As AIC may actually occur at any dose as long as doxorubicin remains part of adjuvant therapy, preventive measures should be applied. However, no effective preventive strategies for cardiotoxicity have been routinely implemented so far. Based on early trials concerning anthracyclines, the role of angiotensin-converting enzyme inhibitors (ACEIs) in cardiotoxicity prevention was hypothesized,¹² but clinical data on this topic are scarce. A prophylactic intervention with an ACEI, although mentioned in Polish recommendations, is not supported by sufficient data.¹³ On the other hand, the 2018 National Comprehensive Cancer Network guidelines for cancer survivorship do not propose any preventive pharmacologic strategy.¹⁴ Thus, the role of ACEIs in cardiotoxicity prevention in patients with BC without significant cardiovascular disease remains undetermined.

The aim of this study was to evaluate the efficacy of ramipril in the prevention of LVEF decline and an increase in the levels of laboratory biomarkers among women with low-risk BC treated with adjuvant anthracycline therapy in a 1-year follow-up.

METHODS Consecutive women with stages I–III BC who underwent breast surgery and were referred for adjuvant anthracycline therapy were eligible for the study. Patients received either an anthracycline + cyclophosphamide (AC) or fluorouracil + epirubicin + cyclophosphamide (FEC) or epirubicin + cyclophosphamide regimen (4–6 cycles). In the AC regimen, doxorubicin was administered at 60 mg/m² per chemotherapy cycle. In the FEC regimen, epirubicin was administered at 75 mg/m² or 100 mg/m² every 3 weeks. In the case of

a dose-dense schedule, doxorubicin was administered every 2 weeks. Patients also received taxoids, trastuzumab, hormone therapy, and radiotherapy, as appropriate.

The exclusion criteria were as follows: 1) advanced BC and referral for induction chemotherapy; 2) pregnancy and breastfeeding; 3) current treatment with ACEIs or angiotensin receptor blockers; 4) contraindications to ACEI treatment; 5) diabetes, coronary artery disease, hypertension (except mild hypertension: 140–159/90–99 mm Hg); 6) refusal to participate in the study; 7) history of chest radiotherapy, another malignancy or treatment with anthracyclines; and 8) baseline LVEF on echocardiography below 50% or elevated baseline cardiac troponin levels (≥ 0.01 µg/l) or N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) levels above 125 ng/ml.

It was a prospective single-center randomized non-placebo-controlled open-label study. Participants were randomized in a 1:1 ratio to a ramipril or control arm by means of a dedicated software. We estimated that with a power of 95% and a 2-sided α level of 0.05, at least 40 patients in each group were required.

Treatment with ramipril was started before chemotherapy and was continued for 1 year. The dose was slowly titrated, starting from 2.5 mg and escalated every 7 to 14 days (depending on tolerance) by 2.5 mg, until the planned maximum dose of 10 mg/d was achieved. In the case of ACEI intolerance, a lower best-tolerated dose was sustained. Patients in the ramipril arm continued with daily treatment for at least 48 weeks. In the presence of medical indications, daily doses higher than 10 mg were allowed. The control arm received standard-of-care treatment without any specified strategies of cardiotoxicity prevention (except treatment of hypertension without an ACEI as appropriate).

All participants underwent electrocardiography, echocardiography, and laboratory tests including the measurement of serum NT-proBNP and troponin I levels, according to the study protocol.

Echocardiography Complete echocardiography examination was performed at the E-med outpatient cardiology clinic, using the VIVID S-6 ECHO unit (GE Medical System, Boston, Massachusetts, United States), equipped with a multifrequency harmonic transducer (2.5–4 MHz). Systolic function of the left ventricle was estimated with LVEF by means of the Simpson method. The average values of 3 consecutive measurements were recorded. Most patients were examined by the same operator (EK), blinded to patient allocation. Echocardiography was performed at baseline, after completing anthracycline chemotherapy, as well as 24 and 48 weeks (with a 4-week deviation allowed)

after enrollment. Cardiotoxicity was defined as a decrease in LVEF below 50% or more than 10-percent points from baseline.

