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CLINICAL TRIAL

Incidence of cardiotoxicity and validation of the Heart Failure Association-International Cardio-Oncology Society risk stratification tool in patients treated with trastuzumab for HER2-positive early breast cancer

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Abstract

Purpose Trastuzumab improves survival in patients with HER2+ early breast cancer. However, cardiotoxicity remains a concern, particularly in the curative setting, and there are limited data on its incidence outside of clinical trials. We retrospectively evaluated the cardiotoxicity rates [left ventricular ejection fraction (LVEF) decline, congestive heart failure (CHF), cardiac death or trastuzumab discontinuation] and assessed the performance of a proposed model to predict cardiotoxicity in routine clinical practice.

Methods Patients receiving curative trastuzumab between 2011 and 2018 were identified. Demographics, treatments, assessments and toxicities were recorded. Fisher's exact test, Chi-squared and logistic regression were used.

Results 931 patients were included in the analysis. Median age was 54 years (range 24–83) and Charlson comorbidity index 0 (0–6), with 195 patients (20.9%) aged 65 or older. 228 (24.5%) were smokers. Anthracyclines were given in 608 (65.3%). Median number of trastuzumab doses was 18 (1–18). The HFA-ICOS cardiovascular risk was low in 401 patients (43.1%), medium in 454 (48.8%), high in 70 (7.5%) and very high in 6 (0.6%). Overall, 155 (16.6%) patients experienced cardiotoxicity: LVEF decline ≥ 10% in 141 (15.1%), falling below 50% in 55 (5.9%), CHF NYHA class II in 42 (4.5%) and class III–IV in 5 (0.5%) and discontinuation due to cardiac reasons in 35 (3.8%). No deaths were observed. Cardiotoxicity rates increased with HFA-ICOS score (14.0% low, 16.7% medium, 30.3% high/very high; $p = 0.002$).

Conclusions Cardiotoxicity was relatively common (16.6%), but symptomatic heart failure on trastuzumab was rare in our cohort. The HFA-ICOS score identifies patients at high risk of cardiotoxicity.

Keywords Breast cancer · Trastuzumab · Cardiotoxicity · Early stage

Introduction

Trastuzumab is a monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2) and is the standard of care for the management of early-stage and advanced HER2-positive breast cancer [1]. However, treatment with HER2-directed agents is associated with a risk of cardiotoxicity. This most frequently involves an asymptomatic decrease in the left ventricular ejection fraction (LVEF) detected during surveillance before presentation with symptomatic heart failure. Less frequently, rapid development of congestive heart failure (CHF) despite surveillance may develop [2, 3]. Cardiotoxicity associated with anti-HER2 agents is usually reversible with cessation of trastuzumab treatment and cardiac medication, but this may compromise optimal breast cancer treatment [4]. Factors associated with a higher risk of cardiotoxicity in patients receiving trastuzumab include older age, previous or concurrent anthracycline use, pre-existing cardiac dysfunction, pre-existing significant cardiovascular (CV) disease, high body mass

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index (BMI), antihypertensive therapy and, in older patients, diabetes mellitus [5–11].

A metanalysis of adjuvant trials reported a risk of advanced heart failure [New York Heart Association (NYHA) class III-IV] of 0.4–2.5% in patients receiving trastuzumab [12]. Even when anthracyclines are not given, a trial investigating the use of trastuzumab along with taxane-based chemotherapy showed an incidence of cardiotoxicity of 3% although this was severe only in 0.5% of trial participants [13]. In contrast, previous real-world experiences have reported a rate of cardiovascular complications in 10–15% of patients receiving this agent in the curative setting [14].

Age is a predictor of impaired cardiac function with trastuzumab treatment. This is a concern due to the higher burden of comorbidities and increased risk of adverse outcomes in older individuals [15]. Nonetheless, trastuzumab improves survival and reduces risk of recurrence and is otherwise well tolerated in older patients. The rate of cardiac events in a systematic review of randomised studies including data on patients aged over 60 years was 5% [16]. However, the incidence is unclear outside of clinical trials, which tend to recruit patients who are younger, with normal baseline cardiac function and who have a lower burden of comorbidities including pre-existing CV disease.

Therefore, predicting the cardiotoxicity of anti-HER2 agents is of considerable importance. Cardiac risk scores have been developed based on prospective trial [12] and retrospective registry data [14]. However, independent validation is needed before they can be considered for general use. The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) together with the International Cardio-Oncology Society (ICOS) have recently developed a risk stratification tool (HFA-ICOS Risk Tool) to evaluate the likelihood of cardiotoxicity at baseline for patients receiving HER2-directed treatments (Table 1) [17]. In this study we investigated the rates of cardiotoxicity secondary to trastuzumab for early-stage HER2-positive breast cancer in a breast cancer service, comparing rates in older versus younger patients, and assessed the performance of HFA-ICOS cardiovascular risk prediction tool in this population.

Methods

This analysis is a retrospective study of patients who received trastuzumab for HER2-positive early breast cancer (EBC) between 01/01/2011 and 31/12/2018 at the Royal Marsden Hospital NHS Foundation Trust. Eligible patients had curable disease (TNM stages: T1-4, N0-3, M0) and received trastuzumab in the neoadjuvant or adjuvant setting. Patients who received part of the course of treatment elsewhere or those with advanced-stage breast cancer were not eligible for the analysis. This analysis was approved as a service evaluation (SE842) at the Royal Marsden NHS Foundation Trust.

Baseline data collection

Baseline patient characteristics at initiation of trastuzumab were collected and included: date of birth, age at diagnosis, date of last follow-up, date of death, weight, body mass index (BMI), comorbidities, smoking history, obesity, alcohol consumption, concurrent medications, Eastern Cooperative Oncology Group Performance Score (ECOG PS), menopausal status. Specifically, data on CV comorbidities and risk factors were collected and included: diabetes mellitus, hypertension, hypercholesterolemia, coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure and NYHA classification, rheumatic heart disease, arrhythmias, congenital heart disease, valvular heart disease, cardiomyopathy, aortic aneurysm, thromboembolic disease, pulmonary hypertension, pericardial disease and chronic kidney disease. A non-age adjusted Charlson Comorbidity Index (CCI) was calculated for each patient based on comorbidities at baseline. Specific data on medications relevant to cardiovascular risk were recorded and included: beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, mineralocorticoid receptor blockers, diuretics, digitalis, calcium channel blockers, antiplatelets, anticoagulants and statins. Blood tests results including haemoglobin, white blood count (WBC) and creatinine measurements and LVEF measured on multiple-gated acquisition (MUGA) scan or echocardiogram as per local practice were also recorded at baseline.

