Risk factors and prevention of anthracycline-related heart failure

Ph.D. Thesis

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LIST OF PUBLICATIONS

This doctoral thesis is based on the following publications:

I. **Fogarassy G**, Vathy-Fogarassy Á, Kenessey I, Kásler M, Forster T. Risk prediction model for long-term heart failure incidence after epirubicin chemotherapy for breast cancer - A real-world data-based, nationwide classification analysis. Int J Cardiol 2019; 285: 47–52. *IF: 3.229*

II. **Fogarassy G**, Fogarassyné Vathy Á, Kováts T, Hornyák L, Kenessey I, Veress G, Polgár C, Forster T. Analysing the risk factors of doxorubicin-associated heart failure by a retrospective study of integrated, nation-wide databases. [Doxorubicin kezeléshez kapcsolódó szívelégtelenség kialakulásának rizikótényezői a hazai országos adatbázisok integrált, retrospektív elemzése alapján]. Orv Hetil 2020; 161: 1094–1102. *[Hungarian] IF: 0.497*

III. **Fogarassy G,** Vathy-Fogarassy Á, Kenessey I, Veress G, Polgár C, Forster T. Prevention of cancer therapy-related heart failure, is it really possible? A population-based study. J Cardiovasc Med (Hagerstown). *Accepted for publication on 21st August 2020. IF: 1.225*

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Publications not directly related to the thesis:

I. Vathy-Fogarassy Á, Szekér S, Szolár B, **Fogarassy G**. The Efficiency of Different Distance Metrics for Keyword-Based Search in Medical Documents: A Short Case Study. Stud Health Technol Inform 2020; 271: 232–239.

II. **Fogarassy G,** Vathy-Fogarassy Á, Hornyák L, Forster T. Risk factors for heart failure after doxorubicin chemotherapy for breast-or colorectal cancer. (abstract) European Heart Journal 2017; 38(suppl. 1), 406.

III. Szekér S, **Fogarassy G,** Vathy-Fogarassy Á. Comparison of Control Group Generating Methods. Stud Health Technol Inform 2017; 236: 311–318.

IV. **Fogarassy G,** Vathy-Fogarassy Á, Hornyák L. Forster T. Risk factors for heart failure after epirubicin chemotherapy for breast or colorectal cancer (abstract). European Journal of Heart Failure 2017; 19 (Suppl. S1), 445.

V. **Fogarassy G,** Fogarassyné Vathy Á, Hornyák L, Forster T. Risk Factors for Heart Failure after Epirubicin Chemotherapy for Breast- or Colorectal Cancer. (abstract) Cardiologia Hungarica 2017; 47: C104.

VI. Tóth K, Machalik K, **Fogarassy G,** Vathy-Fogarassy Á. Applicability of Process Mining in the Exploration of Healthcare Sequences. In: Szakál, Anikó (ed.) 2017 IEEE 30th Neumann Colloquium (NC), Budapest, 2017; 000151–000156.

VII. **Fogarassy G,** Fogarassyné Vathy Á, Hornyák L, Kósa I. Analysis of chemotherapy related cardiac adverse events in breast and colorectal cancer patients based on the national health insurance database. (abstract) Cardiologia Hungarica 2016; 46: F102.

LIST OF ABBREVIATIONS

ACEi: angiotensin-converting enzyme inhibitor

ARB: angiotensin receptor blocker

CAD: coronary artery disease

CI: confidence intervals

CRF: chronic renal failure

CV: cardiovascular

DM: diabetes mellitus

DNA: deoxyribonucleic acid

HR: hazard ratio

ICD: International Statistical Classification of Diseases and Related Health Problems

IR: incidence rate

LVEF: left ventricular ejection fraction

MI: myocardial infarction

OR: odds ratio

PAD: peripheral artery disease

PI3Kγ: phosphoinositide 3-kinase gamma

RCT: randomized controlled trial

ROC: receiver operating characteristic

ROS: reactive oxygen species

SUMMARY

For patients treated with anthracyclines, a comprehensive heart failure risk prediction model, which reflects the contemporary protocols and integrates the additional risk attributable to other chemotherapies has been unavailable so far. Thus, we performed a multivariable regression analysis on a merged, nation-wide, real-world dataset to predict the risk of heart failure. In the Hungarian breast cancer population treated with anthracyclines and free from previous heart failure or dilated cardiomyopathy, the overall cumulative incidence of heart failure was 6.9% in the epirubicin-treated cohort during 3-10 years of follow-up and 6.2% during 3-9 years of follow-up in the doxorubicin-treated cohort.

Heart failure was induced by the higher anthracycline cumulative doses, the threshold doses were 709 mg/m^2 for epirubicin and 400 mg/m^2 for doxorubicin. Since nowadays anthracyclines are mostly administered under these doses, the development of cardiomyopathy is mainly influenced by other factors. The prominent contributing factor in elevated heart failure incidence was the higher age, even over 50 years. The risk rose sharply with older age. Advanced cancer stage with regional spread and especially with distant metastases exhibited high importance for provoking heart failure. Besides the higher age and advanced cancer stage, the presence of capecitabine was the most important contributing factor to the higher heart failure risk, as presented in Figure 8. Except for the 5-fluorouracil in combination with epirubicin, the additional treatments with other pyrimidine-analogues were also associated with higher heart failure risk. For metastatic breast cancer, bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody is ofter administered, we have confirmed an elevated heart failure risk associated with it, as well (Figure 2 and Figure 4). In addition to anthracycline therapy, docetaxel also exhibited a cumulative dose-dependent effect to induce heart failure (higher risk over 510 mg/m^2). When adding to doxorubicin therapy, carboplatin was also associated with higher risk. Furthermore, of the clinical characteristics, diabetes mellitus, hypertension, coronary artery disease (especially the previous myocardial infarction or revascularization) and previous stroke were confirmed as factors associated with higher heart failure risk.

We constructed a risk-prediction score (Table 5) derived from regression coefficients, which was able to classify heart failure risk over a wide range (2–30%) and to identify elevated heart failure risk with good sensitivity (0.79) and acceptable specificity (0.65). For routinely applied epirubicin doses, the prediction of long-term heart failure risk became accurate with the

suggested score. By virtue of this, surveillance, preventive strategies and cancer therapies can be individualized to reach the optimal outcome.

It would be reasonable to administer preventive therapy along with chemotherapy to the patients of elevated risk for the development of heart failure. Nevertheless, we have only limited evidence-based data on the effective preventive approach against chemotherapy-related heart failure. In order to explore the potential preventive ability of cardiovascular therapies, we performed a propensity score matching-based analysis on the merged real-world dataset of the Hungarian breast or colorectal cancer patients treated with any biological or chemotherapy. According to our results, during anticancer therapies, the concomitant ACEi/ARB medication induced a preventive effect against the development of heart failure. This effect was more pronounced in the cohort of elevated baseline cardiovascular risk. Moreover, statin preventive medication exhibited a beneficial effect irrespective of baseline cardiovascular risk. Noteworthy, the benefit increased with higher statin doses. Hence, it should not only be considered for the very high cardiovascular risk patients but also for those with a moderately elevated risk for the development of heart failure. The subgroup treated with anthracycline, platinum or capecitabine mostly benefitted from statins. Nebivolol was identified as the only beta-blocker that may induce preventive effect against chemotherapy-related heart failure. However, this association showed merely a borderline significance and was detected exclusively in anthracycline- or capecitabine-treated patients.

Our results may be considered as a paradigm for future randomized clinical studies in the field of the prevention against cancer therapy-related cardiotoxicity.

1. INTRODUCTION

Over recent decades, through the modern diagnostic and therapeutic methods, the survival rate of patients suffering from malignant diseases has substantially improved in the developed countries [1]. However, chemotherapy and radiotherapy put patients at increased risk of early and late adverse effects on the heart and vasculature. These deteriorative effects may cause dilated cardiomyopathy, atrial and ventricular arrhythmias, myocardial infarction, thromboembolism, hypertension, valvular and pericardial disorders. Consequently, the importance of cardiovascular (CV) mortality is growing among cancer patients [2-5]. Without careful cardiology follow-up and treatment, cancer therapy-related CV diseases may corrupt the survival benefit. Population-based data from the United States presented by Pinder et al confirmed that among patients over 65 years treated for breast cancer, cardiovascular causes make up a greater part of mortality than the malignancy itself [6].

1.1.Characteristics of Anthracycline-Induced Cardiotoxicity

Anthracyclines have been frequently used in cancer therapy since the late 1960s because of their effectivity in the treatment of a wide range of malignant tumours. The most frequently applied members of this class are doxorubicin, epirubicin, daunorubicin, idarubicin and mitoxantrone. These cytotoxic antibiotics have quite a diverse mechanism of action that includes producing reactive oxygen species (ROS), intercalation to deoxyribonucleic acid **(**DNA) and inhibition of topoisomerase II enzyme. Topoisomerase II enzyme has an important role in DNA transcription and repair. Myocyte injury and the subsequent dilated cardiomyopathy is one of the most important limiting factors during anthracycline therapy [4,5,7]. The principal mechanism of cardiotoxicity is now considered to be triggered by the formation of topoisomerase 2β-anthracycline complexes resulting in impaired mitochondrial function and biogenesis. In the anthracycline-damaged mitochondria, iron accumulation and iron-dependent reactive oxygen species (ROS) generation are induced [8,9]. The autophageal clearance of the damaged mitochondria is impaired in a process directed by phosphoinositide 3-kinase gamma (PI3Kγ). By inhibition of PI3Kγ, cardiotoxicity was preventable in an animal model [10]. ROS generation and the mitochondrial dysfunction lead up to apoptosis. Due to their weak ROS scavenging capacities, myocytes are particularly susceptible to anthracycline-induced cellular damage [5].

Cardiotoxicity of anthracyclines was revealed early after their introduction to therapy. It was also recognized that the incidence of heart failure increased with higher cumulative

anthracycline dose [11,12]. The left ventricular deterioration manifests itself in a delayed manner but commonly within the first year after termination of chemotherapy [13]. This delayed and cumulative dose-dependent presentation is the consequence of the intracellular accumulation of the secondary, toxic alcohol metabolites of the anthracyclines, which produces prolonged cellular damage [5]. Traditionally, anthracycline-related heart failure was considered mainly irreversible. However, as recently demonstrated by Cardinale et al, if detected and treated early, full reversibility of left ventricular deterioration can be achieved in 11% and partial reversibility in 71% of patients [13]. Nevertheless, in clinical practice we often encounter new patients with severe systolic heart failure several years after finishing anthracycline chemotherapy, in these cases, presumably, lack of systematic, prolonged echocardiography follow-up after cancer therapy leads up to missing earlier recognition of cardiomyopathy.

Anthracyclines can be administered relatively safely while kept under a threshold cumulative dose, however, the excessive doses raise the risk exponentially. Ryberg et al. published a relatively low (4%) incidence of heart failure after epirubicin therapy with a cumulative dose of 900 mg/m^2, but a rapid increase to 15% was observed with a dose of 1000 mg/m^2 [14]. Likewise, meta-analysis presented by Swain et al found a relatively low rate (5%) of congestive heart failure at patients with a cumulative doxorubicin dose of 400 mg/m^2. However, the risk steeply rose at higher doses, 26% of patients at 550 mg/m^2 and 48% of patients at 700 mg/m^2 exhibited heart failure [15].

There are other risk factors associated with anthracycline-related heart failure identified in meta-analyses of clinical trials and registries: age >65 and < 4 years, female sex (in children), black race and pre-existing cardiovascular disorders [15-17]. Albeit these datasets were insufficient for comprehensive risk analysis, their simple, cumulative dose and age-based heart failure risk-prediction scores could even be used previously for risk assessment [17]. Nonetheless, in these early studies much higher cumulative anthracycline doses were applied than in the practice nowadays. At present, anthracyclines are usually administered at cumulative doses below the heart failure causing threshold [18]. Besides, new anticancer protocols have come into practice, therefore, previous, simple risk-prediction models are no longer effective. In 2007, Pinder et al. published a large analysis of the Medicare database for elderly (>65) breast cancer patients and identified additional predictors for heart failure, e.g. trastuzumab treatment, hypertension, diabetes, coronary artery disease and a more advanced cancer stage. However, in this analysis, the patients treated with and without anthracycline were examined

together. Moreover, the doses of chemotherapeutic agents were not included in the examination [6].

Despite the considerable amount of accumulated data, a comprehensive heart failure risk prediction model, which reflects the contemporary protocols and integrates the additional risk attributable to other chemotherapies remained unavailable for patients treated with anthracyclines.