Laboratory biomarkers Troponin levels were measured at baseline, after the first, middle (ie, depending on the regimen, after the second or third cycle), and last anthracycline chemotherapy cycle, using an enzyme-linked immunosorbent assay. The reference value for troponin I was lower than 0.01 µg/l. Cardiotoxicity was defined as an elevation of troponin levels (≥ 0.01 ng/ml).

The NT-proBNP level was assessed at baseline, after the first and last anthracycline cycle, and simultaneously with the last 2 echocardiography studies—after 24 and 48 weeks (± 4 weeks). The NT-proBNP level was determined with an electrochemiluminescence immunoassay (Elecsys, Roche Diagnostic, France). The reference value for healthy individuals younger than 75 years was less than 125 pg/ml. Cardiotoxicity was defined as an elevation of NT-proBNP concentrations (≥ 125 pg/ml).

Study endpoints Primary endpoints were an increase in the levels of troponin I or NT-proBNP (or both) above the upper limit of normal and a decrease in LVEF below the lower limit of normal (as described above). The secondary endpoint was HF or cardiac death (or both).

Safety procedures In all participants, arterial blood pressure and serum potassium levels were measured to monitor the safety of ramipril administration. All patients could contact a physician throughout the study.

Ethical issues The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Jagiellonian University (no. KBET/208/B/2014). Each study participant provided written informed consent before enrollment. During the whole therapy, effective contraception was applied in all participants (acceptable for BC contraceptive methods).

Statistical analysis The IMAGO PRO Academic 5 software pack (IBM SPSS Statistics 25, Kraków, Poland) was used for statistical analysis. All statistical tests were 2-sided with an α value of 0.05 ($P \leq 0.05$ was considered significant). The statistical power was 0.95. After collection of data from patients, preliminary intention-to-treat (ITT) and per-protocol analyses were performed. Results from the ITT analysis were presented unless described otherwise. Categorical variables were presented as percentages, while continuous variables, as median (interquartile range) or as mean and SD. The normality of distribution was checked with the Shapiro–Wilk test. For quantitative

variables and normal distribution, the *t* test was used. For non-Gaussian distribution, the Mann–Whitney test was applied. Categorical variables were compared using the χ^2 test, χ^2 with Yates correction (as appropriate), or McNemar test. The analysis of variance and multivariate analysis of variance were used to compare the change over time for continuous dependent variables. Results from every patient who received at least 1 chemotherapy cycle with doxorubicin were included in the final analysis.

RESULTS Between the years 2014 and 2017, we screened 450 women with a diagnosis of BC. At baseline, 348 women met the exclusion criteria. The remaining 102 women were randomized in a 1:1 ratio to the ramipril or control arm. After randomization, 4 participants did not keep visits and were excluded from the final analysis. In the ramipril arm, after a few days of treatment, 1 woman discontinued the therapy due to weakness, without a significant drop in systolic blood pressure, while 1 patient died due to cancer progression. The ramipril dose of 8.36 mg/d was the mean achieved dose, with 10 mg as the target (higher doses were not considered as a trial intervention but as cardiac treatment). Three patients received ramipril at a dose of 20 mg/d due to hypertension.

Finally, 96 women (48 in the ramipril arm and 48 in the control arm), at a median age of 47 years (range, 38–54 years) completed all prespecified procedures. The main characteristics of the study population as well as data on cancer treatment are presented in TABLE 1 and in Supplementary material, Tables S1–S3.

Changes of left ventricular ejection fraction

A decrease in LVEF was similar in both arms (5 women [11%] in the ramipril arm and 9 women [18.5%] in the control arm; $P = 0.16$). However, no cases of LVEF below 50% were reported. In the ITT analysis, there were no differences between groups in terms of LVEF changes on repeated measurements ($P = 0.18$). Data are presented in FIGURE 1. At baseline and at the end of the study, no interaction with an introduced intervention with ramipril in terms of LVEF was observed ($P = 0.34$). There were no cases of HF or cardiac deaths.

Serum NT-proBNP levels There were no changes in the percentage of patients with elevated NT-proBNP levels over time in the ramipril arm ($P = 0.42$). However, an increase from 6.9% to 29.4% in the percentage of patients with NT-proBNP levels of 125 pg/ml or higher was observed in the control arm ($P = 0.003$; FIGURE 2).

