VIA MEDICA

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2023, tom 8, nr 5, 336–344

ISSN: 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Artykuł przeglądowy / Review article

Kardioonkologia / Cardiooncology

Pharmacological prevention methods in patients with cardiovascular disease with breast cancer – when, how, and for whom?

Maciej Dyrbuś, Ilona Skoczylas, Aleksandra Majsnerowska, Mariusz Gąsior, Mateusz Tajstra

3rd Department of Cardiology, School of Medical Sciences in Zabrze, Medical University of Silesia, Zabrze, Poland

Breast cancer is the leading cause of cancer-related deaths in women worldwide. Patients with breast cancer are at an increased risk of cardiovascular toxicity, presently defined as cancer therapy-related cardiovascular toxicity (CTR-CVT). This article provides a summary of the current knowledge on pharmacological cardiovascular prevention in breast cancer patients. The European Society of Cardiology (ESC) guidelines on cardio-oncology have defined CTR-CVT. Baseline risk stratification with widely accepted risk scores is essential to identify patients at higher risk of CTR-CVT. The guidelines recommend the use of angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), and β-blockers as preventive medications in high-risk patients. Clinical trials have shown ambiguous results for ACE-I/ARBs and β-blockers in reducing cardiotoxicity, while co-administration of ACE-I/ARBs and β-blockers did not show additional benefits in preventing cardiac dysfunction. Further research is needed to verify the efficacy of novel cardioprotective medication and optimize pharmacological strategies for cardiovascular prevention in breast cancer patients.

Key words: cardio-toxicity, cardiovascular prevention

Introduction

Breast cancer is the most diagnosed cancer and the leading cause of deaths due to cancer among women worldwide. In the United States, it is the second most common cancer among female patients and is the second leading cause of cancer deaths with incidence being relatively stable over the past two decades [1, 2]. As well as in the US, in Europe breast cancer is the most common cancer among female patients, with an estimated 522,000 new cases and 137,000 deaths in 2020 [3, 4]. It should be noted that both in Europe and the USA, the mortality rates of breast cancer have been declining likely due to advances in its successful detection and introduction of more efficacious therapeutic protocols.

Nonetheless, breast cancer patients are often at an increased risk of developing cardiovascular disease, due to a wide variety of factors, including baseline disease, cancer treatment strategies, as well as lifestyle changes associated with cancer [5, 6]. In the recent years, attempts have been made to stratify the risk of development of cardiovascular disease, especially a rather acutely developing cardiac dysfunction, labelled as "cancer therapy-related cardiovascular toxicity (CTR-CVT)" [7]. In patients at risk of CTR-CVT development, the introduction of preventive methods prior to cancer treatment might reduce the risk of the development of such conditions. Among those, pharmacological strategies can play a critical role in reducing this risk of cardio-toxicity, with a possible influence on

Jak cytować / How to cite:

Dyrbuś M, Skoczylas I, Majsnerowska A, Gąsior M, Tajstra M. ***Pharmacological prevention methods in patients with cardiovascular disease with breast cancer – when, how, and for whom?*** *NOWOTWORY J Oncol* 2023; 73: 268–276.

a patient's quality of life, the efficacy of cancer treatment, and long-term outcomes. The aim of the manuscript is to briefly summarize the current knowledge on pharmacological cardiovascular prevention in patients with breast cancer.

Definition and clinical significance of cancer treatment-related cardiovascular toxicity

The definition of cardiotoxicity, or as it should be named at present, CTR-CVT, has been established in the recent European Society of Cardiology (ESC) guidelines on cardio-oncology [7]. The guidelines have divided the broad spectrum of CTR-CVT on the basis of the pathomechanism and clinical manifestation, including the development of heart failure (HF), myocarditis, toxicity to the vascular structures, or the presence of hypertension, or rhythm disorders. Most notable is the definition of cancer therapy-related cardiac dysfunction (CTRCD), which encompasses the wide spectrum of myocardial damage associated with anticancer therapy. The definition of CTRCD according to the ESC guidelines is presented in table I. It should be noted that the definition allows to diagnose CTRCD solely on the basis of echocardiography, even in the absence of any clinical signs or symptoms of HF, although the guidelines recommend other imaging modalities, including magnetic resonance imaging in certain clinical situations [8]. The other important definitions, including the specific criteria for diagnosing myocarditis, defining vascular complications and arterial hypertension or arrhythmias were also thoroughly defined in the guidelines. The unification of those definitions is crucial, since it will allow to more cautiously monitor their real prevalence, as in the past the frequencies reported in the literature could have varied significantly due to differences in diagnostic criteria for each condition [9].

Similar to patients with other types of cancer, patients with breast cancer who receive treatment are at risk of developing CTRCD, which can lead to serious complications and may significantly impact the quality of life. The most prevalent types of cardiovascular adverse effects are presented in table II. Moreover, cardiac failure can interfere with assumed cancer treatment protocol, and result in a necessity to either reduce the dosing or the frequency of administered therapies, thus affecting the effectiveness of the cancer treatment, and affecting outcomes [10–12]. Finally, it has been demonstrated that the development of CTRCD is associated with an increased long-term risk of HF in patients who experienced CTRCD [13, 14].