1.2. Prevention against Anthracycline-Induced Cardiotoxicity

To avoid the potentially irreversible consequences of cancer therapy-related cardiomyopathy, it would be reasonable to start preventive therapy in patients of elevated heart failure risk [19]. Nevertheless, we have only limited clinical data on the effective preventive approach, hence it has not yet been widely adopted in clinical practice.

Exploration of the congenital predispositions for anthracycline-induced cardiotoxicity may help find the way of prevention. Several transporter and metabolic protein gene polymorphisms were found to be associated with a higher risk of anthracycline-induced cardiotoxicity, e.g. heterozygosity for haemochromatosis gene C282Y mutation, which is associated with increased gastrointestinal iron absorption and occurs in 10% of the general population. Through identification of susceptible patients, genetic testing may, therefore, support both the prevention of anthracycline-induced cardiomyopathy and the decisions in anticancer therapy [20-23]. Moreover, these investigations may provide data for evolving specific preventive drugs. Dexrazoxane, which decreases mitochondrial iron level during anthracycline treatment, diminishes intramyocardial ROS production and is supposed to decrease heart failure occurrence. Meanwhile, its use was associated with side effects and a nonsignificant trend to reduce anticancer efficacy [24]. Hence, the therapeutical role of dexrazoxane remained equivocal in the prevention of anthracycline-induced cardiomyopathy.

Several cardiovascular medications were evaluated in term of the prevention of cancer therapy-related cardiomyopathy. Concerning the preventive effect of beta-blockers on anthracycline-induced cardiomyopathy, short-term, low volume randomized studies were published with the result of finding a few per cent higher left ventricular ejection fraction (LVEF) with the carvedilol or nebivolol therapy [25,26]. However, the modest (≤10% points) early changes in LVEF are not predictive of later symptomatic anthracycline-related cardiomyopathy [15]. Hence, it is debatable that the prevention of these early mild declines in LVEF may have any consequences for the long-term risk of developing more severe heart

failure. Other low volume studies with preventive metoprolol and carvedilol strategy showed non-significant change in LVEF [27,28]. The left ventricular deformation measurement, especially the decrease of global longitudinal strain, is considered to have the ability to predict later cancer therapy-related cardiotoxicity [29]. In two studies with carvedilol preventive therapy, lower left ventricular strain decrease was found, but these studies had no enough statistical power to assess the change in heart failure incidence [30,31].

After promising data from experimental models and a small randomized controlled trial (RCT) [32,33], Seicean et al. performed a retrospective, propensity score-matched analysis of 67 statin-pretreated patients with the demonstration of a lower rate of incident heart failure related to anthracycline therapy [34].

Preventive enalapril medication was confirmed to reduce the incident cardiomyopathy in patients treated with high dose chemotherapies and showing early Troponin elevation [35]. Since intracardiac tissue angiotensin-converting enzyme (ACE) activity is elevated during anthracycline therapy [36], enalapril may exert this myocyte protection through local effects. In 2 small, short term RCT, in the PRADA study (breast cancer treated with 5-fluorouracil, epirubicin and cyclophosphamide) [37] with candesartan and in the OVERCOME study (hemopathies treated with protocols mostly containing anthracyclines) [38] with enalapril (plus carvedilol), the preventive angiotensin blocking exhibited a beneficial effect on LVEF. However, these studies could not find a significant effect on the development of cancer therapy-related cardiomyopathy.

As presented, except for enalapril demonstrated effective in terms of heart failure prevention for very high-risk cancer patients with troponin elevation [35], none of the preventive cardiovascular medications have been tested in long-term, high-volume RCTs regarding the rate of incident cancer therapy-related cardiomyopathy and heart failure.

2. AIMS

This research aimed to introduce up-to-date heart failure risk prediction models, which conform to the current protocols and are applicable during anthracycline chemotherapies. Through the large size of the cohort in our retrospective study and the wide range of information retrieved from the analysed nation-wide databases, it was possible to perform more detailed heart failure risk prediction than previously published [6,15-17]. After having taken the applied

chemotherapy cumulative doses into account, we sought to assess the interactions between currently used chemotherapeutic agents in terms of heart failure development.

By more precise and tailored heart failure risk prediction, we aimed to support the clinical decisions during anthracycline therapy. The selection of higher-risk patients before the commencement of chemotherapy may help optimize echocardiography follow-up intensity during and after chemotherapy to ensure that the cardiomyopathy is diagnosed early. Since in anthracycline-related dilated cardiomyopathy, the heart failure medication can only reverse the left ventricular deterioration when initiated at an early stage, it is essential to focus the attention on the susceptible patients during and after anthracycline therapy.

For patients of elevated heart failure risk, preventive strategies might be considered if we had evidence-based data on the effective, risk-oriented preventive medications. However, so far, no convincing data have been recorded on the clinical benefit of the wide-spread use of preventive CV medication against cancer therapy-related heart failure [39]. Thus, aiming to evaluate the potential preventive ability of concomitant CV medications against anthracycline-related heart failure, we were to perform a propensity score matching-based retrospective data analysis to shed light on this important topic.

3. MATERIAL AND METHODS

3.1. Data Source

A retrospective study by integrating Hungarian nation-wide anonymized databases was conducted. The merged dataset consisted of the Hungarian National Cancer Registry and the administrative databases of the National Health Insurance Fund, namely the in- and outpatient healthcare databases and the database of the pharmacy medicine dispensation records.

This investigation conforms with the principles outlined in the *Declaration of Helsinki* [40]. Our analysis of medical data was approved by the institutional review board at the University of Szeged. Given that a retrospective, anonymized method was adopted, no informed consent was required.

3.2.Study Population

3.2.1. General considerations throughout the research

The study population was defined by International Classification of Diseases codes (World Health Organization. (1992). International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Geneva). The cancer patients were identified by the diagnoses assigned in histology reports. To ensure a sufficient follow-up period, the analysis was performed exclusively on patients having at least 3 years of follow-up data after the commencement of pharmaceutical cancer treatment or having the heart failure endpoint fulfilled. Our exclusion criteria were: other primary malignancies; previous treatment with any chemo- or radiotherapy before index cancer diagnosis; assignment of I50 (heart failure) or I420 (dilated cardiomyopathy) ICD-10 codes during either in- or outpatient care before the index chemotherapy; diagnoses of pulmonary embolism, acute myocardial infarction or aortic valve disease in any hospital discharge or autopsy report after the index chemotherapy. The studied database initially covered the period between 1st January 2004 and 31st December 2015 and in the second phase of the study, the database was extended to 31st December 2016.

3.2.2. Cohorts of the heart failure risk analysis

To set up study cohorts free of previous heart failure, dilated cardiomyopathy or anticancer therapies, we did not enrol patients from the first 3 years of the database, this period was exclusively considered as the source for collecting the exclusion criteria. By this means, a preceding observational period of at least 3 years was ensured. After having considered the expected survival, the application strategies of chemotherapeutical protocols and the characteristics of the studied database, we chose the breast cancer cohort for the risk analysis of anthracycline-related heart failure. All the patients diagnosed with primary breast carcinoma confirmed by histology were identified. As we aimed to explore heart failure risk factors and interactions precisely, the members of the anthracycline group were analysed separately. Less than 1% of the breast cancer patients received other anthracyclines but not epirubicin or doxorubicin. Hence, the patients treated with epirubicin or doxorubicin but no other anthracyclines were selected for the analysis.

3.2.3. The cohort of the analysis to explore heart failure prevention

The pharmacy dispensing database had a starting date of 1st January 2010. Since the aim of this study was to identify the concomitant CV therapies that could induce a preventive effect on the development of chemotherapy-related heart failure, with regard to the time frame of this database, the patients undergoing cancer therapy commenced after 1st July 2010 were enrolled. By this means, a preceding observational period of at least 6.5 years was ensured coming from the other components of the merged dataset (starting on 1st January 2004). This period was exclusively used for finding the data records fulfilling the exclusion criteria. In order to explore all the potential beneficial effects against cancer therapy-related heart failure, for this analysis, the patients diagnosed with primary breast or colorectal carcinoma and treated with any biological or chemotherapy were selected. Anthracycline-treated patients were assessed as a prespecified subgroup in this study.

3.3. Definition of Primary Heart Failure Endpoint

The primary endpoint of our research was the occurrence of heart failure following the commencement of chemotherapy as defined by a multilevel algorithm. Since the analysed databases do not contain the echocardiogram results, to define the heart failure outcome event the I50 ICD-10 code was used. For enhanced specificity, a heart failure event was defined by diagnoses assigned during in-patient care or an autopsy, namely in three different ways: (1) hospital discharge from departments of internal medicine, cardiology or intensive care following the diagnosis of the ICD code I50, (2) hospitalization that ended in death and an I50 code issued as a primary or secondary diagnosis or as the underlying (not immediate) cause of death, (3) autopsy report with the I50 code (except for the immediate cause of death). To further clarify the heart failure event, the primary endpoints with criteria fulfilled without administration of loop diuretics or potassium-sparing diuretics were disregarded.

3.4. Composition of Independent Variables

The wide spectrum of the clinical data that was analysed provided several assessable independent variables as follows. Chemotherapeutical treatment is reimbursed in an itemized fashion in Hungary. These claims must be made following a national administrative classification based on the structure of the World Health Organization’s International

Classification of Procedures in Medicine. Thanks to this financial scheme, the doses of drugs applied during chemotherapy were captured in the analysed database. Chemotherapy exposures and their cumulative doses were taken into account exclusively during the period before the earliest heart failure endpoint. The irradiation doses are not captured in the databases of the Health Insurance Fund. Radiotherapy was categorized with regard to the breast tumour localisation (left/right-sided, or both) to assess the potential additional cardiac risk attributable to the left-sided chest irradiation. The laterality data were collected from the Cancer Registry.

As cancer stage is strongly influential in terms of the choice of chemotherapy in addition to its possible impact on heart failure progression, 3 categories for statistical analysis were defined to take this confounding effect into account: (1) low oncological risk in the absence of any feature suggesting a higher risk; (2) medium oncological risk with spread to regional lymph nodes, or with direct tumour extension to the neighbouring tissues/organs; (3) high oncological risk with more distant lymph node metastasis, or another form of distant spread. The highest risk category registered in the Cancer Registry before or within 180 days after the commencement of index chemotherapy was used for statistical analysis. Tumour grade and receptor state were not captured in the databases.

Pre-existing diseases and other conditions were considered as potential predictors in the analysis (see Table 1). The presence of these conditions was collected from the entire database of in- and outpatient care. Age was divided into 5 categories (<40, 40–49, 50–59, 60–69, ≥70).

Table 1. Definitions of conditions considered as variables.

Condition	Qualifying ICD-10[1] codes
diabetes mellitus	E10, E11, E12, E13, E14
hypertension	I10, I11, I12, I13, I15
chronic renal failure	N18, N19, R944
high-risk CAD[2]	I252, I253, I255, Z955, Z951
low-risk CAD	I20, I250, I251, I256, I258, I259
hyperlipidaemia	E780, E781, E782, E783, E784, E785
previous stroke	I64H0, I6910, I6930, I6940, I61, I63
PAD[3]	I7390, I7380, I7710, I70
sten. of precerebral/cerebral arteries	I65, I66

[1] International Statistical Classification of Diseases and Related Health Problems, 10th Revision
[2] Coronary Artery Disease
[3] Peripheral Artery Disease

The CV therapies initiated before the commencement of index cancer therapy and ongoing during it with regular (at least quarterly) pharmacy dispensation (with the period monitored for dispensation starting 6 months before initiation of the cancer therapy and ending 12 months after it or following the occurrence of the heart failure event (whichever comes first)) were considered as a variable in the research. The reference non-treated group was selected by propensity score matching out of the cohort not fulfilling these criteria for regular administration of the corresponding CV medication. In the epirubicin therapy-related heart failure risk analysis angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) medications were considered as a variable. In the cancer therapy-related heart failure prevention study several CV medications were assessed (statins, ACEi/ARB, beta-blockers, trimetazidine).

3.5.Statistical Methods

3.5.1. Construction of heart failure risk models

In statistical analysis, binomial stepwise logistic regression was used to calculate odds ratios for heart failure event associated with chemotherapy exposure or other risk factors. At each step, independent variables were incorporated into the model if the probability of its score statistic was less than 0.11 ($p<0.11$) and removed if $p>0.2$. Significance assessments were performed where $p<0.05$. Statistical analyses were done using IBM SPSS Statistics Version 23 (Armonk, NY).