Baseline data were collected regarding the primary tumour including: date of diagnosis, histology, grade, ER status and Allred score, PR status and Allred score, HER2 testing method, best stage (i.e. the worst stage between clinical stage and pathological stage), laterality.

Radiotherapy and systemic therapy data were collected. These included use of chemotherapy, anthracyclines, taxanes, platinum compounds, pertuzumab, radiotherapy, endocrine agents, along with setting (adjuvant vs. neoadjuvant), cumulative dose of anthracyclines, number of chemotherapy cycles and number of doses of trastuzumab.

The baseline cardiovascular risk of these patients was classified as low/medium/high/very high based on the recommendations of the HFA-ICOS Risk Tool developed for HER2-targeted agents [17].

Follow-up and outcomes

Data on LVEF from MUGA scan or echocardiogram performed as per National Cancer Research Institute recommendations in the UK [18] until trastuzumab completion or discontinuation were recorded (i.e. baseline, 16 and

Table 1 Heart Failure Association-International Cardio-Oncology Society baseline cardiovascular risk stratification tool for anti-HER2 therapies

Domain class	Risk factor	Score
Previous cardiovascular disease	Heart failure or cardiomyopathy	VERY HIGH
	Myocardial infarction or CABG	HIGH
	Stable angina	HIGH
	Severe valvular heart disease	HIGH
	Baseline LVEF < 50%	HIGH
	Borderline LVEF 50–54%	MEDIUM (2 points)
	Arrhythmia[b]	MEDIUM (2 points)
Cardiac biomarkers (where available)	Elevated baseline troponin[c]	MEDIUM (2 points)
	Elevated baseline BNP or NT-proBNP[c]	MEDIUM (2 points)
Demographic and cardiovascular risk factors	Age ≥ 80 years	HIGH
	Age 65–79 years	MEDIUM (2 points)
	Hypertension[d]	MEDIUM (1 point)
	Diabetes mellitus[e]	MEDIUM (1 point)
	Chronic kidney disease[f]	MEDIUM (1 point)
Current cancer treatment regimen	Includes Anthracycline before HER2-targeted therapy[g]	MEDIUM (1 point)[g]
Previous cardiotoxic cancer treatment	Prior trastuzumab cardiotoxicity	VERY HIGH
	Prior (remote) anthracycline exposure[h]	MEDIUM (2 points)
	Prior radiotherapy to left chest or mediastinum	MEDIUM (2 points)
Lifestyle risk factors	Current smoker or significant smoking history	MEDIUM (1 point)
	Obesity (BMI > 30)	MEDIUM (1 point)

LOW RISK no risk factor OR one MEDIUM[1] risk factor, *MEDIUM RISK* MEDIUM risk factors with a total of 2–4 points, *HIGH RISK* MEDIUM risk factors with a total of ≥ 5 points OR any HIGH risk factor, *VERY HIGH RISK* any VERY HIGH risk factorCABG: coronary artery bypass graft, *BNP* brain natriuretic peptide, *NT-proBNP* N-terminal pro b-type natriuretic peptide, *BMI* body mass index

[a]Baseline cardiac biomarkers have been measured only in 27 patients: elevated troponin has not documented in any patients and elevated BNP or NT-proBNP have been documented in 7 patients (0.75%)

[b]Atrial fibrillation, atrial flutter, ventricular tachycardia or ventricular fibrillation

[c]Elevated above the upper limit of normal for local laboratory reference range

[d]Systolic blood pressure (BP) > 140mmg Hg or diastolic BP > 90 mm Hg, or on treatment

[e]HbA1c > 7.0% or > 53 mmol/mol or on treatment

[f]Estimated glomerular filtration rate < 60 ml/min/1.73m^2

[g]HIGH risk if anthracycline chemotherapy and trastuzumab delivered concurrently

[h]Previous malignancy (not current treatment protocol)

23 weeks for patients receiving taxanes alone and before and after anthracycline use for those receiving sequential chemotherapy regimens). Cardiac adverse outcomes were defined as: death due to cardiac reasons, LVEF decline of ≥ 10%, LVEF decline to below 50%, congestive heart failure (CHF) (NYHA class II and III–IV) and trastuzumab discontinuation (temporary or permanent) due to cardiac toxicity. Reasons for discontinuing trastuzumab not related to cardiotoxicity and management of cardiac events with specialist referrals and medications were also recorded.

Statistical analysis

Analyses were performed in Stata/MP 16.0 [19]. A $p < 0.05$ was considered statistically significant. Baseline patients and breast cancer characteristics were tabulated and compared among age groups (≥ 65 and < 65 years) and HFA-ICOS CV risk groups (low vs. medium vs. high vs. very high) using Chi-squared, Fisher's statistics, two-sample *t* tests and 3-way ANOVA. Similarly, exposure to anticancer treatments was compared among age and HFA-ICOS CV risk groups. An age cut-off of 65 years was used to be consistent with previous analyses [15] and since individuals aged ≥ 65 years were under-represented in the pivotal trials of adjuvant trastuzumab [20]. Baseline LVEF measurements were compared with those at trastuzumab completion in the overall population and according to age group for those patients undergoing a MUGA scan or an echocardiogram at treatment initiation and specifically for those undergoing a baseline echocardiogram.

Cardiac event rates occurring at any time during the course of trastuzumab and subsequent follow-up were

estimated and compared according to age (≥ 65 vs. < 65 years) and HFA-ICOS CV risk (low vs. medium vs. high/very high). These rates were also compared based on menopausal status and use of statins at baseline. Reasons for trastuzumab discontinuation and management of cardiac events were also compared among these patient groups.

Logistical regression was used to calculate the odds of cardiac events based on HFA-ICOS risk category. The performance of the HFA-ICOS Risk Tool to predict cardiotoxicity was evaluated by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). We also composed receiver-operating characteristic (ROC) curves and calculated the area under the curve for the prediction model.

Results

Population characteristics

Between January 2011 and December 2018, 1094 patients initiated trastuzumab in the curative setting for HER2+ EBC at The Royal Marsden NHS Foundation Trust. The analysis was restricted to 931 patients who completed the entire course of trastuzumab at our Institution for whom cardiac assessments were available (Fig. 1).