The years of experience with treatment of patients with cancer have demonstrated how to – at the present stage

Table I. Definitions of cancer therapy-related cardiac dysfunction (CTRCD) on the basis of the 2022 ESC guidelines on cardio-oncology [7]

Cardiac dysfunction		Recommendations
symptomatic	very severe	HF requiring support with inotropic drugs, mechanical circulatory support or consideration of heart transplantation
	severe	HF requiring hospitalization
	moderate	need for intensification of diuretic therapy or escalation of HF treatment in the outpatient setting
	mild	mild HF symptoms without necessity to modify the therapy
asymptomatic	severe	new reduction in LVEF to <40%
	moderate	new reduction in LVEF by ≥10% to LVEF of 40–49% or new reduction in LVEF of <10% to LVEF of 40–49% and new relative decrease in GLS of ≥15% or new increase in cardiac biomarkers[a]
	mild	LVEF of ≥50% and new relative decrease in GLS of >15% from baseline and/or new increase in cardiac biomarkers

LVEF – left ventricle ejection fraction; GLS – global longitudinal strain; BNP – B-type natriuretic peptide; HF – heart failure; NT-proBNP – N-terminal pro-B-type natriuretic peptide; [a] – cTnI/cTnT ≥ 99th percentile; BNP ≥ 35 pg/ml; NT-proBNP ≥ 125 pg/ml or a new significant increase from baseline beyond the biological and analytical variability of the test used

Table II. The most common adverse cardiovascular events associated with anti-cancer drugs

Anti-cancer drug group	Cardiovascular adverse events reported most frequently
anthracyclines	heart failure, arrhythmias, pericarditis
HER2-targeted therapies	heart failure, arrhythmias, hypertension
tyrosine kinase inhibitors	QT interval prolongation, hypertension, arrhythmias
aromatase Inhibitors	low risk of cardiotoxicity, potentially: dyslipidemia, atherosclerosis progression, arrhythmias

of knowledge – stratify patients according to their baseline risk for development of CTRCD. As a rule of thumb, an early identification of patients at higher risk of medical procedures has been widely proven to improve prognosis and is therefore recommended. Similarly, the ESC guidelines on cardio-oncology specify that it's best to define the baseline risk right at the time of cancer diagnosis, even before initiation and planning of treatment. Although there is no single, established pathway on how to optimally screen and then risk-stratify patients according to their baseline CV risk, the parameters which according to the ESC should be taken into consideration before initiation of anti-cancer treatment are listed in table III, while the detailed guidelines on cardiovascular prevention in patients with cancer are presented in table IV.

Table III. Parameters requiring verification at baseline in order to define CV risk prior to cancer treatment initiation according to the 2022 ESC guidelines on cardio-oncology [7]

Parameters requiring verification at baseline in order to define CV risk prior to cancer treatment initiation
CV risk factors (with emphasis on the modifiable risk factors)
CVD history
cancer history
cancer treatment history
physical examination (including vital parameters)
baseline ECG (including QTc analysis)
transthoracic echocardiography (including GLS, and 3D echocardiography if possible)
laboratory parameters: BNP/NT-proBNP, cTn, FPG/HbA1c, creatinine/eGFR, lipid profile

BNP – B-type natriuretic peptide; cTn – cardiac troponin; CV – cardiovascular; CVD – cardiovascular disease; ECG – electrocardiography; eGFR – estimated glomerular filtration rate; FPG – fasting plasma glucose; GLS – global longitudinal strain; HbA1c – glycated hemoglobin; NT-proBNP – N-terminal pro-B-type natriuretic peptide; QTc – corrected QT interval

After thorough assessment of patients' baseline cardiovascular risk, the physicians should stratify the patient's therapeutic toxicity risk. In recent years, multiple risk scores for identification of CV toxicity were analyzed, although the detailed risk score, would be recommended to remain as it is. Heart Failure Association–International Cardio-Oncology Society (HFA-ICOS) provides the most comprehensive data and thus has been included in the recent ESC guidelines as the preferred one, with a class IIa recommendation [15–17]. The HFA-ICOS classification is based on almost every factor assessed at baseline and defines the risk with regards to the strategy of anti-cancer treatment, depending on the possible influence of every individual drug group on every risk factor. For instance, the very high risk of cardiotoxicity in patients with cardiac amyloidosis has been highly documented only for multiple myeloma therapies. With regard to chemotherapy schemes utilized in the treatment of breast cancer, most often anthracyclines and/or anti-HER2 drugs, the risk of CTR-CVT is very high only if the patients have had HF or CTR-CVT in the past, or if the patient scheduled for trastuzumab had received trastuzumab before. With regard to other chemotherapeutic groups used in the treatment of breast cancer, such as VEGF inhibitors, there are plenty of factors associated with a very high risk of CTR-CVT, including any history of HF or even asymptomatic left ventricular contractile dysfunction, as well as a history of any significant atherosclerotic cardiovascular disease. Any other factors of known significance, including the history of MI/PCI, decreased LVEF or advanced age should be noted, and, based on their calculable association with CTR-CVT, the total risk score could be then evaluated and subsequently divided into low-, moderate- or high-risk.

The stratification of CV toxicity risk at baseline is important, because on the basis of the initial assessment, all further surveillance should be performed. Those could include routine follow-up visits in the oncology clinic if the patient is at low-risk of CTR-CVT, or a more detailed follow-up if the patient is in the moderate risk group. However, the general rule should

Table IV. Recommendations on the appropriate primary prevention of cancer therapy-related cardiovascular toxicity according to the 2022 ESC guidelines on cardio-oncology [7]

Recommendations	Class of recommendation, level of evidence
management of CVRF according to the 2021 ESC guidelines on CVD prevention in clinical practice is recommended before, during, and after cancer therapy	I, C
dexrazoxane should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated	IIa, B
liposomal anthracyclines should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated	IIa, B
ACE-I or ARB and β-blockers recommended for HF should be considered for primary prevention in high- and very high--risk patients receiving anthracyclines and/or anti-HER2 therapies	IIa, B
ACE-I or ARB and β-blockers recommended for HF should be considered for primary prevention in high- and very high--risk patients receiving targeted cancer therapies that may cause HF	IIa, C
statins should be considered for primary prevention in adult patients with cancer at high and very high CV toxicity risk	IIa, B

ACE-I – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; CV – cardiovascular; CVD – CV disease; CVRF – CV risk factors; ESC – European Society of Cardiology; HER2 – human epidermal receptor 2; HF – heart failure

be that patients with low- and moderate risk of CTR-CVT should not have the anti-cancer therapy delayed and should initiate treatment at the earliest possible stage. In those categories, a referral to a cardiology clinic or at least to an experienced cardiologist is necessary only if the CTR-CVT develops; an exception being that a treating oncologist might consider referral to the cardiology department regardless of the development of CTR-CVT in patients at moderate risk.