The effect of epirubicin or doxorubicin was analysed by taking their cumulative doses into account. Pearson's chi-square *p*-values were calculated for different cumulative doses to assess their association with the heart failure outcome. The cumulative doses versus the corresponding *p*-values were plotted in a probability function. The smallest dose where $p<0.05$ was considered a preliminary threshold dose. Based on the probability function, the epirubicin and doxorubicin cumulative dose was then classified into categories such that the above-mentioned preliminary threshold dose was used as the lowest cut-off value, and higher cut-off values were set at decreasing breakpoints of the function. Breakpoints were defined as local minima of the first derivative of the function.

The effects of concomitant chemotherapeutic agents were assessed separately. In the preliminary analysis, the cumulative doses of concomitant chemotherapeutic agents were divided into categories to estimate dose dependency in terms of heart failure incidence. For agents suspected of possessing a dose-dependent effect, Pearson's chi-square *p*-values were calculated for different cumulative doses to estimate the threshold dose, likewise described above. Different cut-off values for cumulative doses were then tested in the multivariable analysis to identify dose-dependency.

Given that the epirubicin cohort was large enough, to calculate and validate the results, the database was randomly split in a 70/30 ratio, the majority became the derivation cohort used to calculate score points, and the minority the validation cohort. Independent variables in the multivariable model where $p<0.1$ were considered in terms of composing the risk score, similarly to the Framingham risk score [41]. Score points were calculated by dividing each regression coefficient (B) by the smallest B coefficient in the model, then the quotient was rounded to the nearest integer. This score can be determined by simply totalling the risk points of a subject. Natural breakpoints of the score-heart failure incidence diagram were chosen to create 5 risk-score groups. Statistical differences between the risk groups were determined by Pearson's chi-square test.

After having calculated the heart failure risk scores for each subject in the validation cohort, these patients were also grouped into the 5 above-mentioned risk groups, the observed heart failure event rates were then calculated for the groups. Heart failure event incidences observed in the groups of the derivation and validation cohorts were compared.

The suitability of fitting the regression model in terms of the occurrence of heart failure was examined using the Hosmer-Lemeshow test, which was also applied to assess the fitting of the derived risk-score model. The discriminative ability of the score was evaluated by analysis of the receiver operating characteristic (ROC) curve.

3.5.2. Exploring the prevention of cancer therapy-related heart failure

This analysis was performed on the entire breast or colorectal cancer cohort receiving any type of biological or chemotherapy. By applying multivariable logistic regression, a propensity score for the assignment of the CV therapies was calculated to produce comparable treated and untreated cohorts. All available variables that may have affected the CV therapy assignment (age, gender, other CV therapies, CV diseases, diabetes mellitus (DM), renal failure, cancer localisation, stage of cancer) were included in the propensity score (see Table 2, which shows the full list of the variables used for matching). Propensity score matching was performed using nearest neighbour matching with a calliper size of ≤0.006. Based on propensity scores, the patients with the aforementioned CV therapies (see the definition in subsection *3.4. Composition of Independent Variables,* page 14*)* were matched 1:1 or 1:2 (depending on the volume of the treated cohort) with those that did not meet these criteria to undergo the corresponding CV therapy. Furthermore, the matching was additionally balanced in terms of the presence of all the relevant anticancer therapies (5-fluorouracil, capecitabine, trastuzumab bevacizumab, cyclophosphamide, platinum-containing drugs, taxanes, folinic acid, anthracyclines, irinotecan, radiation therapy) and dexrazoxane. The propensity score matching output was assessed by evaluating standardized differences between the characteristics. A

significant imbalance was considered to be present if a standardized mean difference of >10% was observed. The overall balance was checked by Hansen and Bowers test, as well.

Table 2. Variables used for matching the treated and untreated groups.

variables in PSM[1]	additional variables in balancing
demographics	**anticancer medication**
age	*5-fluorouracil*
gender	*capecitabine*
cancer characteristics	*cyclophosphamide*
localisation	*irinotecan*
stage	*platinum-containing drugs*
diseases	*folinic acid*
diabetes mellitus	*anthracyclines*
hypertension	*taxanes*
chronic renal failure	*trastuzumab*
hyperlipidaemia	*bevacizumab*
cerebral/precerebral artery stenosis	**protective medication**
peripheral artery disease	*dexrazoxane*
previous stroke	**irradiation therapy**
low-risk coronary artery disease	
high-risk coronary artery disease	
CV[2] medication	
statin therapy	
ACEi/ARB therapy	
fibrate therapy	

The patients were followed from the start of the index pharmaceutical cancer treatment until either the occurrence of the first heart failure outcome event or the censoring date (whichever was earlier). To focus on the possible preventive effect of the CV medication administered during the cancer therapy, the endpoint of the incident heart failure was assessed over no more than 4 years following the commencement of the cancer therapy. The incidence intensity was presented in incidence rate (IR) expressed over 100 patient-years. The time to the first heart failure event in the CV medication-treated and the matched control groups were compared using the Cox proportional-hazards model. The relationship between the administration of the CV therapies and the risk of the heart failure event during the follow-up

[1] propensity score matching
[2] cardiovascular

was represented as the hazard ratio (HR) with a confidence interval (CI) of 95%. Other covariates were not used in the regression analyses after the propensity score matching. Probabilities of <0.05 were considered significant. Analyses were also performed in the pre-specified subgroups: patients treated with anthracycline or capecitabine and patients with a high CV risk (DM, previous myocardial infarction, myocardial revascularization, stroke, peripheral artery disease). For subgroup analyses, patients were matched using the aforementioned method, as well.

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY).

4. RESULTS

4.1. Epirubicin-Related Heart Failure Risk Analysis

The analysed database covered the period between 1st January 2004 and 31st December 2016, all the patients diagnosed with primary breast carcinoma confirmed by histology were identified. By this means, 84,042 patients were found, of whom 30,957 were administered any biological or chemotherapy after breast cancer verification but previously not, and 25,029 subjects were identified as having the 3-year preceding observational period.

4.1.1. Heart failure risk estimation

Heart failure incidence was assessed in 8,068 epirubicin-treated breast cancer patients, who met the enrolment criteria. The baseline characteristics of patients are shown in Table 3. The cumulative, overall incidence of heart failure was 6.90% during the studied period (median follow-up: 5.89 years). Our crude data showed an apparent heart failure rate dependence on age and epirubicin cumulative dose (Figure 1).

Table 3. Baseline characteristics of the entire cohort in the epirubicin study.

Characteristics	N	Rate	Characteristics	N	Rate
Age range (years)			*Stage of cancer*[1]		
<40	578	7.2%	No spread or invasion	3378	41.9%
40–49	1468	18.2%	Regional lymph node or nearby structure invasion	1927	23.9%
50–59	2439	30.2%			
60–69	2448	30.3%	Distant lymph node or other distant metastasis	837	10.3%
70+	1135	14.1%			
			Missing data	1926	23.9%
Gender			*Pre-existing cardiovascular conditions and risk factors*		
Male	64	0.8%	Diabetes mellitus	1160	14.4%
Female	8454	99.2%	Hypertension	5121	63.5%
Laterality of Cancer			Hyperlipidaemia	1336	16.6%
Left	3774	46.8%	Previous stroke	150	1.9%
Right	3799	47.1%	Previous MI [2] or coronary revascularization	258	3.2%
Both sides	288	3.6%			
Unknown	205	2.5%			

[1] upon initiation of chemotherapy
[2] Myocardial Infarction

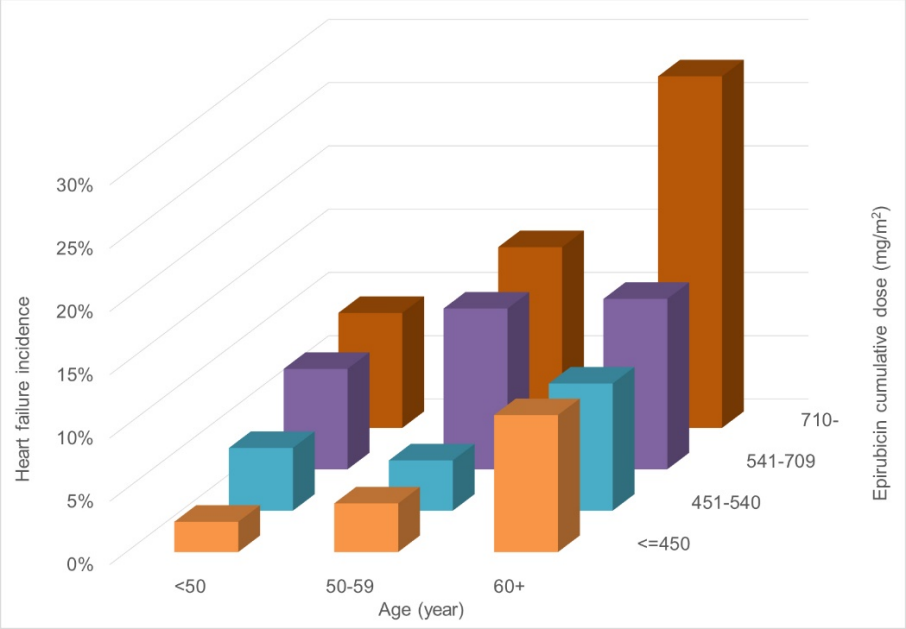

Figure 1: Unadjusted distribution of heart failure event in the full study of the epirubicin cohort grouped according to the cumulative dose of epirubicin and age.

The occurrence of oncological therapies is shown in Table 4. As presented, nowadays higher epirubicin doses are rarely administered. In our cohort, a cumulative dose over 709 mg/m^2 was only administered to 1.4% of patients (median dose: 420 mg/m^2). The results of univariate statistical analysis showed that an epirubicin cumulative dose of <450 mg/m^2 was not associated with heart failure risk, but over this, an increasingly strong association could be observed. The epirubicin cumulative dose was divided into 4 categories for analysing dose-dependency (Table 4). A detailed analysis of heart failure risk was performed on the derivation cohort. All reasonable candidate predictors were included in the logistic regression. Variables included hypertension, diabetes mellitus, coronary artery disease, previous stroke, previous and ongoing treatment with ACEi/ARB, renal failure, hypothyroidism, hyperthyroidism, hyperlipidaemia, age, gender, cancer stage, epirubicin cumulative dose, presence of dexrazoxane and use of other non-anthracycline chemotherapies, namely pyrimidine analogues (capecitabine, gemcitabine, 5-fluorouracil), taxanes (paclitaxel, docetaxel), antifolates (methotrexate), cyclophosphamide, platinum-containing drugs (carboplatin) and targeted therapies (trastuzumab, bevacizumab).

Table 4. Frequencies of cancer therapies in the entire cohort of epirubicin study.

Cancer therapy	N	Rate
Radiation	6597	81.8%
Cumulative dose of epirubicin[1] (mg/m^2)		
≤450	7271	90.1%
451–540	456	5.7%
541–709	203	2.9%
>709	111	1.4%
Non-anthracycline chemotherapies		
Cyclophosphamide	6487	80.4%
Pyrimidine analogues	4408	54.6%
Capecitabine	436	5.4%
Gemcitabine	80	1.0%
5-fluorouracil	4161	51.6%
Taxanes	3424	42.4%
Paclitaxel	1244	15.4%
Docetaxel	2658	31.8%
Carboplatin	282	3.5%
Methotrexate	105	1.3%
Vinca alkaloid	67	0.8%
Targeted therapies (antibodies)		
Trastuzumab	1506	18.7%
Bevacizumab	107	1.3%
Lapatinib	46	0.6%
Protective agents		
Dexrazoxane	267	3.3%

The results of the multivariable regression analysis are summarized in Figure 2. Epirubicin cumulative dose >709 mg/m^2 was an independent variable associated with heart failure (odds ratio (OR): 1.76). The only other form of chemotherapy that exhibited significant cumulative dose-dependency in terms of heart failure, besides epirubicin, was docetaxel; above the threshold dose of 510 mg/m^2 it was more strongly (OR: 1.59) associated with heart failure

[1] Standard 3-week schedule, with the exception of 16 patients

outcome, than under this dose (OR: 1.28). Heart failure risk significantly increased for patients over 40 years of age. Furthermore, the older the patient, the more robust the impact on heart failure: OR for heart failure for those >70 years of age was 9.83 (compared to those <40). The following factors were also confirmed as significant predictors in association with heart failure: diabetes mellitus, hypertension, coronary artery disease (CAD) (with previous MI or revascularization OR: 1.89; without, OR: 1.30), previous stroke, capecitabine, gemcitabine, bevacizumab and advanced cancer with distant metastasis (for more details see Figure 2).