Patient characteristics and tumour characteristics are shown in Table 2. No significant differences in patient and tumour characteristics were observed in those aged ≥ 65 years compared with their younger counterparts. Comorbidities and CV risk factors are outlined in Table 3. Patients aged 65 years and older had a higher prevalence of diabetes mellitus, hypertension and hypercholesterolemia compared with the younger patients (< 65 years old). At trastuzumab initiation, a higher proportion of patients aged ≥ 65 years were on cardioprotective medications including beta-blockers, ACE inhibitors, angiotensin receptor blockers and mineralocorticoid receptor blockers [< 65 years: 86/736 (11.7%)]; ≥ 65 years: 60/195 (30.8%); $p = 0.001$] (Table 3).

Of the 931 patients, based on the HFA-ICOS risk stratification tool 401 (43.1%) had a low baseline CV risk, 454 patients (48.8%) were medium-risk, 70 patients (7.5%) were high-risk, and 6 patients (0.6%) were very high-risk.

Treatment characteristics and cardiac assessments

Trastuzumab was given in the adjuvant setting only in 584 patients (62.7%), whereas 347 (37.3%) received trastuzumab neoadjuvantly and continued treatment in the adjuvant setting. The median number of doses given was 18 (range 1–18). The majority of patients received a sequential combination of anthracyclines and taxanes [594 (63.8%)],

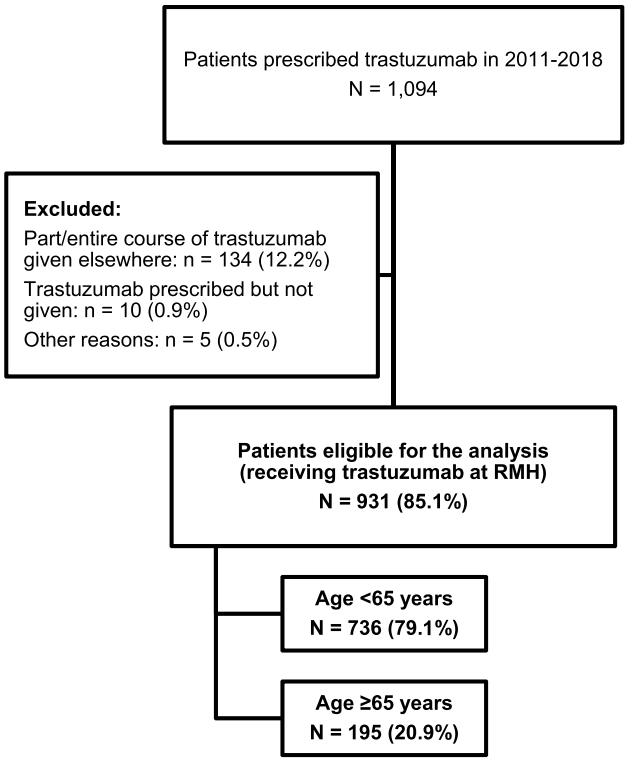

Fig. 1 CONSORT diagram

while 288 (30.9%) received taxanes alone. Pertuzumab was added to trastuzumab in 158 patients (17.0%) and adjuvant radiotherapy was given to 689 patients (74.0%). Among 638 patients with ER-positive disease, tamoxifen was initially prescribed for 379 patients (59.4%) and an aromatase inhibitor for 226 (35.4%).

Table 4 report the treatments given in the overall population and based on age and HFA-ICOS risk category. Anthracyclines were added to a taxane less frequently in older patients [≥ 65 years 68 (34.9%) vs. < 65 years 526 (71.5%); $p = 0.001$] and in those with increasing HFA-ICOS risk score [low 271 (67.6%) vs. medium 291 (64.1%) vs. high 31 (44.3%) vs. very high 1 (16.7%); $p = 0.001$]. Similarly, older patients and those with higher CV risk were more likely to receive trastuzumab only in the adjuvant setting rather than in the neoadjuvant setting.

LVEF at baseline and upon trastuzumab completion in the overall population and according to age group are reported in Fig. 2.

Cardiac events and their management

Cardiac adverse events occurred in 155 patients (16.6%) (Table 5, Fig. 3). No cardiac deaths were observed in this cohort. One hundred and forty-one patients (15.1%) experienced a LVEF decline ≥ 10% and 55 (5.91%) below 50%.

Table 2 Patient and tumour characteristics at baseline in the overall population and according to age group

Characteristics	Overall $N=931$		Age group				p value
			<65 years $N=736$		≥ 65 years $N=195$		
Continuous variables							
Age (years)							
Median	54		50		69		–
IQR	46–63		43–56		67–73		
Mean	54.3		50.0		70.9		
Standard deviation	11.9		9.0		4.6		
Range	24–83		24–64		65–83		
Weight (kg)[a]							
Median	69		69.0		68.8		0.555
IQR	60.8–78.9		60.6–79.0		61.5–77.7		
Mean	71.0		71.3		70.1		
Standard deviation	14.8		15.4		12.4		
Range	42.5–140.0		42.5–140.0		43.7–106.6		
BMI (kg/m^2)[b]							
Median	25.4		25.4		26.7		0.073
IQR	22.7–30.0		22.0–30.0		23.8–30.2		
Mean	26.8		26.7		27.2		
Standard deviation	5.50		5.70		4.7		
Range	15.9–51.8		15.9–51.8		17.3–42.2		
Charlson comorbidity index							
Median	0		0		0		0.259
IQR	0–2		0–0		0–1		
Mean	0.9		0.9		1.0		
Standard deviation	1.1		1.0		1.1		
Range	0–6		0–5		0–6		
	N	%	*N*	%	*N*	%	
Categorical variables							
Sex							
Female	930	99.9	736	100.00	194	99.5	–
Male	1	0.1	0	0.00	1	0.5	–
ECOG PS							
0	826	88.7	679	92.3	147	75.4	0.001
1	102	11.0	57	7.7	45	23.1	0.001
2	3	0.3	0	0.0	3	1.5	0.009
Menopausal status							
Pre/perimenopausal	427	45.9	427	58.0	0	0.0	–
Postmenopausal	504	54.1	309	42.0	195	100.0	0.001
Status (on 13/05/2020)							
Dead	51	5.5	36	4.9	15	7.7	0.155
Alive	880	94.5	700	95.1	180	92.3	–
Previous (remote) use of chemotherapy	45	4.8	35	4.8	10	5.1	0.851
Previous (remote) use of anthracyclines	29	3.1	23	3.1	6	3.1	0.999
Previous (remote) use of trastuzumab	9	1.0	9	1.2	0	0.0	0.217
Histology							
Ductal	885	95.1	706	95.9	179	91.8	0.022
Lobular	38	4.1	25	3.4	13	6.7	0.064
Mixed ductal/lobular	5	0.5	3	0.4	2	1.0	0.282