During follow-up, a steady increase over time in the percentage of patients with elevated NT-proBNP levels in the control arm was noted

TABLE 1 Characteristics of the study population

Parameter		Ramipril arm (n = 48)	Control arm (n = 48)	P value
Age, y, median (IQR)		45 (38–54)	45 (42–53)	0.45
BMI, kg/m ² , median (IQR)		24.3 (23.05–28.48)	23.74 (21.11–25.56)	0.12
Baseline LVEF, %, median (IQR)		67 (65–70)	65 (64–69)	0.16
Baseline NT-proBNP, pg/ml, median (IQR)		59.6 (38.25–84.6)	67.9 (42.2–97)	0.36
Hemoglobin, g/l, mean (SD)		13.06 (0.95)	13.22 (0.97)	0.53
LDL-C, mmol/l, mean (SD)		3.10 (1.25)	2.90 (1.3)	0.08
Menopausal status, %	Postmenopausal	27.3	34.5	0.36
	Premenopausal	72.7	55.2	
Weight gain, %		28.1	27.6	0.96
Smoking history, %		24.2	24.1	0.98
Family history of CVD, %		38	42	0.67
Prediabetes, %		6.1	10.3	0.54
Mild hypertension ^a , %		12	13.8	0.88
SBP, mm Hg, median (IQR)		125 (110–135)	130 (110–135)	0.08
DBP, mm Hg, median (IQR)		79 (65–90)	80 (65–85)	0.18
SCORE, median (IQR)		0.92 (0.86–2.68)	0.8 (0.72–2.56)	0.95
POL-SCORE, median (IQR)		1.32 (0.67–2.24)	1.42 (0.79–2.24)	0.52
Taxanes, %		48.5	58.6	0.43
Trastuzumab, %		15.2	34.5	0.08
Hormone therapy, %		69.7	89.7	0.05
Radiotherapy, %	No radiotherapy	33.3	20.7	0.11
	Right breast	51.5	41.4	
	Left breast	15.2	37.9	
	Total	64.5	78.6	
GnRH analogue, %		18.2	10.3	0.38
Other antihypertensive drugs, %	β-Blockers	27	19	0.33
	CCBs	5	6	0.97
	Diuretics	3	5	0.96

a Only mild hypertension (stage 1) was allowed (SBP, 140–149 mm Hg; DBP, 90–99 mm Hg)

Abbreviations: BMI, body mass index; CCB, calcium channel blocker; CVD, cardiovascular disease; DBP, diastolic blood pressure; GnRH, gonadotropin-releasing hormone; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; POL-SCORE, Systematic Coronary Risk Evaluation for Polish population; SBP, systolic blood pressure; SCORE, Systematic Coronary Risk Evaluation

($P = 0.01$). In the ramipril arm, the percentage of patients with elevated NT-proBNP levels remained the same at all time points ($P = 0.3$).

At the end of chemotherapy with anthracyclines ($P = 0.32$) and at 6 months ($P = 0.19$), we observed no differences between the study arms in the percentage of patients with NT-proBNP decline, stabilization ($\pm 20\%$ from baseline), and elevation. A difference between the arms was noted at 12 months. More patients presented an increase (69% vs 41.9%) and fewer patients presented a decrease in NT-proBNP levels (3.4% vs 32.3%) in the control than in the ramipril arm ($P = 0.01$).

On repeated measurements, we found no interaction with the intervention with ramipril ($P = 0.43$). At baseline and at the end of follow-up, there were no differences in the median serum NT-proBNP concentrations between the intervention and control groups: at baseline, 59.6 pg/ml (range, 38.25–84.6 pg/ml) and 67.9 pg/ml (range, 42.2–97 pg/ml), respectively ($P = 0.36$), and at the end of the follow-up, 81.9 pg/ml (range, 65.4–105.6 pg/ml) vs 89.2 pg/ml (range, 61.1–174.4 pg/ml), respectively ($P = 0.09$). However, in the ramipril arm, the median NT-proBNP level at baseline did

