STATISTICAL ANALYSIS PLAN for PRADA II

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ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
CMR	Cardiovascular Magnetic Resonance
DMC	Data Monitoring Committee
EC	Epirubicin, Cyclophosphamide
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ES	Enrolled Set
FAS	Full Analysis Set
GLS	Global Longitudinal Strain
hs-TnI	High sensitivity-assay Troponin I
hs-TnT	High sensitivity-assay Troponin T
LoD	Limits of Detection
LVEF	Left Ventricular Ejection Fraction
LVS	Left Ventricular Systolic
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-terminal proB-type Natriuretic Peptide
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SD	Standard Deviation
SOC	System Organ Class
URL	Upper Reference Limit

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1 Introduction

1.1 Background and rationale

Recent advances in the treatment algorithms of early breast cancer have markedly improved overall survival. However, anthracycline- and trastuzumab-associated cardiotoxicity may still lead to dose-reduction or halt in potentially life-saving adjuvant cancer therapy. Neurohormonal blockade initiated early may prevent or attenuate the cardiotoxicity-induced myocardial injury and subsequent reduction in cardiac function, but prior studies have been inconclusive. The angiotensin receptor-neprilysin inhibitor sacubitril-valsartan (LCZ696) has been shown to be superior to traditional treatment in heart failure with reduced ejection fraction, but its cardioprotective effects in the cardio-oncology setting remains to be established. Accordingly, in the PRADA II trial we aim to assess whether sacubitril-valsartan, as compared to placebo, given concomitantly with treatment regimens for early breast cancer that include anthracyclines, with or without trastuzumab, may prevent or attenuate the development of cardiac dysfunction and injury during a period of 18 months.

1.2 Trial Objectives

1.2.1 Primary Objective

The primary objective of PRADA II is to assess whether the administration of sacubitril-valsartan in patients with early breast cancer scheduled for anthracycline-containing anti-cancer therapy can prevent or is associated with attenuation of the reduction in left ventricular systolic function measured by cardiovascular magnetic resonance (CMR).

1.2.2 Secondary Objectives

The secondary objectives of this study are to assess whether the administration of sacubitril-valsartan is associated with

- reduced incidence of a significant reduction in left ventricular systolic function
- reduced early, acute, and late chronic cardiotoxic injury measured by cardiac biomarkers
- reduced incidence of cardiotoxicity

1.2.3 Safety Objectives

The safety of sacubitril-valsartan will be assessed.

Secondary and exploratory objectives that will not be covered in the primary publication are defined in the study protocol.

2 Trial Methods

2.1 Trial Design

The PRADA II study is designed as a prospective, multicenter, randomized, placebo-controlled, double-blind, parallel-group study.

2.2 Randomization

Eligible patients are allocated in a 1:1 ratio between sacubitril-valsartan and placebo treatment, using a computer randomization procedure stratified by study site (Akershus University Hospital, St. Olavs Hospital, Stavanger University Hospital, and University Hospital of North Norway) and scheduled treatment with trastuzumab. The randomization is blocked within each stratum and will be performed electronically through the eCRF (Viedoc).

Details of block size and allocation sequence generation is provided in a separate document unavailable to those who enroll patients or assign treatment.

The randomization process is described in full within the clinical trial protocol. Details of the randomization including the final random allocation list are held securely and unavailable to unauthorized trial personnel.

2.3 Sample size

Based on the results from PRADA (Gulati et al., 2016), we assume a decline in LVEF of 3.4% in the placebo group and 0.7% in the sacubitril-valsartan group, and a common standard deviation (SD) of 4.7%.

In the original sample size calculation, PRADA II was overpowered for the primary outcome (>99% power). The study was powered (83%) to detect a treatment difference in the subgroup of patients with troponin I > sex adjusted 99 percentile value, which was estimated to consist of 35% of the total number of patients. The original sample size target was 300 patients.

In September 2020, the Steering Committee decided to reduce the sample size target to 214 patients due to slow recruitment, in particular during the Covid pandemic. The power in the subgroup was reduced from 83% to 68%; however, the power for the primary outcome was still approximately 99% and remained at 80% even for an estimated larger SD of 7.0%.