If the patient is considered as high- or very-high risk of CTR--CVT, after a baseline assessment, a referral to a cardio-oncology clinic is mandatory, and cardioprotective medication should be considered at baseline to mitigate that risk during cancer treatment. Moreover, for those patients, the guidelines recommend discussing all the risks and benefits associated with potentially cardiotoxic treatment in a multidisciplinary team to establish the most optimal strategy going forward.

Cardiovascular prevention

In the general population, the present ESC guidelines on cardiovascular prevention specify non-pharmacological, and pharmacological interventions which should be initiated to reduce the cardiovascular risk [18]. However, many of the suggested preventive strategies were deemed ineffective in patients with cancer. Although a straightforward answer to such discrepancy in outcomes is difficult to be presented, it could be speculated that among patients with cancer, it is the baseline disease, and often the presence of various CV risk factors, that in combination increase the baseline CV risk and thus reduce the reckoned efficacy of preventive strategies.

The ESC guidelines on cardio-oncology recommend initiation of "cardio-preventive" medication in patients with high- or very-high risk of CTR-CVT, stratified according to the initial baseline risk assessment. In those patients, an anti-cancer drug with the lowest possible cardiotoxicity risk should be selected. Moreover, the guidelines recommend consideration of administration of specific cardioprotective drugs in those patients. Those, apart from implementation of strategies mitigating the risk of anthracycline-induced cardiotoxicity, including treatment with dexrazoxane or liposomal anthracyclines, refer to the introduction of neurohormonal therapies, including angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs), β-blockers, and preventive treatment with statins [19]. ACE-I/ARBs and β-blockers are the groups of drugs commonly used as a first-line therapy in patients with heart failure, or hypertension, and have been also shown to improve cardiovascular outcomes in patients with cancer [20].

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

Two large, randomized trials – Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA) and Cardiotoxicity Prevention in Breast Cancer Patients Treated With Anthracyclines and/or Trastuzumab (SAFE) investigated the role of primary prevention of CTR-CVT with the use of ACE-I or ARBs specifically in patients with breast cancer. In PRADA, 130 patients with early breast cancer, treated with anthracyclines, underwent randomization to either candesartan (member of ARBs) or metoprolol (a β-blocker). Prevention with candesartan but not with metoprolol was associated with a statistically significantly lower LVEF reduction (candesartan *vs.* non-candesartan: 0.8% *vs.* 2.6%, $p = 0.026$). On the contrary, treatment with metoprolol was associated with smaller increases in levels of cardiac troponins [21]. However, in the long-term analysis, no differences in LVEF were observed in any of the studied groups [22].

In the SAFE trial, which was performed in a 4-arm design, an interim analysis performed after 12 months of follow-up revealed that in patients with no prior cardiovascular disease, cardioprotective therapy with ramipril (an ACE-I) or bisoprolol (a β-blocker), was associated with improved echocardiography outcomes than in patients treated with a placebo [23]. In detail, patients treated preventively with both drugs demonstrated a slight (0.1%) improvement in left ventricular global longitudinal strain (GLS), while GLS was reduced in the placebo arm (by 6.0%) as well as in patients treated with ramipril or bisoprolol monotherapy (respectively by 1.5% and 0.6%, $p < 0.001$). Moreover, the number of patients experiencing a major reduction of LVEF (by ≥10% in the 3D-echocardiography) was lower in the group treated with ramipril and/or bisoprolol, with 6.8%, 11.5%, and 11.4% of patients experiencing such an endpoint when treated with respectively combined therapy, ramipril or bisoprolol monotherapy. In patients administered with placebo, 19% experienced a major LVEF reduction [23].

The molecular rationale for prevention of CTRCD with either ACE-I or ARB is broad, although it is speculated that it is mostly based on preclinical studies in which mice with knockout of angiotensin II type 1a receptor gene, are at a significantly reduced risk of anthracycline-induced cardiotoxicity [24]. Moreover, in the general population, administration of ACE-I or ARBs was associated with improvements on both macroscopic and microscopic levels. Inhibition of RAA resulted in a reduction of myocardial fibrosis, while intracellularly, in an improvement of mitochondrial function, reduction of oxidative stress, and positive alterations in the calcium homeostasis [25, 26], all mechanisms which might explain the benefits associated with ACE-I/ARBs in patients with cancer.

β-blockers

The efficacy of β-adrenolytics in the prevention of CTR-CVT has already been discussed in the two aforementioned trials, which evaluated metoprolol and bisoprolol, two of four β-blockers recommended in the treatment of heart failure in the overall population. The efficacy of the third was evaluated in the Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity (CECCY) trial [27]. In this placebo-controlled trial performed on 200 patients with HER2-negative breast cancer, chemotherapy

and parallel treatment with carvedilol, a non-cardioselective β-blocker did not reduce the occurrence of cardiotoxicity (defined as the proportion of patients with a ≥10% reduction in LVEF, carvedilol vs placebo: 14.5% *vs.* 13.5%; p = 0.99) and did not influence the LVEF assessed as a continuous variable at 6-month follow-up when compared with the placebo. However, the trial did provide results analogous to those from the PRADA trial, as the use of carvedilol was associated with a lower increase in cardiac troponin I during anthracycline treatment. Thus, it may be speculated that there might be a class-effect of β-blockers in reducing the risk of myocardial injury associated with anthracycline treatment. Among the potential mechanisms of such cardioprotective activity, the anti-oxidative effect exhibited by β-blockers has been proposed, which is demonstrated e.g. in a lower risk of intracellular lipid peroxidation and mitochondrial dysfunction [28].

