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Radiotherapy in patients receiving anthracyclines: phase 3 SAFE trial (NCT2236806) interim analysis

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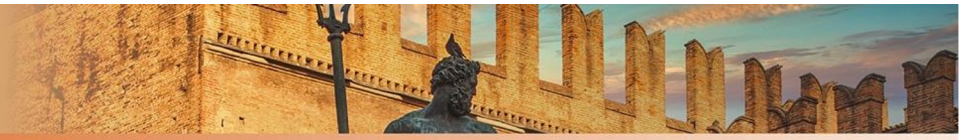


DICHIARAZIONE

Dott. Niccolò Bertini

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board **NIENTE DA DICHIARARE**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Altro **NIENTE DA DICHIARARE**

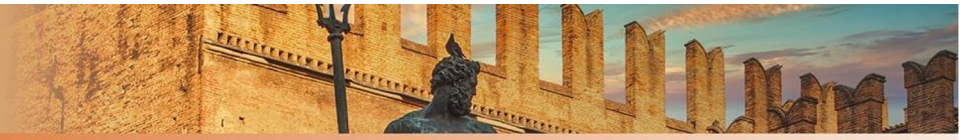
Background

Several studies have evaluated **cardioprotective strategies** to prevent **myocardial dysfunction** in patients receiving **cardiotoxic therapies.**
The **optimal** approach still represents a **controversial** issue.

Echocardiography is considered the gold standard in the cardiac imaging evaluation of patients **during** and **after** cancer therapy.
Remodeling that **precedes ventricular dysfunction** and a reduction in **global longitudinal strain (GLS)** **seems** to be the most **sensitive** parameter to **predict early cardiotoxic effects.**

Angiotensin-converting enzyme inhibitors (ACEis)/angiotensin-II receptor blockers and **ß-blockers** (BB) have been shown to **prevent cardiac remodeling** and reduce mortality in patients with cardiac dysfunction and have been proposed for **cardioprotection in oncology**

Singal PK, et al. N Engl J Med 1998; Wang SY, et al. Breast Cancer Res Treat 2014
Plana JC, et al. Eur Heart J Cardiovasc Imaging 2014; Thavendiranathan P, et al. J Am Coll Cardiol 2014
Oikonomou EK, et al. JAMA Cardiol 2019



Background

The **SAFE trial (NCT2236806)** is a four-arm, randomized, phase 3, double-blind, placebo-controlled study.

The study recruitment was conducted between July 2015 and June 2020.

Patients with non metastatic breast cancer(BC) treated with anthracycline-based chemotherapy +/- trastuzumab were enrolled.

The aim is to determine whether **pharmacological cardioprevention** could reduce subclinical heart damage in BC patients treated with anthracycline-based chemotherapy.

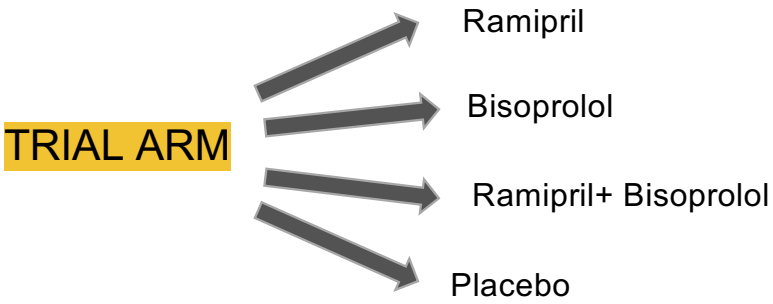
This is a subgroup analysis focused on the impact of **postoperative breast radiation therapy** (RT) of the recently published **pre-specified interim analysis** on the first **174 patients** who had completed **cardiac assessment at 12 months.**

Livi L, et al. JAMA Oncol 2021
Meattini I, et al. SABCS 2021

Methods

Patients were eligible for trial inclusion if they had indication to primary or postoperative systemic therapy using an **anthracycline-based regimen.**

Patients with a prior diagnosis of cardiovascular disease were excluded.