Table 2 (continued)

	N	%	*N*	%	*N*	%	
Other	2	0.2	1	0.1	1	0.5	0.376
Missing	1	0.1	1	0.1	0	0.0	–
Grade							
1	15	1.6	12	1.6	3	1.5	0.999
2	332	35.7	263	35.7	69	35.4	0.867
3	570	61.2	448	60.9	122	62.6	0.868
Missing	14	1.5	13	1.8	1	0.5	–
ER status							
Negative	293	31.5	226	30.7	67	34.4	0.341
Positive	638	68.5	510	69.3	128	65.6	0.341
PgR status							
Negative	447	48.0	340	46.2	107	54.9	0.017
Positive	452	48.5	373	50.7	79	40.5	0.017
Missing	32	3.4	23	3.1	9	4.6	–
HER2 testing method							
IHC	611	65.6	494	67.1	117	60.0	–
ISH	201	21.6	146	19.9	55	28.2	–
Unknown	119	12.8	96	13.0	23	11.8	–
Best stage[c]							
I	212	22.8	163	22.1	49	25.1	0.386
II	551	59.2	442	60.0	109	55.9	0.324
III	162	17.4	127	17.3	35	17.9	0.831
Missing	6	0.6	4	0.5	2	1.0	–
Laterality							
Right	450	48.3	355	48.2	95	48.7	0.936
Left	467	50.2	370	50.3	97	49.7	0.936
Bilateral[d]	14	1.5	11	1.5	3	1.5	0.999

BMI body mass index, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *ER* oestrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *ISH* in situ hybridisation, *IHC* immunohistochemistry

[a]Recorded in 929/931 patients

[b]Recorded in 928/931 patients

[c]Corresponds to the "worst" stage between clinical stage (for patients receiving neoadjuvant systemic therapy) or pathological stage (for those receiving only adjuvant systemic therapy)

[d]Includes patients with bilateral HER2-positive disease (and not patients with monolateral HER2-positive disease plus contralateral HER2-negative disease)

Forty-seven patients (5.0%) developed symptomatic heart failure. In this cohort, 42 patients (4.5%) had mild symptoms (NYHA class II) and 5 patients (0.5%) had more severe symptomatic heart failure (NYHA class III–IV). No differences in cardiac events were observed based on tumour laterality [right: 71/450 (15.8%); left: 81/467 (17.3%); bilateral: 3/14 (21.5%); $p = 0.726$]. The median time to cardiac toxicity was 19.9 weeks (mean: 21.9 weeks; range: 1–120 weeks).

Trastuzumab was discontinued due to cardiotoxicity in 35 patients (3.76%). No significant differences in cardiotoxicity were seen according to age group.

Table 6 outlines the management of cardiotoxicity events. One hundred and seventeen patients (12.6%) required a referral to a cardiologist provided by a specialist cardio-oncology service. Beta-blockers (preferably carvedilol) were prescribed in 57 patients (6.1%), ACE inhibitors or angiotensin receptor blockers in 99 (10.6%), mineralocorticoid receptor blockers (eplerenone) in 5 patients (0.54%), diuretics in 16 patients (1.7%) and statins were started in 17 patients (1.8%) either by the treating oncologist or by the cardiologist. No significant differences were observed in the management of cardiac events based on age. In the older age group, cardioprotective medications (including beta-blockers, ACE inhibitors, angiotensin receptor blockers or mineralocorticoid receptor blockers) were prescribed in 37 patients out of 39 developing cardiac toxicity (94.9%). The use of cardioprotective medications following this specific toxicity increased with increasing HFA-ICOS risk category.

Table 3 Comorbidities, cardiovascular risk factors and concurrent medications at baseline in the overall population and according to age group

			Overall $N=931$		Age group				p value
					< 65 years $N=736$		≥ 65 years $N=195$		
			N	%	N	%	N	%	
Comorbidities and cardiovascular risk factors									
Diabetes mellitus			44	4.7	28	3.8	16	8.2	0.014
Hypertension			176	18.9	96	13.0	80	41.0	0.001
Hypercholesterolemia			91	9.8	44	6.0	47	24.1	0.001
Coronary artery disease			12	1.3	5	0.7	7	3.6	0.005
Cerebrovascular disease			4	0.4	2	0.2	2	1.0	0.195
Peripheral artery disease			1	0.1	0	0.0	1	0.5	0.209
Heart failure	Overall		2	0.21	1	0.14	1	0.51	0.375
	NYHA class	1	1	0.11	1	0.14	0	0.00	–
		3	1	0.11	0	0.00	1	0.51	–
Rheumatic heart disease			1	0.1	1	0.1	0	0.0	0.999
Abnormal heart rhythm			23	2.5	12	1.6	11	5.6	0.003
Congenital heart disease			7	0.7	5	0.7	2	1.0	0.641
Valvular heart disease			9	1.0	6	0.8	3	1.5	0.406
Cardiomyopathy			4	0.4	4	0.5	0	0.0	0.585
Aortic aneurysm			1	0.1	0	0.0	1	0.5	0.209
Thromboembolic disease			9	01.0	7	0.9	2	1.0	0.999
Venous thromboembolism			6	0.6	5	0.7	1	0.5	0.999
Pulmonary hypertension			1	0.1	0	0.0	1	0.5	0.209
Pericardial disease			1	0.1	1	0.1	0	0.0	0.999
Chronic kidney disease			5	0.5	3	0.4	2	1.0	0.282
Cigarette smoking									
Overall			228	24.5	179	24.3	49	24.5	0.851
Current			42	4.5	38	5.2	4	2.0	–
Past			186	20.0	141	19.2	45	23.1	–
Regular alcohol consumption			385	41.3	299	40.6	86	44.1	0.414
Concurrent medications									
Cardioprotective medications[a]			146	15.7	86	11.7	60	30.8	0.001
Beta-blockers			54	5.8	30	4.1	24	12.3	0.001
ACE inhibitors			77	8.3	47	6.4	30	15.4	0.001
Angiotensin receptor blockers			38	4.1	18	2.4	20	10.3	0.001
Mineralocorticoid receptor blockers			1	0.1	0	0.0	1	0.5	0.209