In general, both ACE-I, ARBs, and β-adrenolytics have constituted the cornerstone of modern treatment of heart failure, as they significantly attenuate the pathophysiological neurohormonal pathways in patients with HF. In patients with a decreased cardiac contractile function, a pathological cascade based on the sustained activation of neurohormonal responses develops. The elements of the cascade include the hyperactivity of the adrenergic system, and activation of the renin-angiotensin-aldosterone pathway. All the aforementioned drug groups act as inhibitors of those pathways, and by stabilizing the cardiac homeostasis they were proved to reduce morbidity and mortality in patients with chronic heart failure [29].

Finally, based solely on the data presented above, it could be speculated that if both preventive strategies (ACE-I/ARB and β-blockers) were proved effective, their co-administration might further increase the efficacy of prevention of CTR-CVT. However, in the previously mentioned PRADA trial, one arm of patients were randomized to a parallel preventive strategy with candesartan and metoprolol, and, in comparison with the monotherapy groups, no significant differences were observed with regard to LVEF reduction. Then, on the other hand, there is the important OVERCOME trial, in which 90 patients with malignant hemopathies treated with intensive chemotherapy were randomized to either preventive administration of enalapril and carvedilol, or matching placebo. During a 6-month follow-up, a significantly lower reduction of LVEF was noted in the arm taking ACEI and β-blockers than the placebo (a statistically significant difference of 3.1% in echocardiography and a difference of 3.4% on the verge of significance in magnetic resonance imaging), with a lower risk of combined clinical endpoint demonstrated in the intervention arm [30]. Thus, it appears that by recommending a simultaneous introduction of preventive ACE-I/ARB and β-blockers in patients with high or very high risk of CTR-CVT, the ESC guidelines on cardio-oncology, at least partially follow the newly introduced strategy of an early introduction of all four major "game-changing" drugs for treatment of chronic HF advocated in the ESC guidelines on HF. Nonetheless, at present, the evidence supporting preventive co-administration of ACE-I/ARB + β-blocker is rather scarce.

Statins

Statins are cholesterol-lowering drugs that in patients with high or very high cardiovascular risk have been shown to reduce the risk of myocardial infarction, stroke, and mortality [31]. Research has shown that patients with breast cancer treated with statins might have a lower risk of cardiovascular events compared to those who do not receive this treatment. Moreover, some retrospective data report that a chronic treatment with statins might even increase the LVEF [32]. The postulated molecular mechanisms included pleiotropic effects of statins, including their anti-inflammatory, anti-apoptotic, and even anti-proliferative effect on the tumor cells [33, 34]. Moreover, as cholesterol is a biochemical precursor molecule for estrogens, the modifications to the lipid metabolism equilibrium caused by statins might in result indirectly modulate the response to estrogens at a cellular level [35].

However, data on the efficacy of statins in prevention of CTR-CVT are based mostly on retrospective, observational studies. A recently published PREVENT trial, which included patients with early breast cancer or lymphoma, did not confirm the cardioprotective effect of statins, as the mean (±SD) LVEF values were 61.7 ± 5.5% before treatment and 57.4 ± 6.8% at 24 months in the placebo group and 62.6 ± 6.4% before treatment and 57.7 ± 5.6% at 24 months in patients treated with 40 mg of one of the most potent statins – atorvastatin [36]. Moreover, no difference in the percentages of patients with a major (defined as by ≥10%) reduction of LVEF, or changes in LV strain, LV mass, cognitive function, or levels of inflammation biomarkers were noted between patients treated with atorvastatin and placebo. The results of the Statins to Prevent the Cardiotoxicity From Anthracyclines (STOP-CA) and Statins for the Primary Prevention of Heart Failure in Patients Receiving Anthracyclines Pilot Study (SPARE-HF) are eagerly anticipated in either confirming, or repudiating the cardioprotective effect of statins in patients with cancer [37, 38].

Spironolactone, flozins, ARNI

The ESC guidelines on cardio-oncology do not specifically address the subject of the introduction of preventive treatment with other groups which are at present considered the golden standard in patients with chronic HF. It should be noted that all of them might potentially be beneficial in preventing CTR-CVT in patients with breast cancer who are beginning oncological treatment. Spironolactone, the mineralocorticoid receptor antagonist (MRA), has been proven to reduce morbidity and mortality in patients with HF [39–41]. Its major mechanism of action lies in the inhibition of aldosterone receptors. In patients with HF, when the activity of the RAA axis is pathologically increased,

and subsequently so is the concentration of aldosterone, the end-product of this axis, the hyperactivity of aldosterone increases the myocardial fibrosis developing in response to the myocardial injury. Thus, there might be a pathophysiological rationale for preventive treatment with MRA in patients treated with potentially cardio-toxic drugs.

However, the evidence supporting MRA in such a setting is rather scarce, as to date there has only been one randomized trial, which included only 83 patients with breast cancer treated with either doxorubicin or epirubicin. Those were randomized to preventive therapy with 25 mg daily of spironolactone or placebo. After the completion of a follow-up of approximately 24 weeks, preventive therapy with spironolactone resulted in a lower reduction of LVEF assessed echocardiographically (LVEF decrease from 67.0 ± 6.1 to 65.7 ± 7.4 in the spironolactone group, and from 67.7 ± 6.3 to 53.6 ± 6.8 in the control group between-group $p < 0.001$) [42]. Moreover, similar to the findings from the studies with β-adrenolytic drugs, the trial showed that spironolactone resulted in an attenuated increase in cardiac troponin I elevation, and while in the control group, levels of all serum biomarkers were altered by chemotherapy, no significant difference in any of the measured parameters (including NT-proBNP, troponin, creatinine kinase – myocardial) was observed in patients taking spironolactone. Finally, the authors point a remark that the left ventricular diastolic function was maintained in patients from the spironolactone group, while a progression of diastolic dysfunction was observed in the group administered with a placebo, which further confirms that the mechanism of action of spironolactone might lay in reduced fibrosis caused by excessive aldosterone levels.