In June 2024, the financial sponsor of the trial (KLINBEFORSK) informed the Steering Committee that funding of the study would be halted by the end of 2024, and accordingly, the Steering Committee decided to stop the inclusion of patients after total number of 138 patients had been included in the full analysis set population (see Section 3.3). Still, the power for the primary outcome is approximately 92%. The power for the subgroup is now 50%.

2.4 Statistical Framework

2.4.1 Hypothesis Test

This trial is designed to establish the superiority of sacubitril-valsartan compared to placebo treatment regarding change in left ventricular ejection fraction (LVEF), as determined by CMR, from randomization to end of blinded therapy (18 months).

- The primary null hypothesis is that the mean change in LVEF from randomization to 18 months is equal in the sacubitril-valsartan and placebo treatment groups
- The primary alternative hypothesis is that the mean change in LVEF from randomization to 18 months is not equal in the sacubitril-valsartan and placebo treatment groups

There is only one identified primary analysis in this trial. All other efficacy analyses will be regarded as supportive or exploratory.

2.4.2 Decision Rule

This trial is designed to address a single primary outcome. Superiority of sacubitril-valsartan is claimed if the primary null hypothesis is rejected on the significance level (alpha) of 0.05 (two-sided), and that the estimated reduction in LVEF from randomization to 18 months is less in the sacubitril-valsartan group than in the placebo group.

2.5 Statistical Interim Analyses and Stopping Guidance

The Data Monitoring Committee (DMC) will recommend stopping the trial if there is a safety concern during the conduct of the trial. There is a separate DMC Charter detailing the procedures for the safety meetings in the DMC.

There will be no interim analyses (of efficacy) in this trial.

2.6 Timing of Final Analysis

The main analysis is planned when all patients have concluded 18 months (max 19 months) of treatment, all data for all visits have been entered, verified, and validated and the primary database has been locked.

2.7 Timing of Outcome Assessments

Visit Label	Target Day	Key Measurements
Screening	Before initiation of chemotherapy	
Visit 1 (Baseline/Randomization)	Day 0	CMR Echo Biomarkers
EC1	Day 0 -24	
EC2	Every 3rd week +/- 3 days	
EC3		
EC4		
Visit 2	Minimum 5 days, maximum 3 weeks after last EC administration	CMR Echo Biomarkers
Visit 3 (End of study)	18 months (maximum 19 months) after EC1	CMR Echo Biomarkers

3 Statistical Principles

3.1 Confidence Intervals and p-values

All calculated p-values will be two-sided and compared to a 5% significance level. If a p-value is less than 0.05, the corresponding treatment group difference will be denoted as statistically significant. All efficacy estimates will be presented with two-sided 95% confidence intervals. As there is only one primary null hypothesis to be tested in this trial, there will be no adjustments for multiplicity.

3.2 Adherence and Protocol Deviations

3.2.1 Adherence to Allocated Treatment

Compliance with use of the IMP will primarily be assessed by return of all IMP packages given to the patients. In cases where return of IMP was not consistently performed or recorded, compliance will be calculated by using notes from the study personnel or the medication diary patients were supposed to keep. The minimum compliance definition will be set to 70%.

3.2.2 Protocol Deviations

The following are pre-defined major protocol deviations regarded to affect the efficacy of the intervention:

- Entering the trial when the eligibility criteria should have prevented trial entry
- Not receiving anthracyclines
- Pregnancy
- Less than 70% compliance

Protocol deviations are classified prior to unblinding of treatment. The number (and percentage) of patients with major protocol deviations will be summarized by treatment group with details of type of deviation provided. The patients that are included in the modified ITT analysis data set (FAS, see section 3.3) will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

3.3 Analysis Populations

The Enrolled set (ES) will include all patients who have provided informed consent and have been included into the study data base.

The Full Analysis Set (FAS) will be defined as all patients randomly assigned to a treatment group having received at least one study treatment administration and one dose of anthracyclines after randomization and having completed at least baseline CMR measurement.

The Safety Analysis Set (SAS) will include all patients having received at least one study treatment administration after randomization.