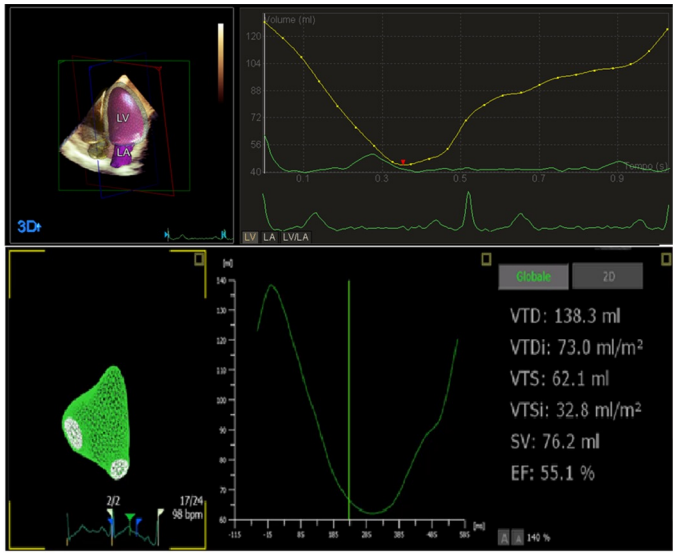
Cardioprotective therapy was administered for **1 year** from the initiation of chemotherapy or **until the end of trastuzumab** therapy in case of HER2 positive patients.

All patients underwent cardiac surveillance at **baseline** (T0), **3-month** (T1), **6-month** (T2), **12-month** (T3, end of treatment [EOT]), and **24-month** (T4, end of study) from enrollment.