The results of the CECCY, PRADA, SAFE, and aforementioned spironolactone trial clearly indicate the possible benefit of RAA axis inhibitors on cardiac contractile function. Moreover, in the preclinical studies it was demonstrated that apart from the RAA axis, an increased activation of natriuretic peptide cellular pathways decreases the risk of anthracycline-induced cardiomyopathy. Another rather novel drug in the treatment of HF is sacubitril-valsartan. Its mechanism of action lays on the inhibition of the RAA axis, owing to the activity of valsartan – an ARB – and activation of the natriuretic peptide pathway mediated by sacubitril – an inhibitor of neprylisin, an enzyme responsible for the degradation of many important molecules, including natriuretic peptides. Thus, the use of a cardioprotective strategy with sacubitril-valsartan in patients treated with potentially cardiotoxic drugs has a strong pathophysiological rationale.

The data on the administration of sacubitril/valsartan in patients with cardiac damage caused by cancer therapy come mostly from retrospective analyses. A Spanish registry investigated 67 patients (of whom 45% were patients with breast cancer) with symptomatic HF caused by cancer therapy, in whom sacubitril/valsartan was introduced. In those subjects, significant increases in LVEF and reductions in NT-proBNP levels, and left ventricular dimensions were noted, followed by a clinically meaningful improvement in patients' HF symptoms [43]. In another single-center analysis, echocardiographically determined cardiotoxicity developed in 28 of 635 patients, most of whom were treated with anthracyclines, and approximately a quarter with anti-HER2 therapy. Treatment with sacubitril/valsartan reduced NT-proBNP and increased patients' exertional capacity and left ventricular ejection fraction (32.3 ± 5.5% *vs.* 26.7 ± 5.4%; $p < 0.001$) [44].

At present, there are data from only one randomized trial investigating the use of sacubitril-valsartan in patients with cancer. The study has been performed in Russia and was restricted to 112 subjects with cancer and a preexisting HF who were administered a preventive treatment with nebivolol and eplerenone, and randomized to either sacubitril-valsartan or candesartan. After 6 months, there was a benefit of smaller LVEF reduction and improvement of quality of life with the former [45].

It should be noted that a multi-center, double-blinded trial evaluating the efficacy and safety of sacubitril/valsartan in the prevention of CTR-CVT in patients with cancer will shortly be starting recruitment [46]. The study, which will be performed in three tertiary oncological centers in Poland will randomize a total of 480 patients with early breast cancer undergoing treatment with anthracyclines and/or anti-HER2 drugs to the highest-tolerated dose of sacubitril/valsartan or placebo in 1:1 ratio. The patients will be monitored, including a routine transthoracic echocardiography (TTE) for 24 months, and the primary endpoint of the trial will be the occurrence of a decrease in LVEF by ≥5% in TTE within 24 months. The first results are expected at the beginning of 2028, pending recruitment of participants.

Finally, the last group of drugs recommended in HF are SGLT-2 inhibitors. In the last years, several clinical trials have demonstrated their beneficial effects on heart failure outcomes, with a reduction in the risk of cardiovascular death and hospitalization for heart failure, regardless of the presence of diabetes [47, 48]. The mechanism of action of SGLT2 inhibitors, which involves blocking glucose reabsorption in the SGLT-2 sodium-glucose co-transporters in kidneys, also leads to other effects that are beneficial in HF. By reducing sodium and water reuptake in the kidneys, SGLT-2 inhibitors increase diuresis and thus decrease blood volume, which can improve cardiac contractility. Additionally, SGLT-2 inhibitors have been shown to improve endothelial function, reduce oxidative stress, and improve myocardial cellular metabolic pathways [49]. To date, no randomized study investigated the efficacy of SGLT-2 inhibitors in the prevention of CTR-CVT, and the sole evidence for their potential benefit is derived from a recent retrospective analysis, which included diabetic patients with cancer treated with SGLT-2 inhibitors; they were compared in a 1:3 ratio to control subjects not being administered SGLT-2 inhibitors. When compared to the control group, patients

Table V. Recommendations for baseline risk assessment and monitoring during endocrine therapy for patients with breast cancer, according to the 2022 ESC guidelines on cardio-oncology [7]

Recommendations	Class of recommendation, level of evidence
baseline CV risk assessment and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP is recommended in BC patients receiving endocrine therapies without pre-existing CVD	I, C
dexrazoxane should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated	IIa, B
liposomal anthracyclines should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated	IIa, B

BC – breast cancer; CV – cardiovascular; CVD – cardiovascular disease; ECG – electrocardiogram; SCORE2 – systematic coronary risk estimation 2; SCORE2-OP – systematic coronary risk estimation 2 – older persons

pretreated with SGLT-2 inhibitors were at a significantly reduced risk of a composite endpoint of cardiac events, including the incidence of HF, admissions due to HF, the development of new cardiomyopathy, or clinically significant arrhythmias (3% *vs.* 20%; $p = 0.025$) [50]. Moreover, the risk of all-cause death was significantly lower (9% *vs.* 43%; $p < 0.001$), albeit such a strong effect on mortality is hardly attributable solely to the action of SGLT-2 inhibitors. Nonetheless, a randomized trial evaluating the efficacy of one of the SGLT-2 inhibitors, empagliflozin (Empagliflozin in the Prevention of Cardiotoxicity in Cancer Patients Undergoing Chemotherapy Based on Anthracyclines – EMPACT) will soon start recruitment in Polish centers, and the first results are expected in 2028 [51].

Non-pharmacological preventive measures

In addition to medication, lifestyle modifications such as exercise, a healthy diet, and smoking cessation are essential for reducing cardiovascular disease risk in breast cancer patients. Prior studies have shown that due to various factors, patients after diagnosis of cancer tend to reduce physical activity and gain weight by an average of 2.7 kg [52, 53]. Physical activity has been shown to reduce the intracellular oxidative stress, and improve exertional capacity in patients with breast cancer. This might suggest a rationale for improvement in prognosis and reduction of the risk of development of CTR-CVT [54, 55]. However, to date, no clear guidelines defining the optimal exertion thresholds for groups at risk of cardiotoxicity were presented. Nonetheless, the guidelines of the American College of Sports Medicine specify the optimal physical exercise type and intensiveness for cancer survivors [56].