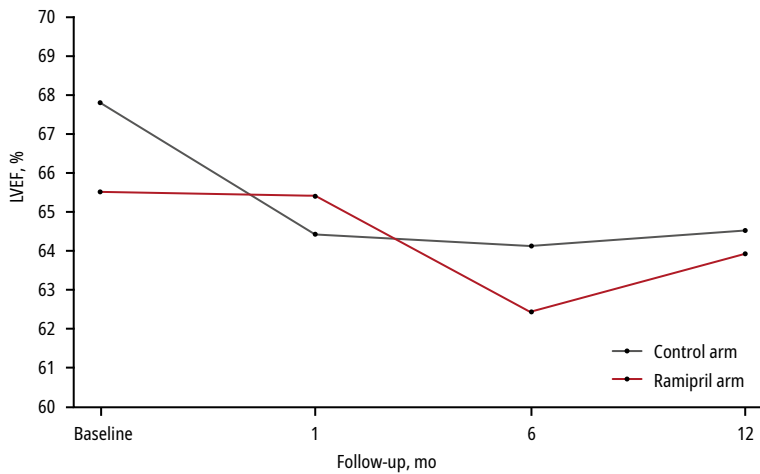


FIGURE 1 Comparison of changes in mean left ventricular ejection fraction (LVEF) values between ramipril and control arms during 1-year follow-up: an intention-to-treat analysis. Vertical bars show 95% CI; P for interaction = 0.1816.

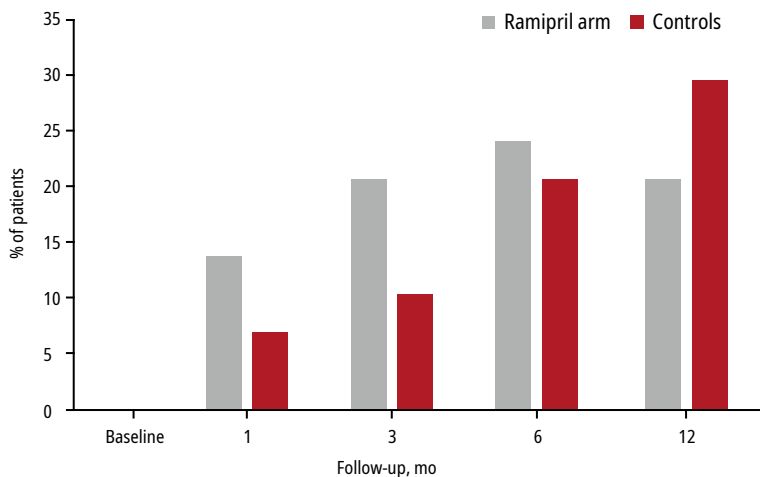


FIGURE 2 Percentage of patients with N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) levels of 125 pg/ml or higher in the ramipril and control arms during 1-year follow-up: intention-to-treat analysis

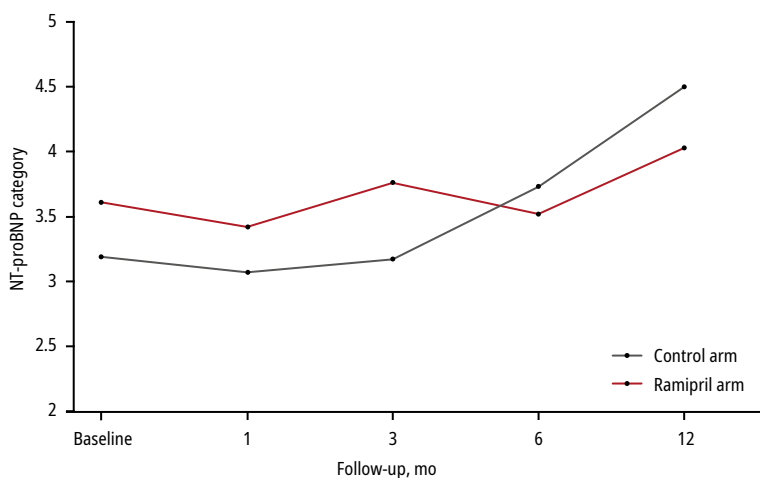


FIGURE 3 Comparison of changes in mean N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) levels between the ramipril and control arms during 1-year follow-up: per-protocol analysis. Vertical bars show 95% CI; P for interaction = 0.2897.