The Per Protocol Analysis Set (PPS) will include all randomised patients meeting the study eligibility criteria and with no major protocol deviations affecting the treatment efficacy.

4 Trial Population

4.1 Screening Data, Eligibility and Recruitment

The total number of screened patients and reasons for not entering the trial will be summarized and tabulated.

A CONSORT flow diagram will be used to summarize the number of patients who were:

- assessed for eligibility at screening
- eligible at screening
- ineligible at screening*
- eligible and randomised
- eligible but not randomised*
- received the randomised allocation
- did not receive the randomised allocation*
- lost to follow-up*
- discontinued the intervention*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*reasons will be provided.

4.2 Withdrawal/Follow-up

The status of randomised patients at trial end will be tabulated by treatment group according to

- completed intervention
- completed the CMR measurements at Visit 1, Visit 2, and Visit 3
- withdrew consent

4.3 Baseline Patient Characteristics

The patient demographics and baseline characteristics to be summarized include age in years, sex (categorical), weight, height, BMI, smoking status (categorical), diabetes, (categorical), systolic blood pressure, heart rate, diastolic blood pressure, anti-hypertensive treatment (categorical), lipid-lowering treatment (categorical), serum creatinine, eGFR, anthracycline (dose), taxanes (categorical), trastuzumab (categorical), and radiation (categorical), left-sided radiation (categorical), tumor characteristics (categorical) .

Patient demographics and baseline characteristics will be summarized by randomised treatment arm and overall using descriptive statistics (N, mean or median, standard deviation or interquartile range) for continuous variables, and number and percentages of patients for categorical variables. There will be no statistical analysis of treatment difference. Any clinical important imbalance between the treatment groups will be noted.

5 Analysis

5.1 Outcome Definitions

5.1.1 General Definitions and Derived Variables

5.1.1.1 Body Mass Index

Body Mass Index (BMI) = Body weight in kilograms divided by the square of the height in meters.

5.1.1.2 Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF) = The end-diastolic volume (EDV) minus the end-systolic volume (ESV) divided by the EDV.

5.1.2 Primary Outcome Definition

The primary outcome is change in left ventricular ejection fraction (LVEF), as measured by cardiovascular magnetic resonance (CMR), and it is defined as the LVEF value at 18 months after initiation of anthracycline treatment (Visit 3/end of study) minus the LVEF value at baseline/randomization (Visit 1). The primary outcome is continuous.

5.1.3 Secondary Outcomes Definitions

5.1.3.1 Change in LVEF from baseline to end of EC treatment

The change in LVEF from baseline to end of EC treatment is defined as the LVEF value at the second visit minus the LVEF value at baseline, both measured by CMR. This is regarded as a continuous outcome.

5.1.3.2 Incidence of clinically significant reduction in LVS function

(LVEF measurements are by CMR and GLS measurements are by echocardiography.)

Incidence of clinically significant reduction in left ventricular systolic function is defined as

- an absolute reduction in LVEF (from baseline) of ≥ 5% points at either end of EC treatment (Visit 2) and/or at 18 months (Visit 3)

or

- an relative reduction in GLS (from baseline) of > 15% at either end of EC treatment (Visit 2) and/or at 18 months (Visit 3)

This is regarded as a dichotomous outcome.

5.1.3.3 Change in hs-TnI from baseline to 18 months/end of EC treatment

The change in high sensitivity assay troponin I from baseline to 18 months is defined as the hs-TnI value at the 18 months visit minus the hs-TnI value at baseline. The change in high sensitivity assay troponin I from baseline to end of EC treatment is defined as the hs-TnI value at the second visit minus the hs-TnI value at baseline. Both outcomes are regarded as continuous.

5.1.3.4 Change in hs-TnT from baseline to 18 months/end of EC treatment

The change in high sensitivity assay troponin T from baseline to 18 months is defined as the hs-TnT value at the 18 months visit minus the hs-TnT value at baseline. The change in high sensitivity assay troponin T from baseline to end of EC treatment is defined as the hs-TnT value at the second visit minus the hs-TnT value at baseline. Both outcomes are regarded as continuous.