Endocrine treatment and its clinical implications

Approximately 65–70% of patients with breast cancer might have a hormone receptor-positive tumor, and in some of those patients therapy with either selective estrogen receptor modulators (SERM) or aromatase inhibitors (AI) might be initiated [57]. Although treatment with SERM or AI does not lead to the development of CTRCD to a degree similar to the one observed in anthracyclines or anti-HER2 treatment, therapy with those two groups of drugs confers an increased risk of dyslipidemia, metabolic syndrome, hypertension, and thus major cardiovascular events such as myocardial infarction [58–60]. Moreover, tamoxifen has consistently been demonstrated to increase the risk of venous thromboembolism (VTE) and therefore therapy based on tamoxifen should not be recommended for patients with an increased risk of thrombotic events [61]. The ESC guidelines on cardio-oncology specify that prior to the introduction of the endocrine therapies in patients with breast cancer, a 10-year risk of fatal and non-fatal cardiovascular events should be assessed, and in those perceived as high risk, such risk should be re-evaluated every year. The detailed recommendations on baseline risk assessment and monitoring during endocrine therapy for breast cancer are listed in table V. The risk scores recommended in the guidelines are either SCORE2 or SCORE2-OP, however other validated risk scores can also be accepted [62, 63]. After risk assessment, it is of the utmost importance to discuss the risks of VTE, and major vascular events with patients at risk, while recognizing that the benefits of breast cancer treatment usually outweigh the cardiovascular risks. However, an emphasis should be placed on the optimal control of CV risk factors, including optimal lipid-lowering therapy, control of blood pressure, with exercise and a healthy diet encouraged.

Article information and declarations

Author contributions

Maciej Dyrbuś – conception and design, analysis and interpretation of data, drafting of the manuscript.
Ilona Skoczylas – acquisition of data.
Aleksandra Majsnerowska – acquisition of data.
Mariusz Gąsior – analysis and Interpretation of data, critical revision of the manuscript for important intellectual content, supervision.
Mateusz Tajstra – conception and design, analysis and Interpretation of data, critical revision of the manuscript for important intellectual content, supervision.

Funding

None declared

Conflict of interest

None declared

Maciej Dyrbuś
Medical University of Silesia
School of Medical Sciences in Zabrze
3rd Department of Cardiology
ul. M. Skłodowskiej-Curie 9
41-800 Zabrze, Poland
e-mail: mdyrbus@op.pl