Of the analysable factors, an epirubicin cumulative dose of 541-709 mg/m^2 and intermediate cancer stage without distant metastasis were shown to be associated with higher heart failure risk of borderline ($0.05<p<0.10$) significance, whilst the regular and ongoing use of ACEi/ARB commenced before chemotherapy (present in 25.9% of the cohort) similarly reduced the heart failure risk (Figure 2). In the analysed cohort, antifolates (methotrexate), cyclophosphamide, platinum-containing drugs (carboplatin) and trastuzumab (targeted therapy) were not proven to be associated with a higher long-term heart failure risk. A protective effect could not be confirmed with dexrazoxane. In our study, an elevated heart failure risk as a result of chest irradiation was not identified, not even for left-sided tumour localisation.

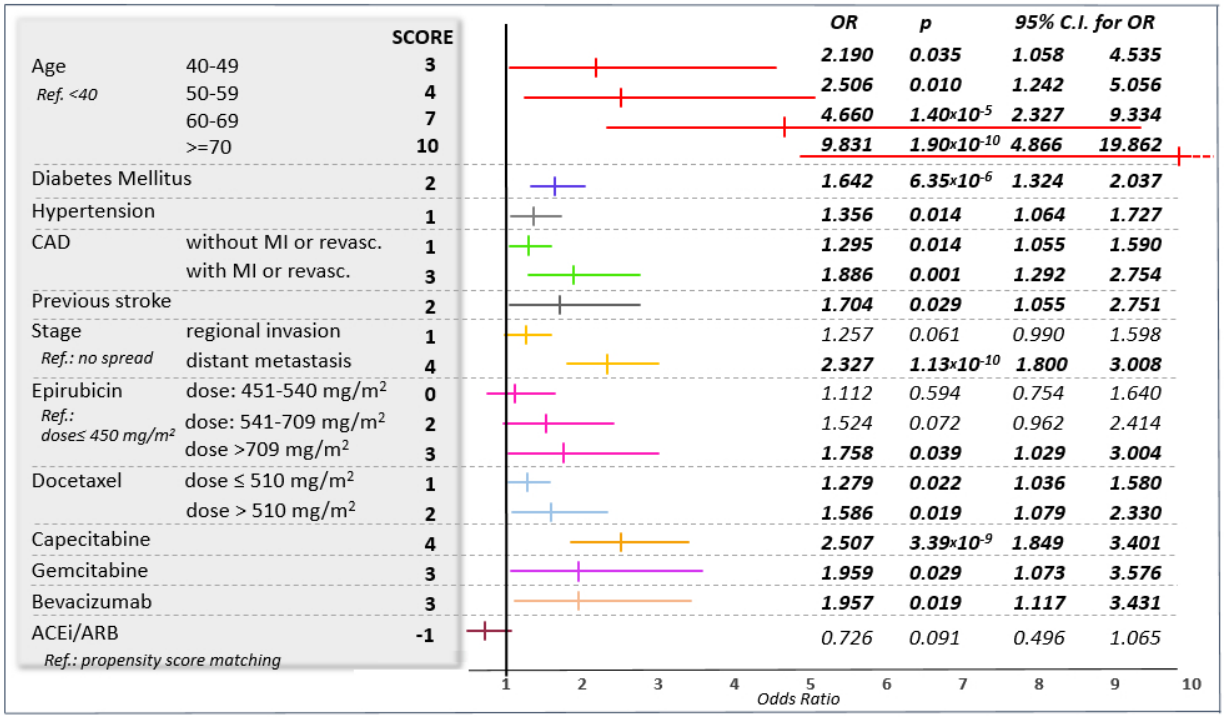

Figure 2: Independent predictors in the epirubicin study for heart failure in the multivariable regression analysis and the corresponding odds ratios (OR) with confidence intervals (CI) and heart failure score points.
DM: Diabetes Mellitus. CAD: Coronary Artery Disease. MI: Myocardial Infarction.

4.1.2. Construction of the heart failure risk score

Independent variables in the multivariable model were considered whilst composing a heart failure risk score model, Table 5 presents the regression coefficients (B) used for the point calculation. The heart failure risk score points assigned to the predictors can also be seen in Figure 2. The score points were calculated for each patient in the derivation cohort. The median number of points was 7. Heart failure event rate increased as the number of score points rose.

Table 5. Construction of the risk score for heart failure**.**

	B[1]	**p**	**OR[2]**	**points**
Age: 40–49	0.784	0.0348	2.190	**3**
50–59	0.919	0.0103	2.506	**4**
60–69	1.539	$1.40*10^{-5}$	4.660	**7**
70+	2.286	$1.90*10^{-10}$	9.831	**10**
Diabetes Mellitus	0.496	$6.35*10^{-6}$	1.642	**2**
Hypertension	0.304	0.0139	1.356	**1**
CAD[3] without MI[4] or revascularization	0.259	0.0136	1.295	**1**
with MI or revascularization	0.635	0.0010	1.886	**3**
Previous Stroke	0.533	0.0294	1.704	**2**
Capecitabine	0.919	$3.39*10^{-9}$	2.507	**4**
Gemcitabine	0.672	0.0285	1.959	**3**
Bevacizumab	0.672	0.0190	1.957	**3**
Epirubicin 541–709 mg/m^2	0.422	0.0724	1.524	**2**
>709 mg/m^2	0.564	0.0390	1.758	**3**
Docetaxel 1–510 mg/m^2	0.246	0.0220	1.279	**1**
>510 mg/m^2	0.461	0.0190	1.586	**2**
Stage: regional invasion	0.224	0.0609	1.257	**1**
distant metastasis	0.844	$1.13*10^{-10}$	2.327	**4**
ACEi/ARB[5]	-0.320	0.0914	0.726	**-1**

Using natural breakpoints of the score-heart failure incidence diagram, score points were divided into 5 categories from very low (2.1%) to very high (31.7%) heart failure incidence. In

[1] Regression Coefficient
[2] Odds Ratio
[3] Coronary Artery Disease
[4] Myocardial Infarction
[5] Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker

Figure 3 the point categories with corresponding heart failure rates observed in the derivation cohort can be seen. Differences in heart failure incidences between the neighbouring score categories were significant (p=2.88*10^{-10}, 6.84*10^{-7}, 1.04*10^{-14}, 0.0219, respectively).

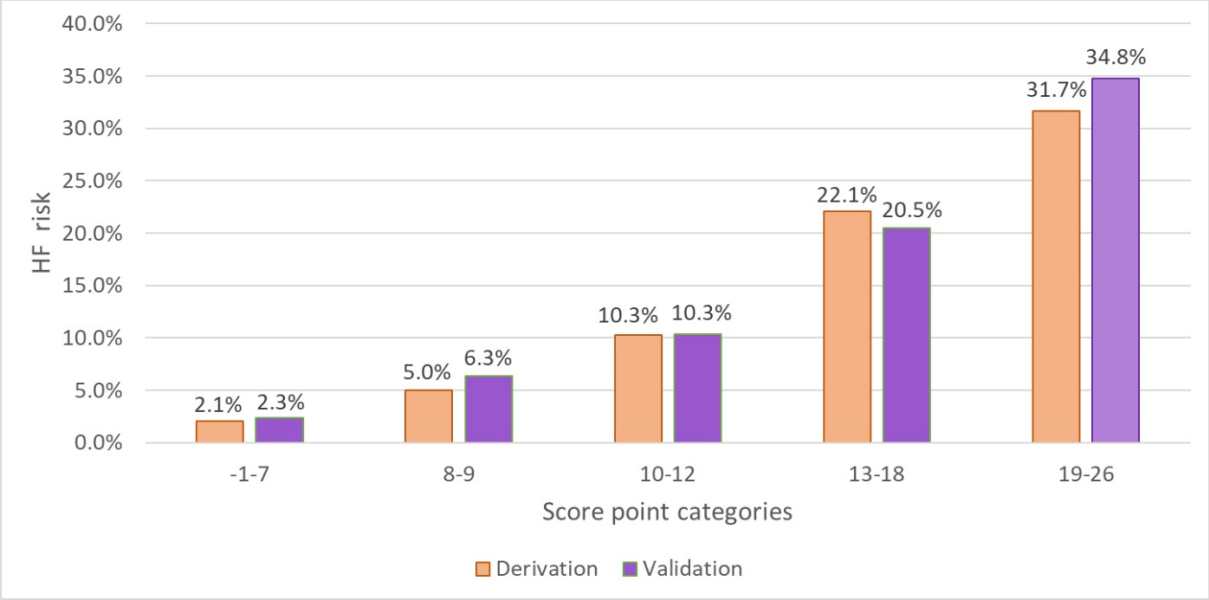

Figure 3: Observed heart failure incidence in the derivation and validation cohorts of the epirubicin study.

4.1.3. Heart failure risk score validation

Hosmer-Lemeshow test was applied to assess the regression and derived score models. The tests indicated that fitting of both models was good when p>0.05, 0.29 for the regression model and 0.78 for the score model, which means that the hypothesis of sufficient fitting cannot be rejected.

Cumulative heart failure incidence was almost identical in the derivation and validation cohorts (6.84% vs. 7.04%). The median of the score points was also 7 in the validation cohort. Detailed statistical data about the categories in the derivation and validation cohort can be found in Table 6. After having classified the subjects into the previously mentioned risk score categories, a similar heart failure distribution pattern was observed in the two cohorts (Figure 3). A 15-fold increase occurred in the observed incidence of heart failure between the outermost risk categories. The incidences observed in the derivation and validation cohorts do not differ to a clinically significant extent. The area under the ROC curve for the score-points model was 0.79 and the optimal cut-off value of the score points was ≥9 (sensitivity: 0.79; specificity: 0.65) to effectively identify patients exposed to an elevated heart failure risk.

Table 6. Descriptive statistics per risk categories in the epirubicin study cohorts.

		Derivation				Validation			
	Point	**N**	**∑N**	**Avg. age**	**Avg. epirubicin dose mg/m²**	**N**	**∑N**	**Avg. age**	**Avg. epirubicin dose mg/m²**
Risk group 1	**-1**	0	2821	49.7	386.8	1	1201	49.6	388.3
	0	110				49			
	1	134				60			
	2	60				31			
	3	320				141			
	4	622				258			
	5	713				289			
	6	416				186			
	7	446				186			
Risk group 2	**8**	568	1041	60.5	390.2	263	457	60.6	402.9
	9	473				194			
Risk group 3	**10**	367	1052	65.8	393.0	151	445	66.2	392.7
	11	364				156			
	12	321				138			
Risk group 4	**13**	205	680	68.2	427.3	88	288	68.1	423.75
	14	168				73			
	15	131				48			
	16	79				37			
	17	48				23			
	18	49				19			
Risk group 5	**19**	27	60	70.9	505.3	10	23	69.5	501.5
	20	19				6			
	21	5				3			
	22	2				2			
	23	3				1			
	24	2				1			
	25	1				0			
	26	1				0			

4.2.Doxorubicin-Related Heart Failure Risk Analysis

3668 doxorubicin-treated breast cancer patients met the enrolment criteria and were eligible for heart failure risk analysis in the period between 2004-2015. 380 patients who received doxorubicin at a cumulative dose under 200 mg/m^2 were excluded from the further analysis due to their short survival and high rate of incomplete cancer data records. The clinical characteristics of the enrolled patients are summarized in Table 7. The representation of the

cancer therapies in the analysed cohort is shown in Table 8. The cumulative incidence of the heart failure event during 3-9 years of follow-up was 6.2%.

Table 7. Baseline characteristics of the entire cohort in the doxorubicin study.

Characteristics	N	%	Characteristics	N	%
Age range (year)			*Stage of cancer*[1]		
<40	347	10.6	No spread or invasion	855	26.0
40–49	693	21.1	Regional lymph node or nearby structure invasion	1025	31.2
50–59	1151	35.0			
60–69	840	25.5	Distant lymph node or other distant metastasis	576	17.5
70+	257	7.8			
			Missing data	832	25.3
Gender			*Pre-existing cardiovascular conditions and risk factors*		
Male	20	0.6	Diabetes mellitus	399	12.1
Female	3268	99.4	Hypertonia	1921	58.3
			Hyperlipidaemia	491	14.9
			Angina pectoris	689	20.9
			Previous MI[2] or coronary revascularisation	67	2.0

The result of the regression analysis is presented in Figure 4. Hosmer-Lemeshow test suggested that fitting of the regression model was good (p=0.757). The incidence of heart failure was essentially influenced by age. Even in the age of 50-59 years, a significant association was found with higher heart failure risk as compared to the subjects under 40 years. Furthermore, the older the patient, the more robust the impact on heart failure: OR for heart failure for subjects >70 years of age was 5.78 (compared to those <40).