not change as compared with the 12th month of follow-up (59.6 pg/ml [range, 38.25–84.6 pg/ml] vs 81.9 pg/ml [range, 65.4–105.6 pg/ml]; $P = 0.44$), but an increase was observed in the control arm (67.9 pg/ml [42.2–97 pg/ml] vs 89.2 pg/ml [61.1–174.4 pg/ml]; $P = 0.002$).

In the whole study group ($n = 96$), an increase of median NT-proBNP levels over time was observed: 65.45 pg/ml (range, 39.25–89.35 pg/ml) at baseline vs 105.10 pg/ml (range, 42.3–174.5 pg/ml) at the end of the study ($P = 0.007$).

We stratified NT-proBNP results into 9 groups (according to NT-proBNP class/category): 8 groups with an ascending threshold of 25 pg/ml, and the last group including the remaining results (ie, >200 pg/ml). Next, we calculated the mean NT-proBNP class at different time points. Consistently with previous results, there was no effect of the intervention on the NT-proBNP class on repeated measurements ($P = 0.44$), but significant changes of the class were observed over time ($P = 0.03$; FIGURE 3). An additional analysis was performed to verify whether the ramipril dose influenced the NT-proBNP level. However, the group treated with a low ACEI dose was very small (a few cases), and from a statistical point of view, it was not powered enough to show any differences.

Effect of other treatments and factors on NT-proBNP levels at 6 months There was no difference in the mean NT-proBNP concentration between patients treated and not treated with radiotherapy. Similarly, taxoids and trastuzumab had no significant effect on the mean NT-proBNP values at 24 weeks ($P = 0.95$ and $P = 0.98$, respectively).

Troponin An increase in troponin levels above the threshold value was reported in 6.9% of patients in the control arm and 6.3% of those in the ramipril arm ($P = 0.92$). An increase in troponin I concentrations always occurred after the last anthracycline infusion. Moreover, a tendency for a persistent rise in troponin levels on repeated testing in the control arm was noted, whereas in the intervention arm, it normalized at first follow-up visit. Eventually, the increase in troponin levels was reversible in all patients, and it was never associated with any changes on echocardiography or clinical symptoms during the 1-year follow-up.

Safety We did not observe any severe adverse effects related to the ramipril treatment in the intervention group. Dry cough was reported by 3 patients. The dose escalation was objectively well tolerated, with no significant hypotension or tachycardia. Four normotensive patients did not reach the 10-mg daily dose because of weakness or fear of hypotensive effects despite maintained normal blood pressure.

DISCUSSION In relatively young women with BC without concomitant cardiovascular disease, who received low cumulative doses of anthracycline (except women with mild hypertension), ramipril did not prevent from LVEF decline in a 1-year follow-up. These negative results were undoubtedly influenced by the low prevalence of early-onset AIC on imaging (according to the adopted echocardiographic definition of cardiotoxicity) in this “low-risk” group. However, to confirm that ACEIs have no effectiveness in this population, longer studies including patients with late-onset chronic cardiotoxicity are needed.

The results of troponin measurements as a marker of AIC were inconclusive in our population. However, in the ramipril arm, in contrast with the control arm, we observed no increase in the percentage of participants with elevated NT-proBNP levels over time. This result may suggest certain preventive properties of ramipril. On the other hand, none of the available strategies for the prevention of cardiotoxicity are sufficiently sensitive to assess subclinical cardiotoxicity. All imaging modalities reveal only the already existing clinical cardiac dysfunction, which in the context of anthracyclines is irreversible.

There is also no ideal biomarker in terms of AIC. In the available literature, NT-proBNP and troponins are the only accepted biomarkers, but they have their limitations.^{13,14} In the context of our own results, NT-proBNP was the most valuable marker. During the 1-year follow-up, we only assessed the short-term preventive effects of the ACEI, and we used changes in NT-proBNP concentrations as a surrogate endpoint because there are data to confirm that an increase in the levels of NT-proBNP can predict left ventricular dysfunction or failure as well as cardiac death. Therefore, especially patients with elevated NT-proBNP levels during chemotherapy should be followed by cardio-oncologists on a long-term basis.