Table 3 (continued)

	Overall $N=931$		Age group				p value
			< 65 years $N=736$		≥ 65 years $N=195$		
	N	%	N	%	N	%	
Diuretics	50	5.4	25	3.4	25	12.8	0.001
Digitalis	3	0.3	1	0.1	2	1.0	0.113
Calcium channel blockers	82	8.8	46	6.2	36	18.5	0.001
Antiplatelets	33	3.5	20	2.7	13	6.7	0.014
Anticoagulants	12	1.3	7	0.9	5	2.6	0.143
Statins	83	8.9	38	5.2	45	23.1	0.001

NYHA New York Heart Association, *ACE* angiotensin-converting enzyme

[a]Cardioprotective medications include beta-blockers, ACE inhibitors, angiotensin receptor blockers and mineralocorticoid receptor blockers

Performance of the HFA-ICOS risk prediction model

Increasing CV risk based on the HFA-ICOS category correlated with increasing rates of cardiac events on trastuzumab: the overall rates of cardiotoxicity was 14.0% in patients classified as low risk versus 16.7% with medium risk versus 30.3% classified as baseline as high or very high risk ($p=0.002$) (Fig. 4).

The HFA-ICOS score also correlated with increasing rates of cardiac toxicity: 7.6% for low-risk patients with a score of 0 ($n=66$); 15.2% for low-risk patients with a score of 1 ($n=335$); 16.0% for medium-risk patients with a score of 2 ($n=263$); 18.3% for medium-risk patients with a score of 3 ($n=120$); 16.9% for medium-risk patients with a score of 4 ($n=71$); 30.3% for high- to very high-risk patients with a score ≥ 5 ($n=76$) ($p=0.0147$) (Fig. 5).

The HFA-ICOS Risk Tool had a sensitivity of 14.8%, a specificity of 93.2%, a PPV of 30.3% and a NPV of 84.6% when predicting any cardiac event on trastuzumab in patients classified as low/medium risk versus those classified as high/very high risk. Area under the ROC curve for the predictive model for any cardiac toxicity was 0.56.

Discussion

This is a large retrospective single-centre study analysing cardiotoxicity incidence and outcomes for patients receiving trastuzumab for curable HER2-positive breast cancer, with a particular focus on outcomes for the older age group and according to baseline HFA-ICOS Risk. A significant proportion of these patients (43.1%) had a low cardiovascular risk profile based on the HFA-ICOS assessment tool. Nonetheless, more than a half had medium, high or very high risk and establishing the rates of cardiotoxicity in the real world is crucial especially in the curative setting.

A key result of our analysis is that the incidence of clinically serious symptomatic heart failure in patients receiving curative trastuzumab outside clinical trials is low (5.0%), with no fatal cardiotoxicity, although various degrees of cardiac toxicity may occur in up to 16.6% of patients on this treatment. These results are comparable to a recent pooled analysis of the trastuzumab registration trials which showed a small to modest risk of cardiotoxicity ranging between 5.5 and 19.4% [20]. The importance of this analysis is that it includes a real-world population of patients not enrolled in clinic trials and therefore may be particularly useful to inform routine clinical practice.

Benchmarking the incidence of cardiac events for patients receiving trastuzumab in the curative setting is also important in the context of the studies investigating de-escalation strategies. In our series one third of patients received taxanes alone and in a similar population with node-negative EBC,

Table 4 Treatment characteristics and exposure in the overall population and according to age and HFA/ICOS risk group

Treatment characteristics	Category	Overall $N=931$		Age group				p value	HFA-ICOS risk group								p value
				< 65 years $N=736$		≥ 65 years $N=195$			Low $N=401$		Medium $N=454$		High $N=70$		Very high $N=6$		
		N	%	*N*	%	*N*	%		*N*	%	*N*	%	*N*	%	*N*	%	
Concurrent chemotherapy	No chemotherapy	10	1.1	7	0.9	3	1.5	0.445	3	0.7	6	1.3	0	0.0	1	16.7	0.002
	Anthracycline + taxanes	594	63.8	526	71.5	68	34.9	0.001	271	67.6	291	64.1	31	44.3	1	16.7	0.001
	Taxanes alone	288	30.9	174	23.6	114	58.5	0.001	111	27.7	141	31.1	33	47.1	3	50.0	0.001
	Anthracyclines alone	14	1.5	13	1.8	1	0.5	0.323	6	1.5	8	1.8	0	0.0	0	0.0	0.714
	Including carboplatin	29	3.1	25	3.4	4	2.0	0.486	12	3.0	14	3.1	2	2.9	1	16.7	0.297
	Other regimen	25	2.7	16	2.2	9	4.6	0.078	10	2.5	8	1.8	6	8.6	1	16.7	0.002
Epirubicin dose ≥ 450 mg/m^2		21	2.3	18	2.4	3	1.5	0.721	6	2.2	13	4.3	2	6.2	0	0.0	0.416
Pertuzumab use		158	17.0	143	19.4	15	7.7	0.001	74	18.4	74	16.3	9	12.9	1	16.7	0.657
Setting	Adjuvant only	584	62.7	434	59.0	150	76.9	0.001	235	58.6	291	64.1	54	77.1	4	66.7	0.023
	Neoadjuvant + adjuvant	347	37.3	302	41.0	45	23.1	0.001	166	41.4	163	35.9	16	22.9	2	33.3	0.023
Radiotherapy use	No	242	26.0	179	24.3	63	32.3	0.027	106	26.4	111	24.4	24	34.3	1	16.7	0.337
	Yes	689	74.0	557	75.7	132	67.7	0.027	295	73.6	343	75.5	46	65.7	5	83.3	0.337
Endocrine therapy	No endocrine therapy	326	35.0	255	34.6	71	36.4	0.673	125	31.2	176	38.8	24	34.3	1	16.7	0.097
	Tamoxifen[a]	379	40.7	338	45.9	41	21.0	0.001	212	52.9	149	32.8	14	20.0	4	66.7	0.001
	Aromatase inhibitor[a]	226	24.3	143	19.4	83	42.6	0.001	64	16.0	129	28.4	32	45.7	1	16.7	0.001
Chemotherapy cycles	Median	6		6		4		0.001	6		6		5		5		0.001
	IQR	4–8		4–8		4–6			4–8		4–8		4–6		4–6		
	Mean	5.9		6.2		4.9			6.1		5.9		5.1		4.7		
	SD	1.9		1.8		2.0			1.9		1.9		2.0		2.7		
	Range	0–10		0–10		0–10			0–10		0–10		1–8		0–8		
Epirubicin cumulative dose (mg/m^2)[b]	Median	360		360		360		0.798	360		360		360		360		0.852
	IQR	300–360		300–360		300–360			300–360		300–360		300–360		360–360		
	Mean	333.4		333.1		335.4			329.7		336.0		338.9		360.0		
	SD	67.8		67.7		69.6			61.5		73.4		66.7		0.0		
	Range	90–600		90–600		90–600			90–600		90–600		180–600		360–360		
Trastuzumab doses	Median	18		18		18		0.001	18		18		18		18		0.193
	IQR	18–18		18–18		17–18			18–18		18–18		17–18		14–18		
	Mean	17.3		17.5		16.8			17.6		17.3		16.4		15.0		
	SD	2.1		1.7		3.1			1.4		2.2		3.7		5.6		
	Range	1–18		3–18		1–18			3–18		1–18		4–18		4–18		