5.1.3.5 Change in NT-proBNP from baseline to 18 months/end of EC treatment

The change in N-terminal proB-type natriuretic peptide from baseline to 18 months is defined as the NT-proBNP value at the 18 months visit minus the NT-proBNP value at baseline. The change in N-terminal proB-type natriuretic peptide from baseline to the end of EC treatment is defined as the NT-proBNP value at the second visit minus the NT-proBNP value at baseline. Both outcomes are regarded as continuous.

5.1.3.6 Change in GLS from baseline to 18 months/end of EC treatment

The change in global longitudinal strain from baseline to 18 months is defined as the GLS value at the 18 months visit minus the GLS value at baseline, both measured by echocardiography. The relative change in percent is defined as the as the absolute change in GLS from baseline to 18 months divided by the baseline GLS value. The change in global longitudinal strain from baseline to the end of EC treatment is defined as the GLS value at the second visit minus the GLS value at baseline, both measured by echocardiography. The relative change in percent is defined as the as the absolute change in GLS from baseline to the second visit divided by the baseline GLS value. Both outcomes are regarded as continuous.

5.1.3.7 Incidence of moderate or severe cardiotoxicity at 18 months

(LVEF measurements are by CMR and GLS measurements are by echocardiography.)

Incidence of moderate or severe cardiotoxicity at 18 months is defined as

- [Severe] LVEF < 40% at either end of EC treatment (Visit 2) or at 18 months

or

- [Moderate] LVEF between 40% and 49% and an absolute reduction in LVEF (from baseline) of ≥ 10% points at either end of EC treatment (Visit 2) or at 18 months

or

- [Moderate] LVEF between 40% and 49% and an absolute reduction in LVEF (from baseline) of < 10% points and an absolute reduction in GLS (from baseline) of ≥ 15 % points at either end of EC treatment (Visit 2) or at 18 months

or

- [Moderate] LVEF between 40% and 49% and an absolute reduction in LVEF (from baseline) of < 10% points and a new rise in cardiac biomarkers above the sex-specific 99 percentile upper reference limit (URL) at either end of EC treatment (Visit 2) or at 18 months. For cardiac troponin T_{Roche}, the sex-specific 99 percentile is 9 ng/L, for cardiac troponin I_{Abbott}, the sex-specific 99 percentile is 15.6 ng/L. For NT-proBNP, the 2022 ESC cardio-oncology guidelines suggest >= 125 ng/L as a cutoff.

This is regarded as a dichotomous outcome.

5.1.3.8 Incidence of mild cardiotoxicity at 18 months

(LVEF measurements are by CMR and GLS measurements are by echocardiography.)

Incidence of mild cardiotoxicity at 18 months is defined as

- LVEF ≥ 50% and an absolute reduction in GLS (from baseline) of ≥ 15 % points at either end of EC treatment (Visit 2) or at 18 months

or

- LVEF ≥ 50% and a new rise in cardiac biomarkers above the sex-specific 99 percentile upper reference limit (URL) at either end of EC treatment (Visit 2) or at 18 months. For cardiac troponin T_{Roche}, the sex-specific 99 percentile is 9 ng/L, for cardiac troponin I_{Abbott}, the sex-specific 99 percentile is 15.6 ng/L. For NT-proBNP, the 2022 ESC cardio-oncology guidelines suggest >=125 ng/L as a cutoff.

This is regarded as a dichotomous outcome.

5.1.4 Overview of Outcomes

Level	Outcome	Timeframe	Type
Primary	Change in LVEF	Baseline to 18 months	Continuous
Secondary	Change in LVEF	Baseline to end of EC treatment	Continuous
	Incidence of clinically significant reduction in LVS function	Baseline to 18 months	Dichotomous
	Change in hs-TnI	Baseline to 18 months	Continuous
	Change in hs-TnI	Baseline to end of EC treatment	Continuous
	Change in hs-TnT	Baseline to 18 months	Continuous
	Change in hs-TnT	Baseline to end of EC treatment	Continuous
	Change in NT-proBNP	Baseline to 18 months	Continuous
	Change in NT-proBNP	Baseline to end of EC treatment	Continuous
	Change in GLS	Baseline to 18 months	Continuous
	Change in GLS	Baseline to end of EC treatment	Continuous
	Incidence of moderate or severe cardiotoxicity	Baseline to 18 months	Dichotomous
	Incidence of mild cardiotoxicity	Baseline to 18 months	Dichotomous

5.2 Analysis Methods

5.2.1 Primary Outcome

Primary analysis

The primary analysis of the primary outcome will be performed on the full analysis set (FAS).