The role of ACEIs and β -blockers in anthracycline- and trastuzumab-induced cardiotoxicity is still debated. Most trials with ACEIs in AIC prevention focus on enalapril. We decided to use ramipril, because it belongs to the newer generation of ACEIs. However, Cernecka et al,¹⁵ in a paper published 2 years after our trial was launched, revealed that ramipril was insufficient to restore proper cardiac function due to the lack of effect on a shift in myosin heavy chain.

A recent cohort study on 6542 elderly patients with BC retrospectively analyzed data on ACEI or β -blocker exposure. It showed the hazard ratio of 0.77 (95% CI, 0.62–0.95) for cardiotoxicity and all-cause mortality in favor of ACEI use.¹⁶ However, in this trial, ACEIs were used not as prevention but as treatment of cardiovascular disease, and the study population included elderly individuals. On the contrary, most patients in our study

received an ACEI only as preventive treatment (merely 12.9% of women had mild hypertension without other significant cardiovascular disease).

Cardinale et al^{12,17} proved that ACEIs have a protective effect in a high-risk group defined as elevated troponin levels after high-dose chemotherapy. Earlier, the same authors showed that in patients with elevated troponin concentrations, an intervention with ACEIs prevented deterioration of LVEF.¹⁸ In contrast, the recent ICOS-ONE trial (International CardioOncology Society-one), comparing prevention of primary vs troponin-induced AIC, did not demonstrate significant benefits of an early intervention with enalapril.¹⁹ However, the incidence of LVEF decline (<50% and \geq 10% reduction) among patients with BC on standard cumulative doses of anthracycline was low (1.1%), similar to our study (0%). Nonetheless, the ICOS-ONE trial did not include the arm without any intervention, which made it impossible to verify the hypothesis of enalapril's protective effect in this particular population. This issue was addressed in our trial. Moreover, routine laboratory biomarker testing (suggested in the ICOS-ONE trial) was not implemented in clinical practice, mainly due to additional costs of cardiac biomarker measurement and a need for repeated blood collection.²⁰ It is of interest that, in our study, chemotherapy delays were observed more frequently in the ramipril arm, mostly due to neutropenia. However, the significance of this finding is unknown.

Our study has several limitations. First, there was no active follow-up after 1 year. The study did not focus on late-onset cardiotoxicity, especially late cardiovascular mortality. However, the follow-up (the second part extending beyond the first year as planned in the protocol) without any intervention or procedures for the assessment of HF development and overall survival analysis will be continued.

Additionally, our study was performed in relatively young women without severe cardiovascular disorders (except mild hypertension). As a consequence, our results cannot be applied to all women with BC. Further research focusing on the prevention of cardiotoxicity in a diverse population of patients with BC is needed, because more aggressive BC phenotypes are common, especially in young women, who require an intensive treatment. Recurrence risk in those phenotypes is higher, and further treatment, including chemotherapy, may be needed. Normal heart function is required for most treatments (chemotherapy, anti-human epidermal growth receptor 2 therapy) that are offered in case of BC recurrence.

Another limitation of our study is the lack of placebo in the control arm. We also did not include subgroup analyses (eg, patients receiving trastuzumab because of a small number of patients in this subgroup).

Conclusion In relatively young women with BC without serious comorbidities, who received anthracycline therapy, 1-year treatment with ramipril exerts a potentially protective effect on cardiotoxicity assessed with NT-proBNP. However, its efficacy in long-term prevention of AIC was not investigated in this study; therefore, further research is needed. In the context of our own results, NT-proBNP was the most valuable marker of cardiotoxicity. NT-proBNP testing seems reasonable even in a low-risk population receiving anthracyclines. In clinical practice, patients with elevated NT-proBNP levels due to chemotherapy may need closer and long-term surveillance for AIC development. However, the correlation between NT-proBNP levels and myocardial dysfunction should be further investigated, especially in selected cancer patients.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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