[a]Initial choice of endocrine agent (regardless of subsequent changes based on menopausal status and tolerance)

[b]Two patients who received doxorubicin instead of epirubicin have been excluded from this analysis

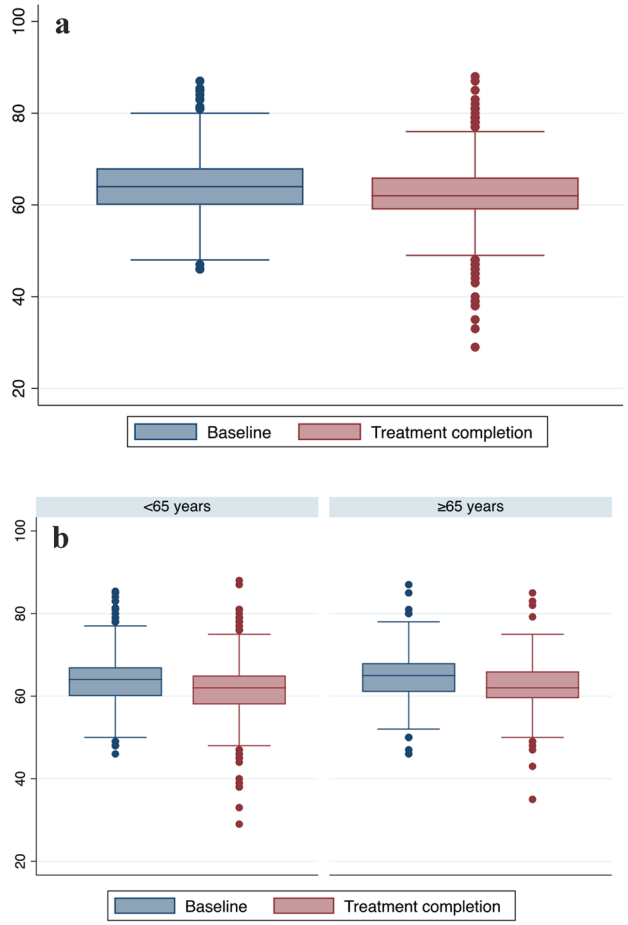

Fig. 2 Left ventricular ejection fraction at baseline and upon trastuzumab completion in the overall population (**a**) and according to age group (**b**)

the APT study reported even lower rates of cardiac toxicity, with 0.5% of patients experiencing grade 3 left ventricular systolic dysfunction and 3% reporting asymptomatic LVEF decline [13]. In our series only 3.8% of patients did not complete a full one-year course of trastuzumab due to cardiac toxicity. The PERSEPHONE study suggested non-inferior efficacy of 6 months of treatment compared with 12 months along with a substantial reduction in cardiac events from 12 to 9% [21].

This study suggests that there are no differences in the rates of cardiac adverse events according to age. This is consistent with previous analyses showing that most patients aged ≥ 66 years are able to complete a one-year course of trastuzumab without complications [22], although comorbidities remain critical in determining the risk of cardiotoxicity [23]. One variable that may explain the lack of effect of age alone is the rate of anthracycline chemotherapy which was significantly lower in the patients ≥ 65 years (34.9%) versus the younger patients < 65 years (71.5%). Therefore, the increased risk portended by increasing age may be balanced by the higher anthracycline chemotherapy use in the younger patients.

Our analysis also included a substantial proportion of patients with medium/high cardiovascular risk (56.9%). The registration trials of trastuzumab mandated stringent cardiac monitoring, limited the cumulative dose of anthracyclines to 300 mg/m^2 and excluded subjects with abnormal baseline cardiac function. This consideration makes real-world experiences useful since the risk of cardiac toxicity on trastuzumab varies according to the use of previous chemotherapy, pre-existing heart disease and cardiovascular risk factors [24]. Therefore, identifying the baseline

Table 5 Rates of cardiac events at any time following trastuzumab initiation in the overall population and according to age group and HFA-ICOS risk group

Cardiac events[a]	Overall *N* = 931		Age group				*p* value	HFA-ICOS risk category								*p* value
			< 65 years *N* = 736		≥ 65 years *N* = 195			Low *N* = 401		Medium *N* = 454		High *N* = 70		Very high *N* = 6		
	N	%	*N*	%	*N*	%		*N*	%	*N*	%	*N*	%	*N*	%	
Overall	155	16.6	116	15.8	39	20.0	0.161	56	14.0	76	16.7	20	28.57	3	50.0	0.003
LVEF decline ≥ 10%	141	15.1	106	14.4	35	17.9	0.218	51	12	70	15.42	17	24.3	3	50.0	0.007
LVEF decline below 50%	55	5.9	43	5.8	12	6.1	0.865	18	4.5	29	6.4	6	8.6	2	33.3	0.014
CHF																
NYHA class II	42	4.5	34	4.6	8	4.1	0.757	12	3.0	24	5.3	4	5.7	2	33.3	0.002
NYHA class III–IV	5	0.5	3	0.4	2	1.0	0.294	0	0.0	4	0.9	1	1.4	0	0.0	0.236
Trastuzumab discontinuation due to cardiotoxicity																
Overall	35	3.8	26	3.5	9	4.6	0.040	9	2.2	17	3.7	7	10.0	2	33.3	0.001
Temporary	23	2.5	18	2.4	5	2.6	0.999	5	1.2	12	2.6	4	5.7	2	33.3	0.001
Permanent	12	1.3	8	1.1	4	2.0	0.289	4	1.0	5	1.1	3	4.3	0	0.0	0.144