Among the analysed co-morbidities shown in Table 7 diabetes mellitus was associated with increased heart failure risk.

[1] upon initiation of chemotherapy

[2] Myocardial Infarction

Table 8. Frequencies of cancer therapies in the entire cohort of the doxorubicin study.

Cancer therapy	N	Rate	Cancer therapy	N	Rate
Radiation	2784	84.7	Pyrimidine analogues		
Doxorubicin cumulative dose (mg/m^2)			Capecitabine	277	8.4
200-300	2671	81.2	5-fluorouracil	738	22.4
301-400	520	15.8	Carboplatin	188	5.7
400+	97	3.0	Targeted therapies (antibodies)		
Taxanes			Trastuzumab	710	21.6
Paclitaxel	753	22.9	Bevacizumab	95	2.9
Docetaxel	1835	55.8	Protective agents		
Cyclophosphamide	2988	90.9	Dexrazoxane	194	5.9

A doxorubicin cumulative dose of 301-400 mg/m^2 was shown to be associated with higher heart failure risk of borderline ($0.05<p<0.10$) significance, whilst the doses above raised the risk significantly (OR: 2.27), compared to those with 200-300 mg/m^2 (see Figure 4).

We could not confirm a significant association between cancer stage and heart failure in this analysis. The cancer stage was neither proven a confounder for the effect of doxorubicin cumulative dose on heart failure.

The irradiation therapy did not cause heart failure risk elevation, not even at the patients with left-sided breast tumour.

Of the anticancer drugs, the treatment of carboplatin (OR: 1.85), capecitabine (OR: 2.52), 5-fluorouracil (OR: 1.46) and bevacizumab (OR: 2.48) were proven independent predictors for heart failure, without showing any sign of cumulative dose-dependency. Although awaited, trastuzumab (targeted therapy) and taxanes were not proven to be associated with a higher long-term heart failure risk.

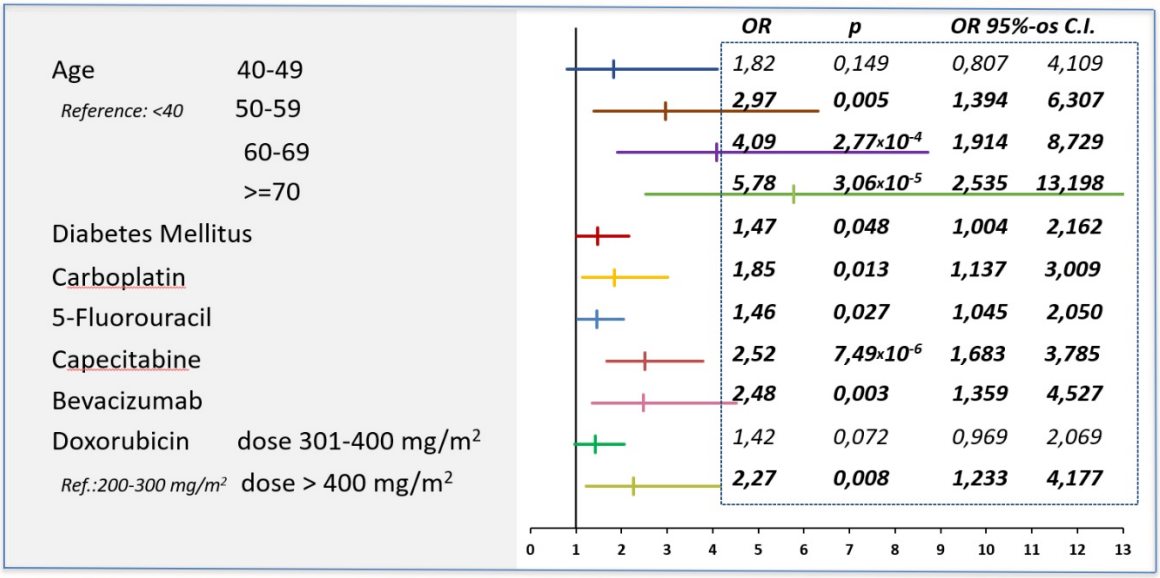

Figure 4. Independent predictors in the doxorubicin study for heart failure in the multivariable regression analysis and the corresponding odds ratios (OR) with confidence intervals (CI).
DM: Diabetes Mellitus. CAD: Coronary Artery Disease. MI: Myocardial Infarction.

4.3.Prevention of Cancer Therapy-Related Heart Failure

With the retrospective analysis of a merged nation-wide dataset, 9,575 breast (5,210) or colorectal (4,365) cancer patients were enrolled. To focus on the possible preventive effect of the medications ongoing during the chemotherapy, we analysed the 4-year cumulative incidence rate for heart failure outcome event, which was 6.9% (mean follow-up: 3.68 years). The preventive ability of the concomitant CV medication was assessed against the cancer therapy-related heart failure. The benefit of CV medications started before the commencement of chemotherapy and ongoing for at least 1 year after was assessed in this analysis (see subsection 3.4. *Composition of Independent Variables* on page 14 for definitions). The relationship between the administration of CV therapies (angiotensin-converting enzyme inhibitors (ACEi) / angiotensin II receptor blockers (ARB), statins, beta-blockers, trimetazidine) and the risk of heart failure was evaluated by propensity score matching. In Table 9 the demographic and clinical characteristics of the studied cohorts are shown after propensity score matching. Thanks to propensity score matching and balancing, the matched cohorts did not differ to a clinically significant extent concerning the baseline CV diseases, demographics and cancer stage or therapy.

Table 9. Baseline characteristics of the matched cohorts.

		Statins				ACEi/ARB				Beta-blockers			
		treated		untreated		treated		untreated		treated		untreated	
demography	number	1057		1892		2458		2458		1514		1514	
	median age (years)	65		65		64		63		64		65	
	age Q1-Q3[1] (years)	60-70		60-70		57-69		57-69		57-70		58-70	
		N	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
	female	761	72.0	1368	72.30	1780	72.4	1776	72.3	1154	76.2	1166	77.0
CV[2] diseases and risk factors	diab. mell.	387	36.6	634	33.5	505	20.5	544	22.1	438	28.9	444	29.3
	hypertension	958	90.6	1726	91.2	2315	94.2	2311	94.0	1414	93.4	1433	94.6
	hyperlipidaemia	475	44.9	771	40.8	679	27.6	617	25.1	466	30.8	490	32.4
	CRF[3]	33	3.1	59	3.1	70	2.8	60	2.4	53	3.5	49	3.2
	CAD[4] without MI[5] or revasc.	401	37.9	702	37.1	750	30.5	757	30.8	560	37.0	561	37.1
	CAD with MI or revasc.	107	10.1	137	7.2	118	4.8	141	5.7	103	6.8	102	6.7
	PAD[6]	90	8.5	196	10.4	207	8.4	192	7.8	142	9.4	145	9.6
	sten. of precerebral/ cerebral arteries	103	9.7	160	8.5	179	7.3	152	6.2	117	7.7	122	8.1
	prev. stroke	90	8.5	122	6.4	135	5.5	116	4.7	89	5.9	101	6.7
CV med.	ACEi/ARB	716	67.7	1227	64.9	2458	100.0	0	0.0	983	64.9	974	64.3
	statins	1057	100.0	0	0.0	312	12.7	294	12.0	357	23.6	316	20.9
cancer loc.	breast	577	54.6	1031	54.5	1261	51.3	1210	49.2	816	53.9	831	54.9
	colorectal	480	45.4	861	45.5	1197	48.7	1248	50.8	698	46.1	683	45.1
cancer spread or invasion	no	386	36.5	671	35.5	914	37.2	867	35.3	564	37.3	526	34.7
	locoregional	306	28.9	539	28.5	674	27.4	721	29.3	428	28.3	411	27.1
	distant	153	14.5	274	14.5	361	14.7	381	15.5	226	14.9	240	15.9
	unknown	212	20.1	408	21.6	509	20.7	489	19.9	296	19.6	337	22.3
cancer therapy	anthracyclines	531	50.2	946	50.0	1155	47.0	1126	45.8	760	50.2	768	50.7
	dexrazoxane	8	0.8	19	1.0	20	0.8	23	0.9	15	1.0	17	1.1
	taxanes	285	27.0	551	29.1	668	27.2	675	27.5	430	28.4	436	28.8
	cyclophosphamide.	477	45.1	812	42.9	992	40.4	984	40.0	654	43.2	688	45.4
	platinum	224	21.2	358	18.9	531	21.6	534	21.7	294	19.4	311	20.5
	irinotecan	42	4.0	84	4.4	105	4.3	124	5.0	77	5.1	63	4.2
	folinic acid	435	41.2	760	40.2	1072	43.6	1092	44.4	609	40.2	595	39.3
	capecitabine	89	8.4	165	8.7	210	8.5	253	10.3	153	10.1	138	9.1
	5-fluorouracil	695	65.8	1167	61.7	1587	64.6	1566	63.7	943	62.3	932	61.6
	trastuzumab	122	11.5	248	13.1	285	11.6	309	12.6	178	11.8	205	13.5
	bevacizumab	37	3.5	89	4.7	92	3.7	106	4.3	64	4.2	46	3.0
	radiation	554	52.4	1048	55.4	1276	51.9	1210	49.2	793	52.4	811	53.6

[1] Quartiles 1-3
[2] Cardiovascular
[3] Chronic Renal Failure
[4] Coronary Artery Disease
[5] Myocardial Infarction
[6] Peripheral Artery Disease

4.3.1. Statin therapy

Unmatched cohort

1,204 patients received statin therapy. Compared to those who did not, the treated patients were older and suffered from more common CV diseases, DM or hypertension. The oncological characteristics did not differ notably. The baseline characteristics of the unmatched cohorts are presented in Table 10.

Matched cohorts

By propensity score matching, well-balanced statin-treated and untreated cohorts with a standardized difference of <0.1 for all covariates were obtained. The incidence rate (IR) of heart failure was lower in the statin group compared to the untreated cohort (1.88 and 2.51 per 100 patient-years, respectively). The details of the descriptive statistics of the matched statin-treated and untreated cohorts are presented in Table 11.

Cox-regression results showed that among matched cohorts (Table 9), the risk of heart failure was significantly lower for the statin-treated patients versus the untreated patients (HR: 0.748, p=0.038) (Figure 5). According to the hazard ratios, a beneficial impact was supposed in the subgroup treated with anthracyclines (HR: 0.742, p=0.253). Whilst in the subjects treated without anthracyclines, a meaningful effect was not observed (HR: 0.917, p=0.628). A borderline significant trend (p=0.086) was observed for the interaction between the statin effect on the risk of heart failure and the presence of anthracyclines. Among anthracycline-, platinum- or capecitabine-treated patients, a significant association was found with a lower risk of heart failure (HR: 0.660, p=0.032) for statin therapy (Figure 5). Since we did not find significant interaction (p=0.245) between the effect of statins on heart failure and the level of CV risk, moreover, the subgroup analysis showed the hazard ratios to be homogeneous across the cohorts exposed to high and non-high CV risk (defined in subsection *3.5.2.*, page 17) (HR: 0.740, p=0.071 and HR: 0.677, p= 0.109, respectively), the potential beneficial effect of statin therapy was considered independent of baseline CV risk (Figure 5). In the subgroup analysis by gender, a much less pronounced effect was observed in male than female patients (HR: 0.830, p= 0.436 and HR: 0.712, p=0.07, respectively). Accordingly, the result of the interaction analysis approached the level of significance (p=0.054). To analyse the dose-dependency of the statin effect, dosage subgroups were defined according to the low-density lipoprotein (LDL)-cholesterol-lowering capacity (≥40% or <40%). One subgroup was treated with a high-intensity statin dosage that consisted of simvastatin ≥40mg, atorvastatin ≥30mg and rosuvastatin ≥15mg, another with a non-high intensity dosage containing all the other statin therapies. In the latter

subgroup, a considerable association with heart failure was not identified (HR: 0.928, p=0.729). Contrarily, at high-dose therapy, the hazard ratio suggested a beneficial effect but without statistical significance (HR: 0.722, p=0.234) (Figure 5). Moreover, analysing the entire, matched statin cohort, using the dosage categories as the covariate in the Cox regression, with a lower risk of heart failure a significant association was found for the high-dose group but not for the lower doses (p=0.045 and p=0.11, respectively).