Livi L, et al. JAMA Oncol 2021

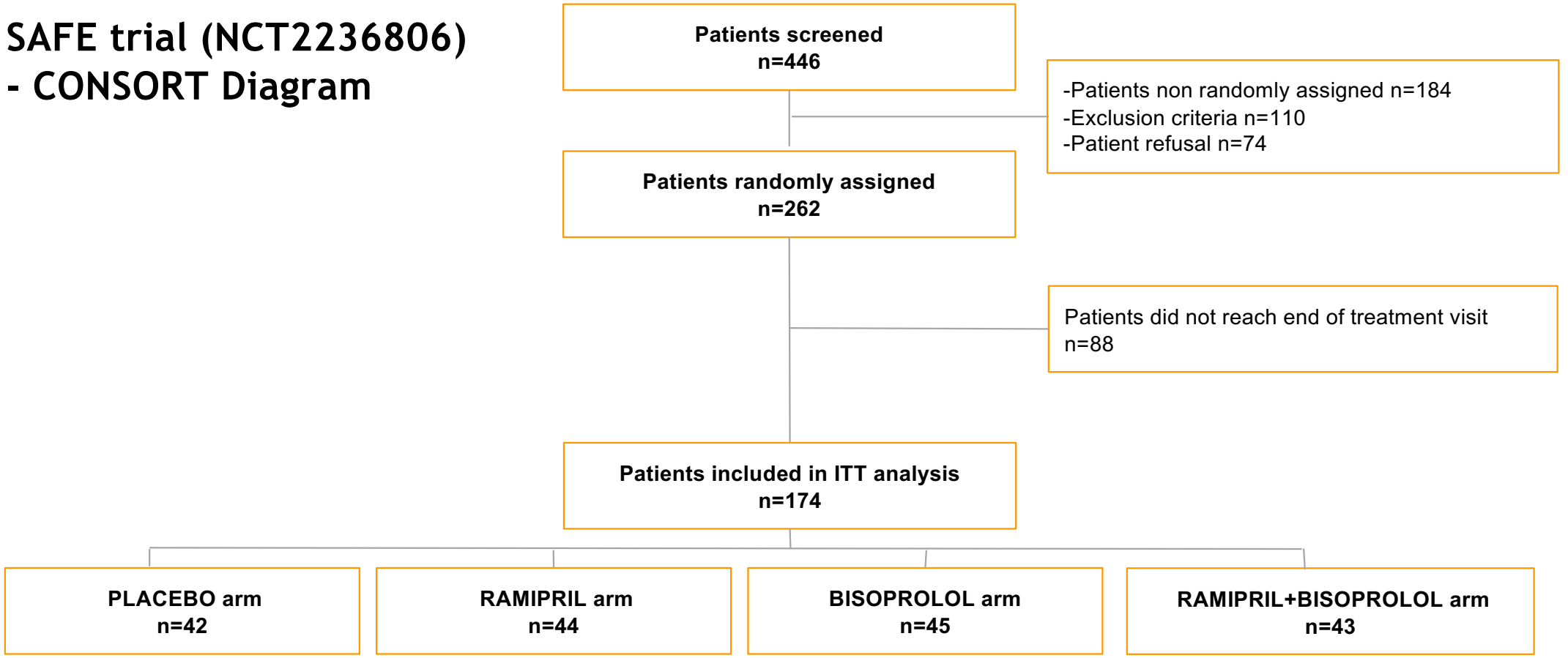
Methods

Primary endpoint ➡ any **subclinical impairment (worsening ≥10%)** in myocardial function and deformation measured with standard and **3-dimensional echocardiography**, **left ventricular ejection fraction (3D-LVEF)** and **global longitudinal strain (GLS)**.



Courtesy of Giuseppe Barletta, Florence University Hospital

SAFE trial (NCT2236806) - CONSORT Diagram

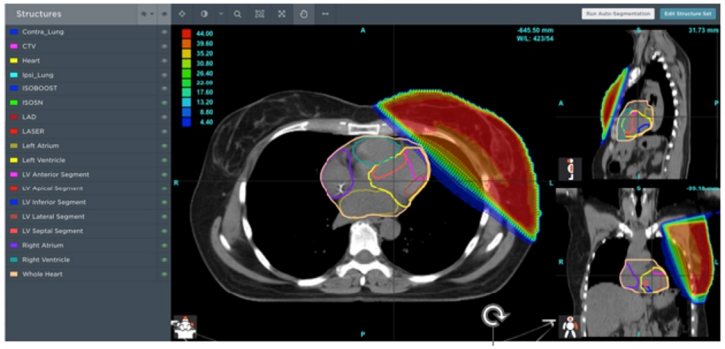


adapted from Livi L, et al. JAMA Oncol 2021;7(10):1544-1549

Results - Left-sided breast RT cohort QART

Feature	N (%)
Available DVH	39/46 (84.8)
WBI	31/39 (79.5)
40-44Gy/15-16#	24
50Gy/25#	6
60Gy/30#	1
PMRT	8/39 (20.5)
50Gy/25#	8
RNI	11/39 (28.2)
50Gy/25#	11
Tumour bed boost	30/39 (76.9)
10Gy/5#	17
13.3Gy/5#	11
16Gy/8#	1
18.9Gy/7#	1

OAR	Dose-constraint	OAR	Dose-constraint
Heart	Dmean	**RV**	Dmean
	Dmax		Dmax
	V60%		D98%
	V10Gy		D2%
	V2Gy		V10%
LAD	Dmean	**LA**	Dmean
	Dmax		Dmax
	D98%		D98%
	D2%		D2%
	V60%		V10%
LV	Dmean	**RA**	Dmean
	Dmax		Dmax
	D98%		D98%
	D2%		D2%
	V10%		V10%



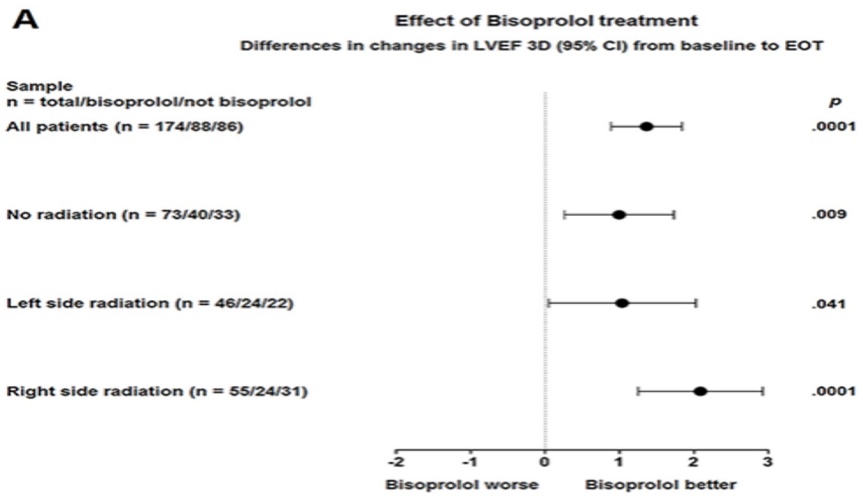
Courtesy of Livia Marrazzo, University of Florence (IT)