LVEF left ventricular ejection fraction, *CHF* congestive heart failure, *NYHA* New York Heart Association

[a]Cardiac event categories are not mutually exclusive (e.g. patients may have had a LVEF decline > 10% AND below 50%)

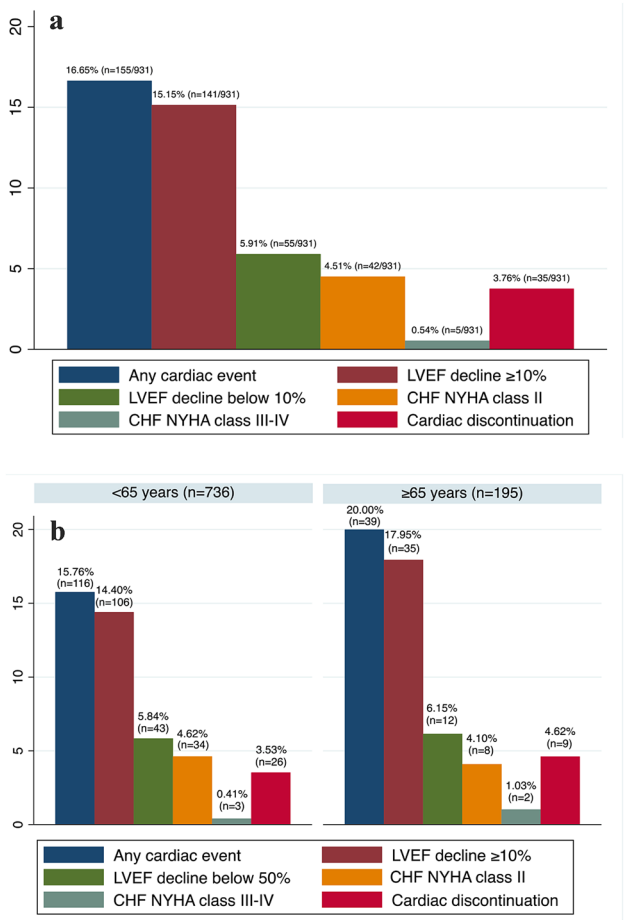

Fig. 3 Rates of cardiac events at any time following trastuzumab initiation in the overall population (**a**) and according to age group (**b**). *LVEF* left ventricular ejection fraction, *CHF* congestive heart failure, *NYHA* New York Heart Association

cardiovascular risk and developing prediction models able to identify those patients at higher risk of experiencing cardiac events remains particularly valuable [17].

The HFA-ICOS risk score had a good correlation with the incidence of cardiotoxicity in our analysis, with 30.3% of patients with a high- to very high-risk score experiencing any cardiac event compared with 16.7% of those with medium risk and 14.0% of those with low risk. We documented a similar pattern also for specific types of cardiac adverse events, including LVEF decline, CHF and trastuzumab discontinuations. Importantly, the HFA-ICOS score had a high NPV (86.0%) which is highly desirable to identify those patients who are not at lower risk of cardiac toxicity in this setting. The score did not discriminate between the low and medium-risk cohorts who had similar event rates and did not identify the cohort at absolute low risk (< 5%). In practical terms the low sensitivity of the HFA-ICOS score would suggest that this should not be used to de-escalate cardiac monitoring in patients with lower cardiovascular risk (as a 14% risk of cardiovascular events is still an appreciable rate in a curative setting). On the other hand, our findings might imply that enhanced monitoring (for example involving natriuretic peptides measurements, blood pressure control and earlier cardiology reviews if indicated) could be an appropriate strategy in those deemed at higher risk of cardiac toxicity. These findings would benefit from prospective validation in a larger cohort of patients.

This study has a number of limitations. At our institution, the measurement of cardiac biomarkers such as troponin and natriuretic peptides is not routine practice; therefore, despite their desirability where available [17], they have not been included in the model. In this series, baseline cardiac assessments involved either MUGA scans or echocardiograms to measure LVEF which may have introduced bias. Measuring the global longitudinal strain (GLS) using speckle tracking echocardiography has become standard practice in our hospital only since 2016 and therefore this parameter has not been captured in our cohort. GLS has recently emerged as a new marker of subclinical ventricular dysfunction demonstrating a stronger association with prognosis compared with LVEF in patients with cardiac conditions not related to cancer [25]. Various observational studies suggested its potential role accurately to predict the cardiotoxicity of anticancer agents and guide cardioprotective treatment [26, 27]. Our analysis is retrospective and therefore may be subject to selection bias as we included patients who were deemed fit to receive trastuzumab. Finally, excluding patients who did not receive a full course of trastuzumab at our institution may have also contributed to selection bias.

This analysis has some major strengths as well. We have demonstrated within a large cohort that overall rates of serious cardiotoxicity associated with trastuzumab are low, but absolute rate of all cardiotoxicity is clinically significant (16.6%), and dependent on the individual cardiovascular risk profile at baseline. Our study provides evidence that rates of cardiotoxicity on trastuzumab do not differ based on age in a real-world population. Furthermore, we have included patients receiving contemporary chemotherapy and targeted treatment regimens which make our findings applicable to current practice. Our study fills a gap of knowledge by providing evidence of external validation of a prediction model of cardiac toxicity in a population receiving treatment with substantial chances of cure [1]. This aspect is particularly valuable in the older patient population where competing risks of morbidity and mortality are more relevant.

These data should be considered when discussing risks and benefits of trastuzumab in older patients with HER2-positive EBC and prospective validation of the use of the HFA-ICOS Risk Tool is warranted.