The primary outcome variable, LVEF (CMR), is measured at three time points: Visit 1/baseline, Visit 2 (after between 5 days and 3 weeks after last EC administration), and at Visit 3 (End of study, 18-19

months after initiation of EC). The primary outcome, change in LVEF (CMR) from baseline to 18 months), will be analyzed with a linear mixed model. The model will be fit to data from all three time points, with fixed effects for treatment (sacubitril-valsartan vs placebo), time point, treatment x time point interaction, and the factors used to stratify the randomization (study site and scheduled treatment with trastuzumab). A random intercept at the patient level will be used.

Based on the fitted model, we will estimate and present the mean LVEF (95% CI) for each treatment group for each time point. We will also estimate and present the change from baseline to 18 months and the change from baseline to end of EC treatment (Visit 2) for each treatment group, with 95% CIs.

The primary effect estimate will be the model-estimated between-group difference in mean change from baseline to 18 months (sacubitril-valsartan vs placebo), which will be presented with a 95% CI and a P-value for the null hypothesis of a zero difference.

The observed values of LVEF will be presented with box plots stratified by treatment group and time point.

Assumption checks

The distribution of the primary outcome will be assessed with descriptive statistics and histograms. With a sample size of 138, the linear mixed model will be robust to quite large deviations from the normal distribution. Still, in the case that the distribution of the outcome is deemed to deviate too much from the normal distribution, a log transformation of the outcome will be done prior to fitting the linear mixed model. In that case, an analysis of the untransformed data will be performed as an additional sensitivity analysis.

After fitting the model (original scale or log transformed), plots of observed and model-fitted values (by treatment group and time point) will be compared to assess the fit of the model.

Missing data

The linear mixed model will handle missing data in one or two time points per patient under the assumption of missing at random. No patient in the FAS has missing data on all three time points, per the definition of FAS (see section 3.3).

Secondary/sensitivity analyses

The following sensitivity analyses will be performed for the primary outcome:

- Restricting the analysis to the per protocol set (PPS)
- Unadjusted analysis, i.e. without adjusting for study site and scheduled treatment with trastuzumab (factors used to stratify the randomization)
- Analysis on untransformed data (only if the primary analysis is done on log-transformed data)

Subgroup analyses

Subgroup analyses of the primary outcome will be performed on the subgroups of patients with

- HER-2 positive tumor receiving treatment with trastuzumab

- High- and very high-risk patients as defined by the Heart Failure Association-International Cardio Oncology (HFA-ICOS) score for anthracycline and trastuzumab (see Appendix 9.1)
- Baseline cardiac troponin T > 3 ng/L (LoD)
- Baseline cardiac troponin I > 1.6 ng/L (LoD)

The subgroup analyses will be done by fitting a new linear mixed model to data restricted by the subgroup. The results will be presented in a forest plot.

5.2.2 Continuous Secondary Outcomes

Primary analysis

All secondary continuous outcomes will be analyzed on the FAS.

All secondary continuous outcomes (see Table in Section 5.1.4) are measured at the same time points as the primary outcome and will be analyzed and presented in the same manner as the primary outcome, except that no hypothesis test for treatment effect will be performed.

Assumption checks

The same assumption checks as for the primary outcome will be performed for all secondary continuous outcomes.

Biomarkers with values below the detection limit

Any measurements of a biomarker below the detection limit (1.6 ng/L for hs-TnI, 3.0 ng/L for hs-TnT, and 5 ng/L for NT-proBNP) will be imputed by a uniformly distributed random value between 0 and the detection limit. The number (%) of patients with values below the detection limit will be reported for each biomarker and each time point in the statistical analysis report.