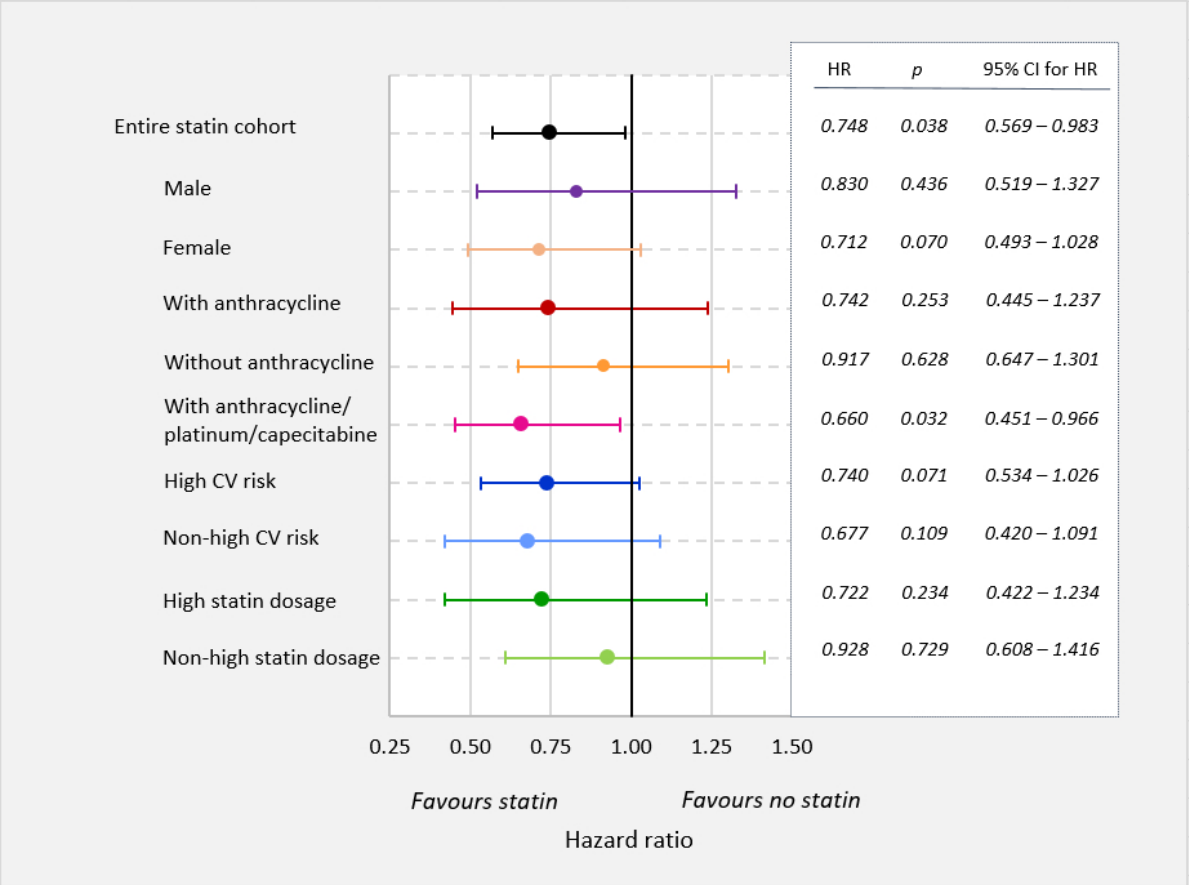

Figure 5. Relationship of statin therapy and the risk of cancer therapy-related heart failure.
HR: hazard ratio, CI: confidence interval, CV: cardiovascular.

Table 10. Baseline characteristics of the cohorts before matching.

		Statins				ACEi/ARB				Beta-blockers			
		treated		untreated		treated		untreated		treated		untreated	
demography	number	1204		8371		3431		6144		1701		7764	
	median age (years)	65		59		65		57		64		59	
	age Q1-Q3[1] (years)	60-71		51-67		59-71		48-65		58-70		50-67	
		N	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
	female	854	70.9	6263	74.82	2444	71.2	4673	76.1	1291	75.9	5738	73.9
CV diseases and risk factors	diab. mell.	472	39.2	1251	14.9	1045	30.5	678	11.0	556	32.7	1136	14.6
	hypertension	1104	91.7	5392	64.4	3286	95.8	3210	52.2	1601	94.1	4788	61.7
	hyperlipidaemia	607	50.4	1375	16.4	1059	30.9	923	15.0	597	35.1	1357	17.5
	CRF[2]	53	4.4	150	1.8	115	3.4	88	1.4	60	3.5	142	1.8
	CAD[3] without MI[4] or revasc.	450	37.4	1905	22.8	1155	33.7	1200	19.5	643	37.8	1666	21.5
	CAD with MI or revasc.	174	14.5	232	2.8	248	7.2	158	2.6	167	9.8	230	3.0
	PAD[5]	169	14.0	453	5.4	344	10.0	278	4.5	190	11.2	425	5.5
	sten. of precerebral/ cerebral arteries.	168	14.0	328	3.9	268	7.8	228	3.7	145	8.5	342	4.4
	prev. stroke	116	9.6	277	3.3	233	6.8	160	2.6	99	5.8	290	3.7
CV med.	ACEi/ARB	846	70.3	2585	30.9	3431	100.0	0	0.0	1167	68.6	2212	28.5
	statins	1204	100.0	0	0.0	846	24.7	358	5.8	511	30.0	667	8.6
cancer loc.	breast	651	54.1	4559	54.5	1695	49.4	3515	57.2	928	54.6	4222	54.4
	colorectal	553	45.9	3812	45.5	1736	50.6	2629	42.8	773	45.4	3542	45.6
cancer spread or invasion	no	454	37.7	3132	37.4	1238	36.1	2348	38.2	631	37.1	2912	37.5
	locoregional	342	28.4	2301	27.5	963	28.1	1680	27.3	475	27.9	2139	27.6
	distant	175	14.5	1220	14.6	527	15.4	868	14.1	262	15.4	1121	14.4
	unknown	233	19.4	1718	20.5	703	20.5	1248	20.3	333	19.6	1592	20.5
cancer therapy	anthracyclines	598	49.7	4254	50.8	1555	45.3	3297	53.7	857	50.4	3940	50.7
	dexrazoxane	10	0.8	94	1.1	26	0.8	78	1.3	16	0.9	87	1.1
	taxanes	313	26.0	2636	31.5	888	25.9	2061	33.5	480	28.2	2441	31.4
	cyclophosphamide	536	44.5	3574	42.7	1353	39.4	2757	44.9	745	43.8	3318	42.7
	platinum	258	21.4	1741	20.8	771	22.5	1228	20.0	336	19.8	1642	21.1
	irinotecan	49	4.1	388	4.6	170	5.0	267	4.3	85	5.0	344	4.4
	folinic acid	498	41.4	3374	40.3	1536	44.8	2336	38.0	673	39.6	3152	40.6
	capecitabine	110	9.1	723	8.6	333	9.7	500	8.1	171	10.1	652	8.4
	5-fluorouracil	789	65.5	5194	62.0	2228	64.9	3755	61.1	1057	62.1	4854	62.5
	trastuzumab	137	11.4	1127	13.5	374	10.9	890	14.5	203	11.9	1044	13.4
	bevacizumab	40	3.3	336	4.0	141	4.1	235	3.8	69	4.1	301	3.9
	radiation	617	51.2	4596	54.9	1700	49.5	3513	57.2	885	52.0	4272	55.0

[1] Quartiles 1-3
[2] Chronic Renal Failure
[3] Coronary Artery Disease
[4] Myocardial Infarction
[5] Peripheral Artery Disease

Table 11. Descriptive statistics of the matched statin cohorts.

	N of patients		total duration of F-U[1] (patient-year)		mean F-U (years)		*N* of HF[2] events		HF incidence rate (per 100 patient-years)	
	treated	untreated	treated	untreated	treated	untreated	treated	untreated	treated	untreated
entire cohort	1057	1892	3886.65	6856.81	3.68	3.62	73	172	1.88	2.51
male	246	421	876.51	1496.04	3.56	3.55	26	53	2.97	3.54
female	742	1318	2771.40	4826.73	3.73	3.66	40	98	1.44	2.03
anthracycline	489	854	1837.11	3179.24	3.76	3.72	21	49	1.14	1.54
w/o anthracycline	496	870	1789.98	3119.77	3.61	3.59	48	91	2.68	2.92
anthracycline/platinum /capecitabine	626	1068	2322.41	3883.60	3.70	3.70	37	94	1.59	2.42
high CV[3] risk	544	873	1969.86	3083.79	3.62	3.53	53	112	2.69	3.63
non-high CV risk	502	940	1872.07	3468.29	3.73	3.69	23	63	1.23	1.82
high statin dosage	307	528	1131.95	1930.50	3.69	3.66	19	45	1.68	2.33
non-high statin dosage	513	898	1898.84	3313.62	3.70	3.69	33	62	1.74	1.87

4.3.2. ACEi/ARB therapy

Unmatched cohort

3,431 patients were administered ACEi/ARB medication during their anticancer therapy. Compared to ACEi/ARB-untreated subjects, these patients were older, more frequently suffered from DM and CV diseases, and almost all were hypertensive (Table 10).

Matched cohorts

The propensity score matching produced comparable groups (Table 9) with a standardized mean difference of <0.1 for all the covariates. The matched cohorts did not exhibit a significant overall imbalance (p=0.264). The heart failure incidence was lower in the ACEi/ARB group compared to the untreated group (IR: 2.06 per 100 patient-years and 2.55 per 100 patient-years, respectively). The details of the descriptive statistics of the matched ACEi/ARB-treated and untreated cohorts are presented in Table 12.

The Cox regression of the relationship between the treatment and heart failure risk confirmed a significantly lower risk for the patients treated with ACEi/ARB (HR: 0.809, p=0.032) (Figure 6). No interaction was observed between their preventive effects and the presence of anthracyclines in the chemotherapy (p=0.722). Accordingly, the HRs for heart

[1] follow-up
[2] heart failure
[3] cardiovascular

failure of the cohorts treated and untreated with ACEi/ARB were similar in the patients with and without anthracyclines (HR: 0.711, p=0.069 and HR: 0.781, p=0.045, respectively). A significant reduction in heart failure risk was also associated with the ACEi/ARB treatment in the high CV risk (defined in subsection *3.5.2. Exploring the prevention of cancer therapy-related heart failure,* page 17) subgroup (HR: 0.707, p=0.035), while the non-high-risk CV patients only exhibited a trend suggesting a lower heart failure risk, without reaching significance (HR: 0.805, p=0.117) (Figure 6) (for details of statistics, see Table 12). However, interaction analysis did not confirm the level of CV risk as significant influencing factor on ACEi/ARB preventive effect against heart failure (p=0.458).

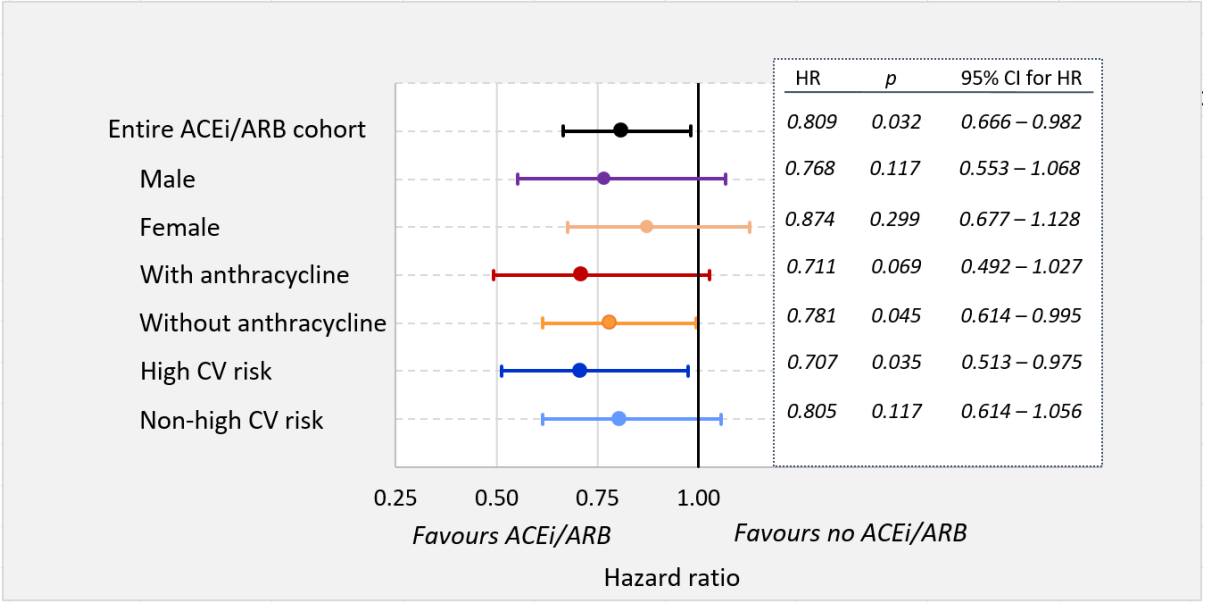

Figure 6. Relationship of ACEi/ARB therapy and the risk of cancer therapy-related heart failure.
HR: hazard ratio, CI: confidence interval, CV: cardiovascular

Table 12. Descriptive statistics of the matched ACEi/ARB cohorts.