Received: 7 Jul 2023
Accepted: 11 Jul 2023

References

1. American Cancer Society. Breast Cancer Facts & Figures 2022-2024. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209–249, doi: 10.3322/caac.21660, indexed in Pubmed: 33538338.
3. Ferlay J. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. 2020. https://gco.iarc.fr/today/home.
4. Miklewska MJ, Klaudia B, Urszula W, et al. Morbidity and mortality trends of the most common cancers in 1990–2019. Poland's position compared to other European countries. Nowotw J Oncol. 2023; 73(1): 46–55, doi: 10.5603/NJO.a2022.0065.
5. Cherukuri SP, Chikatimalla R, Dasaradhan T, et al. Breast Cancer and the Cardiovascular Disease: A Narrative Review. Cureus. 2022; 14(8): e27917, doi: 10.7759/cureus.27917, indexed in Pubmed: 36110451.
6. Koric A, Chang CP, Mark B, et al. Cardiovascular disease risk in long-term breast cancer survivors: A population-based cohort study. Cancer. 2022; 128(14): 2826–2835, doi: 10.1002/cncr.34224, indexed in Pubmed: 35561317.
7. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022; 43(41): 4229–4361, doi: 10.1093/eurheartj/ehac244, indexed in Pubmed: 36017568.
8. Bobek-Billewicz B, Jurkowski M. The role of magnetic resonance imaging in the diagnosis of breast cancer. Nowotwory. Journal of Oncology. 2017; 67(3): 185–192, doi: 10.5603/njo.2017.0031.
9. Perez IE, Taveras Alam S, Hernandez GA, et al. Cancer Therapy-Related Cardiac Dysfunction: An Overview for the Clinician. Clin Med Insights Cardiol. 2019; 13: 1179546819866445, doi: 10.1177/1179546819866445, indexed in Pubmed: 31384135.
10. Yeh E, Bickford C. Cardiovascular Complications of Cancer Therapy. J Am Coll Cardiol. 2009; 53(24): 2231–2247, doi: 10.1016/j.jacc.2009.02.050.
11. Curigliano G, Cardinale D, Dent S, et al. Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA Cancer J Clin. 2016; 66(4): 309–325, doi: 10.3322/caac.21341, indexed in Pubmed: 26919165.
12. Bowles EJ, Wellman R, Feigelson HS, et al. Pharmacovigilance Study Team. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst. 2012; 104(17): 1293–1305, doi: 10.1093/jnci/djs317, indexed in Pubmed: 22949432.
13. Armenian SH, Xu L, Ky B, et al. Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. J Clin Oncol. 2016; 34(10): 1122–1130, doi: 10.1200/JCO.2015.64.0409, indexed in Pubmed: 26834065.
14. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of Anthracyclines. Front Cardiovasc Med. 2020; 7: 26, doi: 10.3389/fcvm.2020.00026, indexed in Pubmed: 32258060.
15. Santana BR, Codon JC, Olmos VJ, et al. HFA-ICOS cardiovascular toxicity risk score validation in CARDIOTOX registry. European Heart Journal. 2022; 43(Supplement_2), doi: 10.1093/eurheartj/ehac544.2591.
16. Tini G, Cuomo A, Battistoni A, et al. Baseline cardio-oncologic risk assessment in breast cancer women and occurrence of cardiovascular events: The HFA/ICOS risk tool in real-world practice. Int J Cardiol. 2022; 349: 134–137, doi: 10.1016/j.ijcard.2021.11.059, indexed in Pubmed: 34848212.
17. Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies : a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society. 2020.
18. Visseren FLJ, Mach F, Smulders YM, et al. ESC National Cardiac Societies, ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021; 42(34): 3227–3337, doi: 10.1093/eurheartj/ehab484, indexed in Pubmed: 34458905.
19. Yamaguchi N, Fujii T, Aoi S, et al. Comparison of cardiac events associated with liposomal doxorubicin, epirubicin and doxorubicin in breast cancer: a Bayesian network meta-analysis. Eur J Cancer. 2015; 51(16): 2314–2320, doi: 10.1016/j.ejca.2015.07.031, indexed in Pubmed: 26343314.
20. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
21. Gulati G, Heck S, Ree A, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart. 2016; 37(21): 1671–1680, doi: 10.1093/eurheartj/ehw022.
22. Heck SL, Mecinaj A, Ree AH, et al. Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): Extended Follow-Up of a 2×2 Factorial, Randomized, Placebo-Controlled, Double-Blind Clinical Trial of Candesartan and Metoprolol. Circulation. 2021; 143(25): 2431–2440, doi: 10.1161/CIRCULATIONAHA.121.054698, indexed in Pubmed: 33993702.
23. Livi L, Barletta G, Martella F, et al. Cardioprotective Strategy for Patients With Nonmetastatic Breast Cancer Who Are Receiving an Anthracycline-Based Chemotherapy: A Randomized Clinical Trial. JAMA Oncol. 2021; 7(10): 1544–1549, doi: 10.1001/jamaoncol.2021.3395, indexed in Pubmed: 34436523.
24. Toko H, Oka T, Zou Y, et al. Angiotensin II type 1a receptor mediates doxorubicin-induced cardiomyopathy. Hypertens Res. 2002; 25(4): 597–603, doi: 10.1291/hypres.25.597, indexed in Pubmed: 12358147.
25. Brilla CG, Rupp H, Maisch B. Effects of ACE inhibition versus non-ACE inhibitor antihypertensive treatment on myocardial fibrosis in patients with arterial hypertension. Retrospective analysis of 120 patients with left ventricular endomyocardial biopsies. Herz. 2003; 28(8): 744–753, doi: 10.1007/s00059-003-2524-6, indexed in Pubmed: 14689110.
26. Lou Q, Janardhan A, Efimov IR. Remodeling of calcium handling in human heart failure. Adv Exp Med Biol. 2012; 740: 1145–1174, doi: 10.1007/978-94-007-2888-2_52, indexed in Pubmed: 22453987.
27. Avila M, Ayub-Ferreira S, Wanderley Md, et al. Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity. J Am Coll Cardiol. 2018; 71(20): 2281–2290, doi: 10.1016/j.jacc.2018.02.049.
28. Abreu RV, Santos DL, Moreno AJ. Effects of carvedilol and its analog BM-910228 on mitochondrial function and oxidative stress. J Pharmacol Exp Ther. 2000; 295(3): 1022–1030, indexed in Pubmed: 11082437.
29. Lueder Tv, Kotecha D, Atar D, et al. Neurohormonal Blockade in Heart Failure. Cardiac Failure Review. 2017; 03(01): 19, doi: 10.15420/cfr.2016:22:2.
30. Bosch X, Rovira M, Sitges M, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol. 2013; 61(23): 2355–2362, doi: 10.1016/j.jacc.2013.02.072, indexed in Pubmed: 23583763.
31. Baigent C, Blackwell L, Emberson J, et al. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010; 376(9753): 1670–1681, doi: 10.1016/S0140-6736(10)61350-5, indexed in Pubmed: 21067804.
32. Chotenimitkhun R, D'Agostino R, Lawrence JA, et al. Chronic statin administration may attenuate early anthracycline-associated declines in left ventricular ejection function. Can J Cardiol. 2015; 31(3): 302–307, doi: 10.1016/j.cjca.2014.11.020, indexed in Pubmed: 25662284.
33. Sim Y, Lim C, Phyu N, et al. The Impact of Statin Use and Breast Cancer Recurrence - A Retrospective Study in Singapore. Front Oncol. 2022; 12: 835320, doi: 10.3389/fonc.2022.835320, indexed in Pubmed: 35433431.
34. Van Wyhe RD, Rahal OM, Woodward WA. Effect of statins on breast cancer recurrence and mortality: a review. Breast Cancer (Dove Med