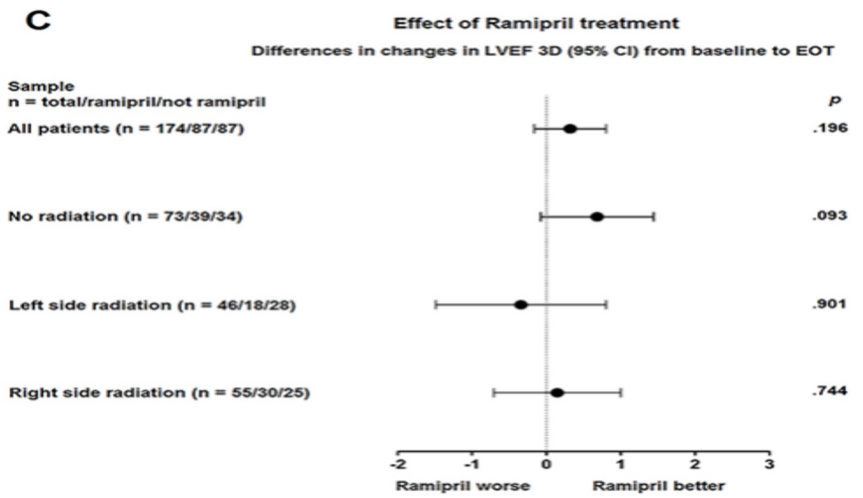
Results - Whole series at 12 months

	placebo arm	ramipril arm	bisoprolol arm	ramipril + bisoprolol arm	P
Worsened by 3D LVEF	4.4%	3%	1.9%	1.3%	P=0,05
Worsened by GLS	6%	1.5%	0.6%	unchanged(0.1% improvement)	P<0,001

% of patients	placebo arm	ramipril arm	bisoprolol arm	ramipril + bisoprolol arm
Reduction ≥10% 3D LVEF	19%	11.5%	11.4%	6.8%
Worsening ≥10% GLS	35.7%	15.9%	13.6%	13.6%