Missing data

The linear mixed model will handle missing data in one or two time points per patient under the assumption of missing at random. There is a possibility that patients may have missing values of echo measurements (GLS) or any of the biomarkers (hs-TnI, hs-TnT, NT-proBNP) for all three time points. In that case, the missing data will be handled by multiple imputation. The imputation model will be truncated regression with the following covariates: age, BMI, education, smoking status, diabetes, blood pressure, hypertension, and creatinine. LVEF will have a lower limit of 0 and an upper limit of 100. GLS will have a lower limit of 0 and an upper limit of 100. The biomarkers will have a lower limit of 0 with no upper limit. The number of imputations will be equal to the percentage of missing data (White et al., 2011), i.e. 10 imputations for 10% missing data. The assessment of missing data will be performed after biomarkers below the detection limit have been imputed.

5.2.3 Dichotomous Secondary Outcomes

Primary analysis

All secondary dichotomous outcomes will be analyzed on the FAS.

The dichotomous outcomes will be analyzed with logistic regression models, with treatment as the main independent variable and with adjustments for the factors used to stratify the randomization (study site and scheduled treatment with trastuzumab).

The effect estimate will be the difference between the predicted proportions (sacubitril-valsartan minus placebo) of the dichotomous outcomes, calculated from the fitted logistic regression model with the delta method (Norton, Miller, and Kleinman; 2013). The effect estimate will be presented as a percentage with a 95% CI.

In addition, we will present the number and percentage of the observed (unadjusted) outcomes, as well as the model-predicted percentages, for each treatment group. The number and percentage of patients that have an incidence at Visit 2 (end of EC treatment) and Visit 3 will also be presented separately, for each treatment group. Note that the outcome to be compared between the two treatment groups (for all the dichotomous outcomes) equals satisfying the criteria for an incidence at either Visit 2 or Visit 3, and that no comparison is done at each time point separately.

Assumption checks
A Hosmer-Lemeshow (HL) goodness-of-fit test will be performed to assess whether the logistic regression model shows signs of poor fit. If $P < 0.10$ for the HL test, further scrutiny will be performed on the model by reducing the number of covariates by removing the factors used to stratify the randomization and refitting the model and recalculating the HL test. The results for all models and HL tests will be reported in the statistical analysis report.

Sensitivity analysis
As a sensitivity analysis, an unadjusted difference between probabilities will be estimated by the Newcombe hybrid score confidence interval (Chapter 4 of Fagerland et al., 2017).

Missing data
All dichotomous outcomes are based on values at time points and changes between time points in one or more continuous outcomes. Missing values at either time points or changes between time points will be imputed by model-predicted values and changes from the linear mixed models in sections 5.2.1 and 5.2.2.

6 Safety Analyses/Adverse Events

Safety and adverse events have been thoroughly monitored throughout the trial by an independent data monitoring committee (DMC), who included two clinical experts and a statistician. There have been no specific comments or concerns from the DMC for the safety of the patients during the trial.

For the main publication of PRADA II, only serious adverse events will be reported. The number (%) of patients with serious adverse events and the total number of serious adverse events will be tabulated by treatment group and by intensity level (mild, moderate, and severe).

7 Statistical Software

All statistical analyses will be done in Stata/SE 17.0 or newer version (StataCorp LLC, Station, TX, USA).

8 References

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9 Appendix

9.1 Calculation of the HFA-ICOS risk score

HER-2 negative			
Risk factors (Parameters as given in VieDoc)	**Score**	**Points**	**PRADA II population**
Heart failure or cardiomyopathy (VieDoc: Heart Disease --> yes History of heart failure)	Very high	5	NA (all 0 points)
Severe valvular heart disease (VieDoc: Exclusion criteria)	High	5	NA (all 0 points)
Myocardial infarction or previous coronary revascularization (PCI or CABG) (VieDoc: Heart Disease --> yes Myocardial infarction, other)	High	5	
Stable angina (VieDoc: Heart Disease --> yes Myocardial infarction, other)	High	5	
Baseline LVEF < 50 %	High	5	NA (all 0 points)
Borderline LVEF 50-54% (VieDoc: Echo CMR EF)	Medium[2]	2	
Elevated baseline troponin I or T • Batch analyses with value above: For cardiac troponin T_{Roche}, the sex-specific 99 percentile URL is 9 ng/L, for cardiac	Medium[1]	1	