Press). 2017; 9: 559–565, doi: 10.2147/BCTT.S148080, indexed in Pubmed: 29238220.
35. Casaburi I, Chimento A, De Luca A, et al. Cholesterol as an Endogenous ERRα Agonist: A New Perspective to Cancer Treatment. Front Endocrinol (Lausanne). 2018; 9: 525, doi: 10.3389/fendo.2018.00525, indexed in Pubmed: 30254608.
36. Hundley WG, D'Agostino R, Crotts T, et al. Statins and Left Ventricular Ejection Fraction Following Doxorubicin Treatment. NEJM Evid. 2022; 1(9), doi: 10.1056/evidoa2200097, indexed in Pubmed: 36908314.
37. Clinicaltrials.gov Identifier: STOP-CA (Statins TO Prevent the Cardiotoxicity From Anthracyclines). https://clinicaltrials.gov/ct2/show/NCT02943590.
38. Clinicaltrials.gov identifier: Statins for the Primary Prevention of Heart Failure in Patients Receiving Anthracycline Pilot Study (SPARE-HF). https://clinicaltrials.gov/ct2/show/NCT03186404.
39. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999; 341(10): 709–717, doi: 10.1056/NEJM199909023411001, indexed in Pubmed: 10471456.
40. Pitt B, Remme W, Zannad F, et al. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003; 348(14): 1309–1321, doi: 10.1056/NEJMoa030207, indexed in Pubmed: 12668699.
41. Zannad F, Gattis Stough W, Rossignol P, et al. Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integrating evidence into clinical practice. Eur Heart J. 2012; 33(22): 2782–2795, doi: 10.1093/eurheartj/ehs257, indexed in Pubmed: 22942339.
42. Akpek M, Ozdogru I, Sahin O, et al. Protective effects of spironolactone against anthracycline-induced cardiomyopathy. Eur J Heart Fail. 2015; 17(1): 81–89, doi: 10.1002/ejhf.196, indexed in Pubmed: 25410653.
43. Martín-Garcia A, López-Fernández T, Mitroi C, et al. Effectiveness of sacubitril-valsartan in cancer patients with heart failure. ESC Heart Fail. 2020; 7(2): 763–767, doi: 10.1002/ehf2.12627, indexed in Pubmed: 32022485.
44. Gregorietti V, Fernandez TL, Costa D, et al. Use of Sacubitril/valsartan in patients with cardio toxicity and heart failure due to chemotherapy. Cardiooncology. 2020; 6(1): 24, doi: 10.1186/s40959-020-00078-4, indexed in Pubmed: 33292750.
45. Kanorskiy SG, Pavlovets VP. First experience of using valsartan/sacubitril in women with heart failure and breast cancer receiving anthracycline-based adjuvant chemotherapy. Medical Counc. 2019(16): 42–48, doi: 10.21518/2079-701x-2019-16-42-48.
46. Clinicaltrials.gov identifier: Sacubitril/Valsartan in PriMAry preventIoN of the Cardiotoxicity of Systematic breaST canceR trEAtMent (MAINSTREAM).
47. Zinman B, Wanner C, Lachin JM, et al. EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015; 373(22): 2117–2128, doi: 10.1056/NEJMoa1504720, indexed in Pubmed: 26378978.
48. McMurray JJ, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019; 381(21): 1995–2008, doi: 10.1056/NEJMoa1911303, indexed in Pubmed: 31535829.
49. Joshi S, Singh T, Newby D, et al. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart. 2021; 107(13): 1032–1038, doi: 10.1136/heartjnl-2020-318060.
50. Gongora CA, Drobni ZD, Quinaglia Araujo Costa Silva T, et al. Sodium--Glucose Co-Transporter-2 Inhibitors and Cardiac Outcomes Among Patients Treated With Anthracyclines. JACC Heart Fail. 2022; 10(8): 559–567, doi: 10.1016/j.jchf.2022.03.006, indexed in Pubmed: 35902159.
51. Clinicaltrials.gov Identifier: Empagliflozin in the Prevention of Cardiotoxicity in Cancer Patients Undergoing Chemotherapy Based on Anthracyclines (EMPACT).
52. Rock CL, Flatt SW, Newman V, et al. Factors associated with weight gain in women after diagnosis of breast cancer. Women's Healthy Eating and Living Study Group. J Am Diet Assoc. 1999; 99(10): 1212–1221, doi: 10.1016/s0002-8223(99)00298-9, indexed in Pubmed: 10524383.
53. Irwin ML, Crumley D, McTiernan A, et al. Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. Cancer. 2003; 97(7): 1746–1757, doi: 10.1002/cncr.11227, indexed in Pubmed: 12655532.
54. Ma ZY, Yao SS, Shi YY, et al. Effect of aerobic exercise on cardiotoxic outcomes in women with breast cancer undergoing anthracycline or trastuzumab treatment: a systematic review and meta-analysis. Support Care Cancer. 2022; 30(12): 10323–10334, doi: 10.1007/s00520-022-07368-w, indexed in Pubmed: 36322246.
55. Tranchita E, Murri A, Grazioli E, et al. The Beneficial Role of Physical Exercise on Anthracyclines Induced Cardiotoxicity in Breast Cancer Patients. Cancers (Basel). 2022; 14(9), doi: 10.3390/cancers14092288, indexed in Pubmed: 35565417.
56. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010; 42(7): 1409–1426, doi: 10.1249/MSS.0b013e3181e0c112, indexed in Pubmed: 20559064.
57. Curigliano G, Lenihan D, Fradley M, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol. 2020; 31(2): 171–190, doi: 10.1016/j.annonc.2019.10.023, indexed in Pubmed: 31959335.
58. Yang H, Bhoo-Pathy N, Brand JS, et al. Risk of heart disease following treatment for breast cancer - results from a population-based cohort study. Elife. 2022; 11, doi: 10.7554/eLife.71562, indexed in Pubmed: 35293856.
59. Bundred NJ. The effects of aromatase inhibitors on lipids and thrombosis. Br J Cancer. 2005; 93 Suppl 1(Suppl 1): S23–S27, doi: 10.1038/sj.bjc.6602692, indexed in Pubmed: 16100522.
60. Amir E, Seruga B, Niraula S, et al. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. J Natl Cancer Inst. 2011; 103(17): 1299–1309, doi: 10.1093/jnci/djr242, indexed in Pubmed: 21743022.
61. Hernandez RK, Sørensen HT, Pedersen L, et al. Tamoxifen treatment and risk of deep venous thrombosis and pulmonary embolism: a Danish population-based cohort study. Cancer. 2009; 115(19): 4442–4449, doi: 10.1002/cncr.24508, indexed in Pubmed: 19569248.
62. SCORE2-Diabetes Working Group and the ESC Cardiovascular Risk Collaboration, SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021; 42(25): 2439–2454, doi: 10.1093/eurheartj/ehab309, indexed in Pubmed: 34120177.
63. SCORE2-OP working group and ESC Cardiovascular risk collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021; 42(25): 2455–2467, doi: 10.1093/eurheartj/ehab312, indexed in Pubmed: 34120185.