Table 6 Management of trastuzumab-related cardiac toxicity in the overall population and according to age group and HFA-ICOS risk group

Variable	Category	Overall $N=931$		Age group				p value	HFA-ICOS risk group								p value
				< 65 years $N=736$		≥ 65 years $N=195$			Low $N=401$		Medium $N=454$		High $N=70$		Very high N=6		
		N	%	N	%	N	%		N	%	N	%	N	%	N	%	
Referral to cardiologist		166	17.8	129	17.5	37	19.0	0.674	54	13.5	86	18.9	20	28.6	6	100.0	0.001
Referral	Baseline	49	5.2	33	4.5	16	8.2	0.047	13	3.2	21	4.6	11	15.7	4	66.7	0.001
	Reactive[a]	117	12.6	96	13.0	21	10.8	0.466	41	10.2	65	14.3	9	12.9	2	33.3	0.131
Medications prescribed	Beta-blocker	57	6.1	42	5.7	15	7.7	0.314	11	2.7	38	8.4	7	10.0	1	16.7	0.002
	ACE inhibitor	81	8.7	63	8.6	18	9.2	0.775	25	6.2	41	9.0	12	17.1	3	50.0	0.001
	Angiotensin receptor blocker	18	1.9	14	1.9	4	2.0	0.778	6	1.5	10	2.2	2	2.9	0	0.0	0.799
	Mineralocorticoid receptor blocker	5	0.5	5	0.7	0	0.0	0.590	1	0.2	4	0.9	0	0.0	0	0.0	0.565
	Diuretic	16	1.7	13	1.8	3	1.5	0.999	1	0.2	14	3.1	1	1.4	0	0.0	0.016
	Ivabradine	3	0.3	3	0.4	0	0.0	0.999	1	0.2	2	0.4	0	0.0	0	0.0	0.917
	Digitalis	2	0.2	1	0.1	1	0.5	0.375	0	0.0	0	0.0	1	1.4	1	16.7	0.001
	Calcium channel blocker	4	0.4	3	0.4	1	0.5	0.999	0	0.0	2	0.4	2	2.9	0	0.0	0.010
	Antiplatelets	17	1.8	12	1.6	5	2.6	0.373	3	0.7	10	2.2	4	5.7	0	0.0	0.030
	Anticoagulants	8	0.9	3	0.4	5	2.6	0.012	0	0.0	6	1.3	2	2.9	0	0.0	0.047
	Statins	17	1.8	10	1.4	7	3.6	0.063	1	0.2	11	2.4	5	7.1	0	0.0	0.001

[a]Reactive referrals due to cardiac reasons

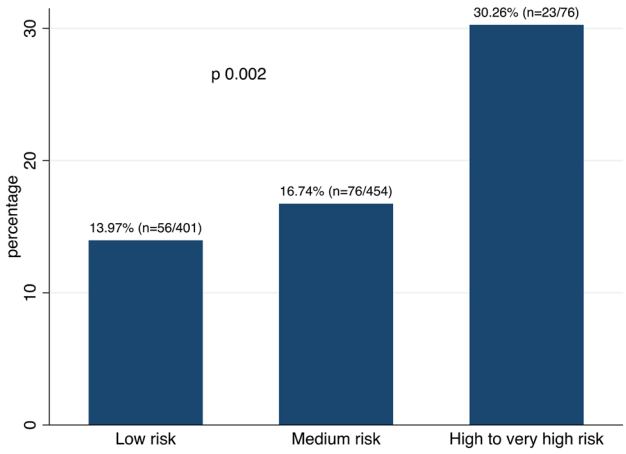

Fig. 4 Rates of overall cardiac events by HFA-ICOS risk category

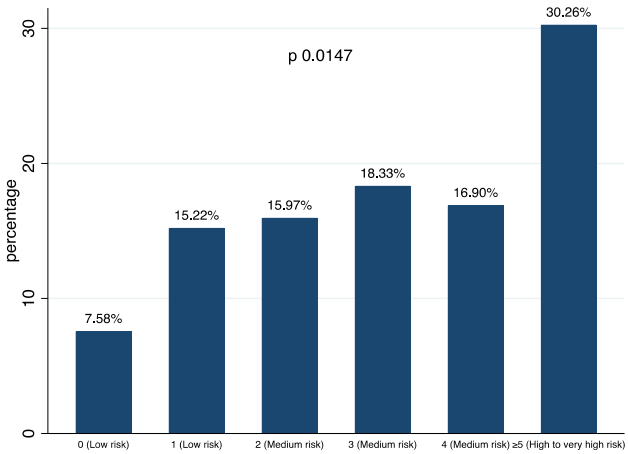

Fig. 5 Rates of overall cardiac events by HFA-ICOS risk score

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Author contributions NMLB, MA, ARL and AR conceived and designed the analysis. NMLB, KAL, TN, SM, NS, KA, MO, EST, VA, EF, EFG, SJ collected the data. NMLB performed the analysis. NMLB, MSA, KAL, SR, TN, SM, NS, KA, MO, EST, VA, EF, EFG, SJ, SDR, MA, SS, ARL and AR wrote the paper.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability The statistical analysis code generated during the current study is available from the corresponding author on reasonable request.

Declarations

Conflict of interest Dr. Battisti has received travel grants from Genomic Health and Pfizer and speaker fees from Pfizer and AbbVie. Dr. Lyon has received speaker, advisory board or consultancy fees and/or research grants from Pfizer, Novartis, Servier, Astra Zeneca, Bristol Myers Squibb, GSK, Amgen, Takeda, Roche, Janssens-Cilag Ltd, Clinigen Group, Eli Lily, Eisai Ltd, Ferring Pharmaceuticals, Boehringer Ingelheim, Akcea Therapeutics, Myocardial Solutions, iO-WNA Health and Heartfelt Technologies Ltd. Dr. Ring has received advisory board and speaker fees from Roche, Novartis, Pfizer, MSD and Lilly. Dr. Andres, Dr. Lee, Dr Ramalingam, Dr. Nash, Dr Mappouridou, Dr. Senthivel, Dr. Asavisanu, Dr. Obeid, Dr. Tripodaki, Dr. Angelis, Dr. Fleming, Dr. Goode, Dr. John, Professor Rosen, Dr. Allen, Dr. Stanway have no conflicts of interest.

Ethical approval This analysis was approved as a Service Evaluation by The Committee for Clinical Review of The Royal Marsden NHS Foundation Trust.

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