	N of patients		total duration of F-U[1] (patient-year)		mean F-U (years)		*N* of HF[2] events		HF incidence rate (per 100 patient-years)	
	treated	untreated	treated	untreated	treated	untreated	treated	untreated	treated	untreated
entire cohort	2458	2458	9016.95	8908.60	3.67	3.62	186	227	2.06	2.55
male	619	619	2217.56	2185.07	3.58	3.53	63	81	2.84	3.70
female	1732	1732	6404.41	6349.70	3.70	3.66	111	126	1.73	1.98
anthracycline	1131	1481	4258.97	5501.85	3.77	3.71	44	80	1.03	1.45
w/o anthracycline	1263	1263	4564.72	4495.97	3.61	3.56	118	149	2.59	3.31
high CV[3] risk	675	675	2441.76	2389.48	3.62	3.54	64	89	2.62	3.72
non-high CV risk	1613	1613	5969.96	5933.28	3.70	3.68	95	117	1.59	1.97

4.3.3. Beta-blocker therapy

Unmatched cohort

Due to their low representation and special indications, the medications of sotalol, propranolol and atenolol were not included in this analysis (110 patients were excluded). 1,701 patients pursued one or more of the remaining beta-blocker therapies (bisoprolol, betaxolol, metoprolol, nebivolol, carvedilol). Relative to the untreated ones, these patients were older, more frequently suffered from CV diseases and DM, of which almost all were hypertensive and much more frequently took other CV medications (Table 10).

Matched cohorts

By propensity score matching, well-balanced cohorts (Table 9) treated with and without beta-blockers with a standardized mean difference of <0.1 for all covariates were obtained. The matched cohorts did not show significant overall imbalance (p=0.679). The heart failure incidence was similar in the beta-blocker-treated and untreated cohorts (IR: 2.34 per 100 patient-years and 2.47 per 100 patient-years, respectively). The details of the descriptive statistics of the matched beta-blocker-treated and untreated cohorts are presented in Table 13.

Among the matched cohorts, Cox regression did not reveal a significant association between the incident heart failure and beta-blocker treatment (HR: 0.946, p=0.653). A

[1] follow-up
[2] heart failure
[3] cardiovascular

preventive effect was neither observed in the high CV risk subgroup nor the anthracycline-treated subgroup (HR: 1.095, p=0.542 and HR: 1.006, p=0.979, respectively) (Figure 7).

Regarding the different adrenergic-receptor affinities of the unique beta-blockers, a propensity score matching-based Cox regression was performed on the following subdivisions: second-generation selective beta-blockers (metoprolol, betaxolol, bisoprolol); alpha- and beta-blocker (carvedilol); and third-generation selective beta-blocker (nebivolol). For matching, the untreated control groups were selected from the cohort not treated with any beta-blocker. For second-generation selective agents and carvedilol, no result suggesting a preventive effect against heart failure was identified (HR: 1.208, p=0.261 and HR: 1.433, p=0.230, respectively). A significant association was neither confirmed for the nebivolol cohort with incident heart failure (HR: 0.940, p=0.801), but within this cohort, the anthracycline- or capecitabine-treated patients were less prone to heart failure with borderline significance (HR: 0.584, p=0.069) (Figure 7) (for details of statistics, see Table 13).

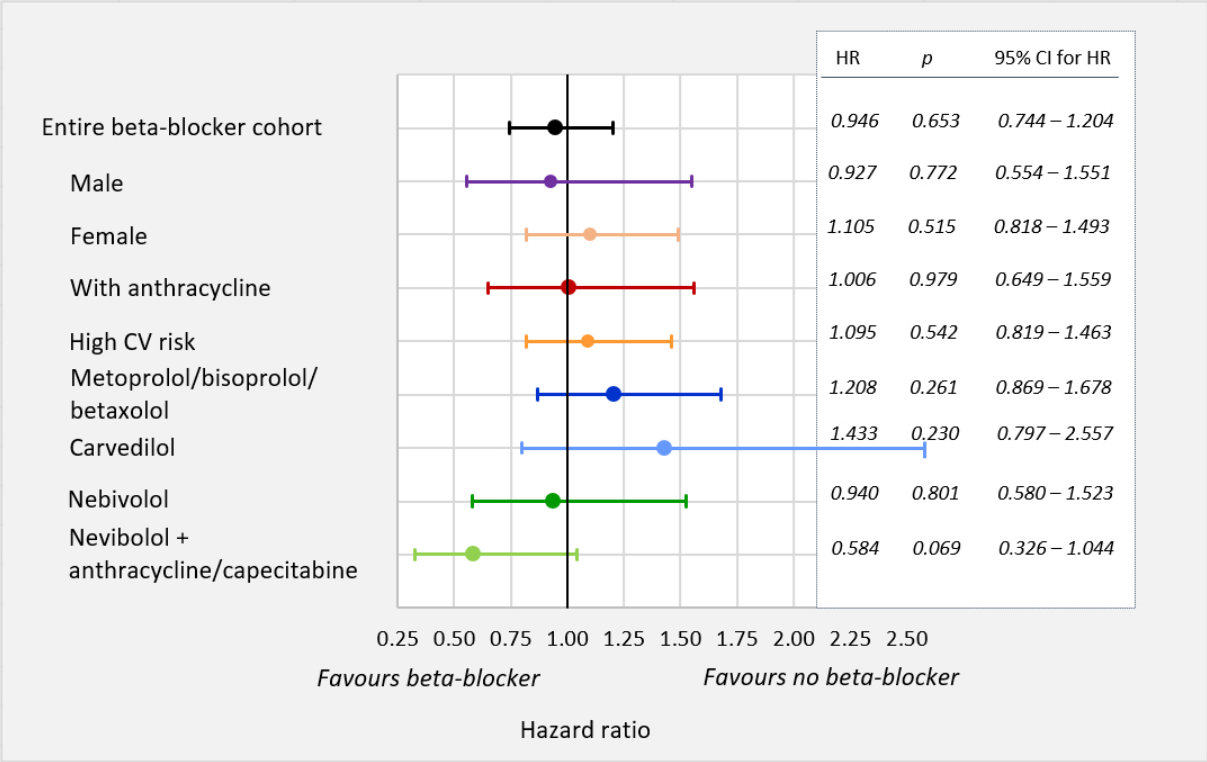

Figure 7. Relationship of beta-blocker therapies and the risk of cancer therapy-related heart failure.
HR: hazard ratio, CI: confidence interval, CV: cardiovascular

Table 13. Descriptive statistics of the matched beta-blocker cohorts.

	N of patients		total duration of F-U[1] (patient-year)		mean F-U (years)		*N* of HF[2] events		HF incidence rate (per 100 patient-years)	
	treated	untreated	treated	untreated	treated	untreated	treated	untreated	treated	untreated
entire cohort	1514	1514	5520.46	5498.85	3.65	3.63	129	136	2.34	2.47
male	288	288	1041.79	1034.32	3.62	3.59	28	30	2.69	2.90
female	1114	1114	4076.08	4099.89	3.66	3.68	89	81	2.18	1.98
anthracycline	728	728	2707.94	2719.95	3.72	3.73	40	40	1.48	1.47
high CV[3] risk	618	954	2209.83	3411.45	3.58	3.58	78	110	3.53	3.22
metoprolol/bisoprolol /betaxolol	878	878	3211.36	3233.20	3.66	3.68	78	65	2.43	2.01
carvedilol	257	257	924.51	933.61	3.59	3.63	27	19	2.92	2.03
nebivolol	415	415	1505.52	1508.83	3.63	3.64	32	34	2.13	2.25
nebivolol+anthracycline /capecitabine	241	446	884.22	1618.99	3.67	3.63	15	47	1.70	2.90

4.3.4. Trimetazidine

By propensity score matching with a ratio of 228:421, a significant standardized mean difference was not present between the cohorts, while for those trimetazidine was administered to, no significant association with incident heart failure was observed (HR: 0.907, 95% CI for HR: 0.556-1.480, p=0.696).

5. DISCUSSION

5.1. Heart Failure Risk Estimation during Anthracycline Therapy

Our study is the first multivariable analysis that defines the effect of common comorbid conditions, medication, cancer stage and chemotherapy cumulative doses together comprehensively with regard to the likelihood of heart failure in a large anthracycline-treated population. The analysed, nation-wide, real-world database represents the current therapeutical practise, therefore, the derived score model is suitable to assess the long-term heart failure risk of a patient. We analysed the heart failure risk factors separately for doxorubicin- and epirubicin-treated patients.

[1] follow-up
[2] heart failure
[3] cardiovascular

The overall cumulative incidence of heart failure was 6.9% in the epirubicin cohort during 3-10 years of follow-up and 6.2% during 3-9 years of follow-up in the doxorubicin cohort. These data are in good agreement with the previously published results [13,14].

Previous papers showed that patients over 65 years were at a greater risk of heart failure after anthracycline chemotherapy [5,6,15-17]. Our data indicate that age affects heart failure incidence even for patients over 40 years (over 50 in doxorubicin cohort), and the risk of heart failure increases rapidly with age. The higher age was confirmed as the most important contributing factor in heart failure risk elevation (see Figure 8).

As it was expected [42], we found higher heart failure risk with advanced cancer stage (see Figure 2.). When analysing the contribution of covariates to the elevation of heart failure risk, advanced cancer exhibited notable importance (Figure 8.).

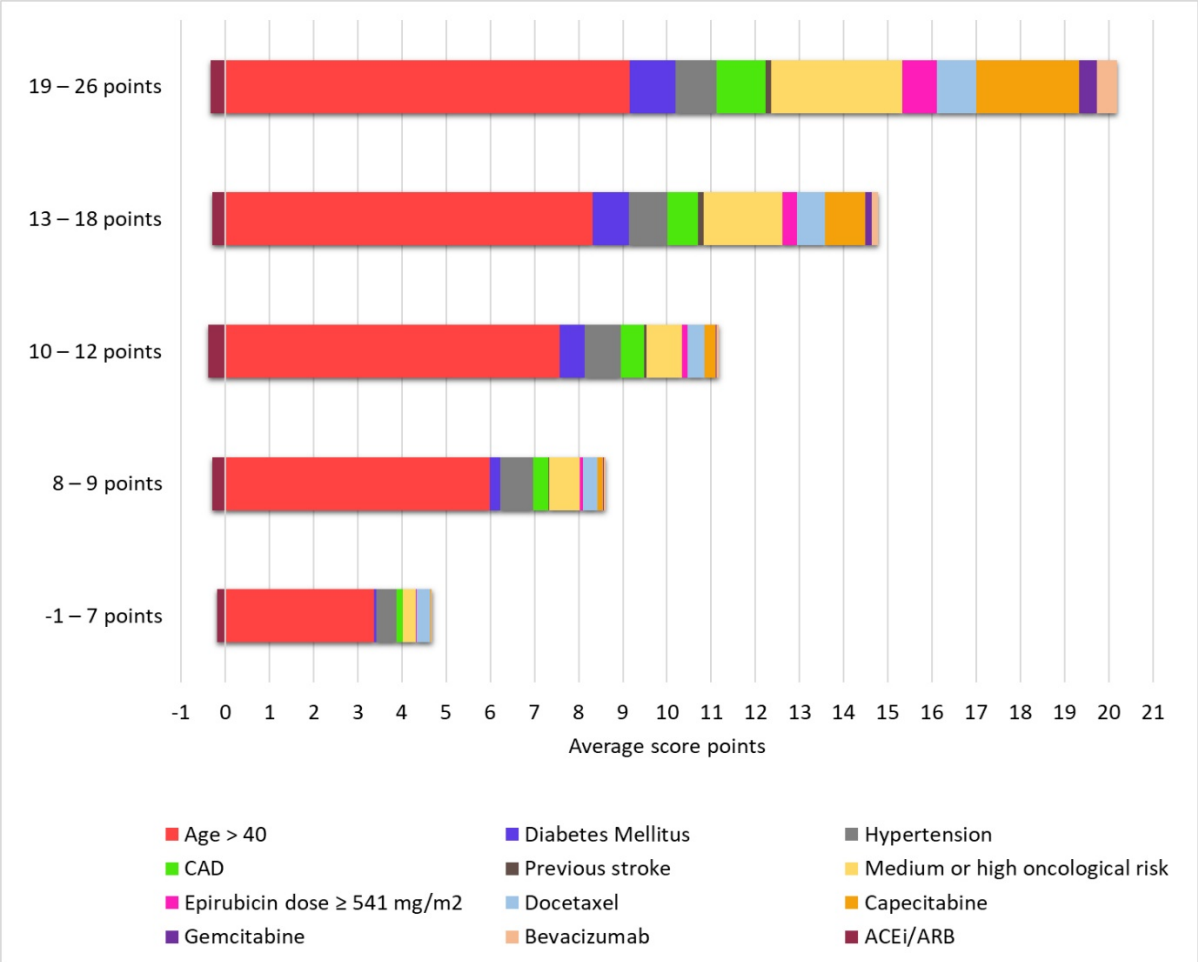

Figure 8: Contribution of the independent predictors to the average heart failure score points per risk categories.