troponin I_{Abbott}, the sex-specific 99 percentile URL is 15.6 ng/L.			
Elevated baseline BNP or NT-proBNP (Batch analyses with NT-proBNP value above xx)	Medium[1]	1	
Age	-	-	-
≥80	High	5	
65-79	Medium[2]	2	
<65	Low	0	
Hypertension (VieDoc: on hypertension medication or blood pressure systolic >140 mmHg or diastolic >90 mmHg)	Medium[1]	1	
Diabetes (VieDoc: on antidiabetic medication)	Medium[1]	1	
Chronic Kidney Disease	Medium[1]	1	NA (all 0 points)
Previous anthracycline exposure (VieDoc: previous chemotherapy → yes → specify)	High	5	
Prior radiotherapy to left chest or mediastinum (VieDoc: Previous radiation therapy to the chest → yes (because of cancer left side, lung cancer, lymphoma)	High	5	
Previous non-anthracycline-based chemotherapy (VieDoc: previous chemotherapy → yes → specify)	Medium[1]	1	
Current smoker or significant smoking history (VieDoc: Smoking → current or previously)	Medium[1]	1	
Obesity (BMI > 30)	Medium[1]	1	

HER-2 positive			
Risk factors (Parameters as given in VieDoc)	**Score**	**Points**	**PRADA II population**
Heart failure or cardiomyopathy (VieDoc: Heart Disease --> yes History of heart failure)	Very high	5	NA (all 0 points)
Myocardial infarction or previous coronary revascularization (PCI or CABG) (VieDoc: Heart Disease --> yes Myocardial infarction, other)	High	5	
Stable angina (VieDoc: Heart Disease --> yes Myocardial infarction, other)	High	5	
Severe valvular heart disease (VieDoc: Exclusion criteria)	High	5	NA (all 0 points)
Arrythmia (VieDoc: Heart Disease --> yes	Medium[2]	2	

other)			
Baseline LVEF < 50 %	High	5	NA (all 0 points)
Borderline LVEF 50-54% (VieDoc: Echo CMR EF)	Medium[2]	2	
Elevated baseline troponin • Batch analyses with value above: For cardiac troponin T_{Roche}, the sex-specific 99 percentile URL is 9 ng/L, for cardiac troponin I_{Abbott}, the sex-specific 99 percentile URL is 15.6 ng/L.	Medium[2]	2	
Elevated baseline BNP or NT-proBNP (Batch analyses with value above xx)	Medium[2]	2	
Age	-	-	-
≥80	High	5	
65-79	Medium[2]	2	
<65	Low	0	
Hypertension (VieDoc: on hypertension medication or blood pressure systolic >140 mmHg or diastolic >90 mmHg)	Medium[1]	1	
Diabetes (VieDoc: on antidiabetic medication)	Medium[1]	1	
Chronic Kidney Disease	Medium[1]	1	NA (all 0 points)
Current treatment with anthracycline before trastuzumab	Medium[1]	1	All patients
Previous trastuzumab cardiotoxicity (VieDoc: previous chemotherapy → yes → specify)	Very high	5	
Previous anthracycline exposure (VieDoc: previous chemotherapy → yes → specify)	Medium[2]	2	
Prior radiotherapy to left chest or mediastinum (VieDoc: Previous radiation therapy to the chest → yes (because of cancer left side, lung cancer, lymphoma)	Medium[2]	2	
Current smoker or significant smoking history (VieDoc: Smoking → current or previously)	Medium[1]	1	
Obesity (BMI > 30)	Medium[1]	1	

Explanation

Risk factors	Score	Calculated risk in points
no risk factor OR one medium[1] risk factor	Low risk	≤1

medium risk factors with a total of 2–4 points	Medium risk	2-5
medium risk factors with a total of ≥5 points OR any high-risk factor	High risk	≥5
any very high-risk factor	Very high risk	≥5