Results – Differences in 3D-LVEF changes from baseline to end of treatment

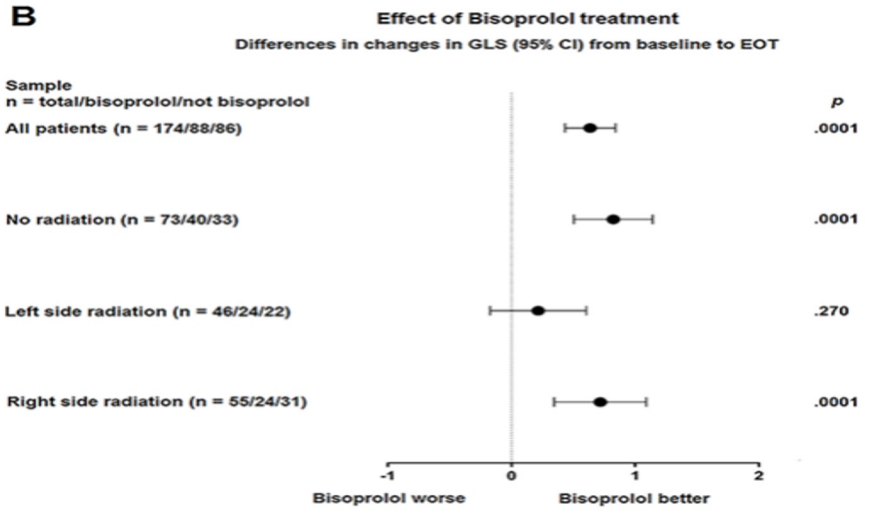


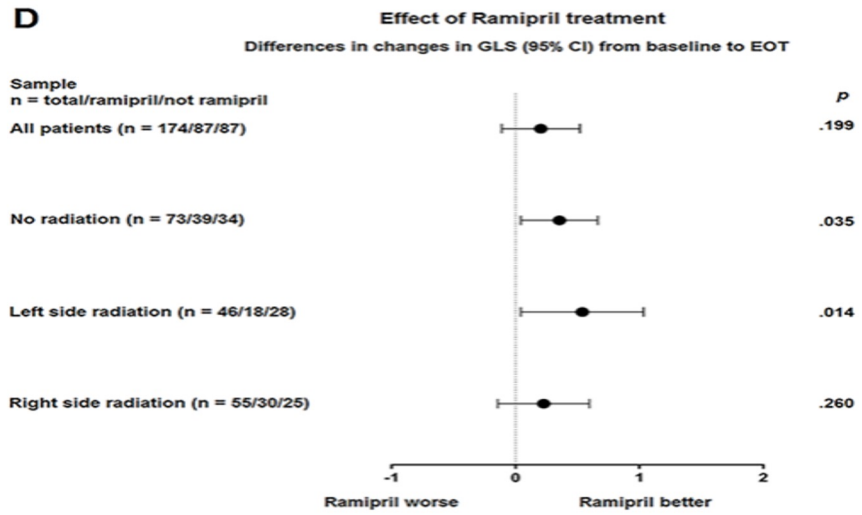


Bisoprolol-containing arms showed significant **benefit**:
- in patients not receiving RT (P = 0.09)
- in patients receiving right-sided breast RT (P = 0.0001), and
- with lesser extent, in patients receiving left-sided RT (P = 0.041)

No significant benefit was shown in **ramipril-containing arms**

Results – Differences in GLS changes from baseline to end of treatment





Bisoprolol-containing arms showed significant **benefit**:
- in patients not receiving RT (P = 0.0001)
- in patients receiving right-sided breast RT (P = 0.0001)
- no benefit in patients receiving left-sided breast RT (P = 0.270)

Ramipril-containing arms showed significant **benefit**
- in patients not receiving RT (P = 0.035)
- in patients receiving left-sided breast RT (P = 0.014)
- no benefit in right-sided breast RT (P = 0.260)

Results - dosimetry and primary outcome

Subclinical heart damage at 12 months		MHD (Gy)	V10 (%) Heart	V2 (%) Heart	Dmax (Gy) Heart	D2% (Gy) Heart	D98% (Gy) Heart	V60 (%) Heart	D2% (Gy) LAD	D98% (Gy) LAD	Dmean (Gy) LAD	Dmax (Gy) LAD	V60% (%) LAD
No	Mean	1,517	1,077	19,615	28,998	6,979	,358	,195	10,938	1,000	14,223	2,213	4,126
	N	27	27	27	27	27	27	27	27	27	27	27	27
	SD	,9408	1,9143	17,0088	11,5053	7,1456	,3210	,5212	12,3479	,4122	13,4781	6,5854	3,7675
	Median	1,185	,235	13,882	30,039	4,211	,278	,005	4,802	,845	7,105	,000	2,560
	Min	,6	,0	4,4	9,1	2,7	,1	,0	2,7	,4	4,1	,0	1,4
	Max	4,1	6,6	78,3	51,0	32,1	1,7	2,2	44,9	1,9	49,1	26,3	17,8
Yes	Mean	1,580	1,209	21,432	30,140	7,083	,364	,222	12,429	1,012	17,554	1,465	3,552
	N	12	12	12	12	12	12	12	12	12	12	12	12
	SD	,9964	1,8967	19,7904	14,6732	5,4942	,2792	,4133	12,0176	,5341	15,6454	3,8579	2,3286
	Median	1,376	,507	16,627	33,995	5,902	,273	,032	6,335	,841	9,473	,000	2,654
	Min	,6	,0	3,1	4,9	2,3	,1	,0	2,4	,4	3,2	,0	1,4
	Max	4,1	6,5	69,7	47,0	18,0	1,2	1,5	36,0	2,2	46,1	13,4	9,4
Mann-Whithney U test		***0.94***	***0.80***	***0.94***	***0.69***	***0.69***	***0.73***	***0.56***	***0.64***	***0.82***	***0.94***	***0.92***	***0.46***

No significant correlation between heart and LAD dosimetric parameters and subclinical heart damage at 12 months

Conclusions

At the interim analysis, cardioprotective pharmacological strategies in patients affected by breast cancer receiving an anthracycline-based chemotherapy **are well tolerated and seem to protect against cancer therapy-related LVEF decline and heart remodeling.**

This favorable effect seems to be reduced in patients receiving postoperative left-sided brest RT , this calling for further investigations on potentially radiation-related early subclinical heart damage.

Grazie per l'attenzione

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