Since cumulative doses of chemotherapeutic agents were incorporated, the dose-dependency in terms of heart failure has become assessable. The cumulative dose threshold for epirubicin was 709 mg/m^2 and for doxorubicin 400 mg/m^2, at higher doses, a significant increase in heart failure incidence was observed (see Figure 2 and Figure 4).

In terms of taxanes, the potential effect on left ventricular systolic function deterioration is known, especially after administration of anthracyclines [5,43,44]. Our results from epirubicin cohort supported the relevance of these previous findings for docetaxel, but not for paclitaxel. Moreover, a cumulative dose-dependent effect of docetaxel for initiating heart failure was observed (higher risk at doses >510 mg/m^2). In our analysis, no other chemotherapeutic drugs exhibited a cumulative dose-dependent effect on heart failure.

Fluoropyrimidine analogues (capecitabine, gemcitabine, 5-fluorouracil) are well known for their adverse cardiac effects, but these are mainly caused by coronary vasospasm or thrombosis [45-47]. Concerning 5-fluorouracil, some case reports revealed direct myocardial damage [46], the clinical impact of this effect remained unclear. Although case reports concerning capecitabine-related cardiomyopathy have also been published [48], its incidence has not yet been clarified. Our results from epirubicin and doxorubicin study suggest that capecitabine is associated with a notably higher heart failure risk, nevertheless, an elevation in risk was also found for 5-fluorouracil in our doxorubicin study but not in epirubicin study. The risk associated with gemcitabine was not assessable in doxorubicin cohort due to low representation, however, an elevated risk was found in epirubicin study. Besides the higher age and advanced cancer stage, the presence of capecitabine was the most important contributing factor to the higher heart failure risk, as presented in Figure 8.

Trastuzumab, the well-known ErbB2 receptor antagonist antibody, exhibits a well-understood cardiotoxic effect. In adjuvant clinical trials involving patients without a cardiovascular history, it was associated with a symptomatic heart failure rate of 2-5% [5,49,50]. However, thanks to the obligatory echocardiographic monitoring prescribed during this therapy and the dominantly rapidly reversible characteristic of trastuzumab-related systolic dysfunction, the long-term heart failure risk was only slightly elevated following this medication [51]. Accordingly, this drug was not associated with an elevated heart failure risk in our long-term analysis based on data from hospitalizations and autopsies. Contrarily, for bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, administered for metastatic cancer, an elevated heart failure risk was observed in both cohorts. A common side effect of this drug is hypertension. Its influence on heart failure has yet to be thoroughly explored, but it may be partly mediated by its hypertensive effect [5,52].

As a protective agent, the ability of dexrazoxane to reduce heart failure risk was not confirmed in our research. Nevertheless, despite our screening process to filter out patients with previous heart failure from the analysis, selection bias cannot be excluded from such a retrospective analysis. Therefore, these data should be interpreted with care.

As expected, diabetes mellitus, hypertension and coronary artery disease were also proven heart failure risk factors. Moreover, a previous stroke was also found to be an independent heart failure predictor.

Since a protective effect had been supposed, modifications to heart failure risk associated with ACEi/ARB treatment were assessed. Compared to a propensity score-matched reference group, a reduction in the risk of heart failure of borderline significance was observed in the epirubicin study for regular, previously initiated and ongoing ACEi/ARB therapy.

Similarly to the previously published data [6,18], radiotherapy treatment did not cause an elevated heart failure risk. Presumably, modern radiation therapies, which are carried out in respect of heart protection, do not have an impact on heart failure development.

The suggested risk-score-point model (Figure 2) can differentiate heart failure risk between 2 and 30% (Figure 3). Using our score (≥9), an elevated long-term heart failure risk can be identified with good sensitivity (0.79) and acceptable specificity (0.65). A tailored assessment of heart failure risk can help clinicians determine the appropriate treatment. For high-risk patients, preventive strategies such as initiation of ACEi/ARB, beta-blockers, statins, aldosterone antagonists or dexrazoxane may be considered [34,35,53,54]. Moreover, by this score, echocardiography follow-up intensity can also be optimized during and after anthracycline therapy to ensure the cardiomyopathy is diagnosed at an initial stage. Early recognition is crucial in this disease, because combined heart failure therapy initiated at the early stage of anthracycline-related dilated cardiomyopathy can, at least partially, reverse the deterioration of left ventricular function [13].

5.2.Prevention of Anthracycline-Related Heart Failure

Since no convincing data was recorded on the clinical benefit of the wide-spread use of preventive CV medication against cancer therapy-related heart failure [39], we performed a propensity score matching-based analysis to shed light on this important topic. Our study confirmed that concomitant ACEi/ARB and statin medications were associated with a significantly lower risk of incident heart failure in the unselected breast or colorectal cancer patients treated with any chemo- or biological therapy. Considering the increasing risk of cancer

therapy-related cardiomyopathy with higher CV risk [6] [55], subgroup analysis was performed by CV risk.

Previous RCT confirmed the preventive ACEi medication administered to patients exhibiting early troponin positivity due to high-dose chemotherapy as having a beneficial effect against chemotherapy-induced cardiomyopathy [35]. Nevertheless, whether lower-risk cancer patients benefit from preventive CV therapy in relation to heart failure remained controversial.

Regarding the hazard ratios, our results showed consistent preventive effect for ACEi/ARB therapy across the prespecified subgroups (Figure 6). The patients treated without anthracyclines or characterized as having high CV risk (DM, previous myocardial infarction, myocardial revascularization, stroke, peripheral artery disease) benefitted unambiguously from this medication. No interaction was observed between the preventive effects of ACEi/ARB therapy and the presence of anthracyclines in the chemotherapy However, at the patients without characteristics of high CV risk, ACEi/ARB therapy did not induce a significant risk reduction in our study. The potential explanation for the preventive effect of ACEi/ARB medication observed in patients of probably normal left ventricular ejection fraction might be a result of elevated intracardiac tissue ACE activity induced by chemotherapy [36].

In accordance with the assumptions based on small previous studies [33,34], our results confirmed the statin therapy as unequivocally associated with lower heart failure risk (Figure 5). The subgroup treated with anthracycline, platinum or capecitabine mostly benefitted from statins showing a risk reduction of statistical significance. Reactive oxygen species-mediated oxidative processes play important roles in the anthracycline-induced cardiomyopathy, presumably, their antioxidative properties make statins able to prevent left ventricular function deterioration. The preventive effect against heart failure was homogeneous irrespective of the baseline CV risk. More intense statin therapy (simvastatin ≥40mg, atorvastatin ≥30mg, rosuvastatin ≥15mg) showed association with a greater reduction in heart failure risk than less-intense therapies.

In terms of the preventive ability of beta-blockers against the cancer therapy-related deterioration of left ventricular ejection fraction, controversial data were published [25-28,30,31,37]. In a general aspect, our results did not support the preventive effect of beta-blockers against incident heart failure in this population (Figure 7). Cardioprotection was neither confirmed at high CV risk subgroup nor anthracycline-treated subgroup. Nevertheless, lower risk of heart failure was identified of borderline significance for nebivolol administered to patients treated with anthracycline or capecitabine (Figure 9). Neither other selective beta-blockers nor carvedilol exhibited any results suggesting a preventive ability. This potential

beneficial effect of nebivolol may be a consequence of its nitric oxide-restoring property. In an experimental model, nebivolol exerted a prominent protective effect against anthracycline-induced cardiotoxicity [56].

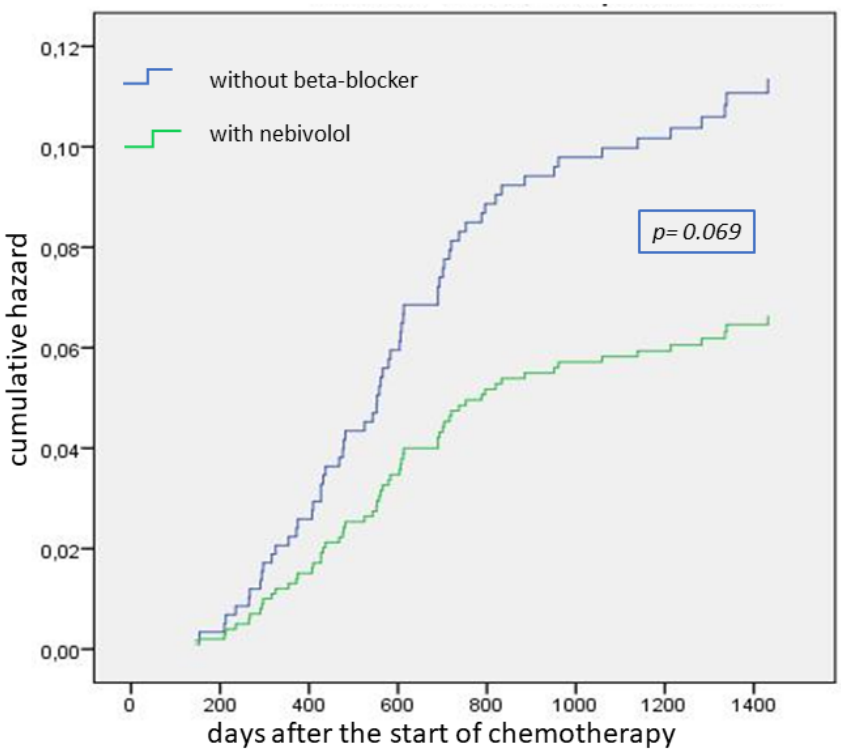

Figure 9. Cumulative hazard of the heart failure event at patients treated with nebivolol compared to those untreated with any beta-blocker in the anthracycline/capecitabine cohort.

6. CONCLUSIONS

(i) By multivariable regression analysis on a merged, nation-wide, breast cancer, real-world dataset, the threshold cumulative dose inducing heart failure was 709 mg/m^2 for epirubicin and 400 mg/m^2 for doxorubicin.

(ii) The prominent contributing factor in elevated heart failure incidence at anthracycline-treated patients was the higher age, even over 50 years.

(iii) Advanced cancer stage with distant metastases exhibited high importance in provoking heart failure.

(iv) Among the additional anticancer therapies, the capecitabine was the most important contributing factor to the higher heart failure risk.

(v) Bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody was confirmed associated with a notably elevated heart failure risk.

(vi) In addition to anthracycline therapy, docetaxel exhibited a cumulative dose-dependent effect to induce heart failure.

(vii) Diabetes mellitus, hypertension, coronary artery disease (especially with previous myocardial infarction or revascularization) and previous stroke were confirmed as factors associated with higher heart failure risk.

(viii) The constructed risk-prediction score was able to classify heart failure risk over a wide range (2-30%) and to identify elevated heart failure risk (score points≥ 9) with good sensitivity (0.79) and acceptable specificity (0.65).

(ix) According to the results of our propensity score matching-based analysis performed on the merged real-world dataset of the Hungarian breast or colorectal cancer patients, the concomitant ACEi/ARB medication induced a preventive effect against the development of cancer therapy-related heart failure, which was more pronounced in case of elevated baseline cardiovascular risk.

(x) The statin medication exhibited a beneficial effect irrespective of baseline cardiovascular risk, showing increasing benefit with higher statin doses.

(xi) The subgroup treated with anthracycline, platinum or capecitabine mostly benefitted from statins.

(xii) Nebivolol was confirmed the only beta-blocker showing association (borderline significance) with lower heart failure risk, detected exclusively in anthracycline- or capecitabine-treated patients.

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