Cardiotossicità da antracicline e farmaci anti-HER2

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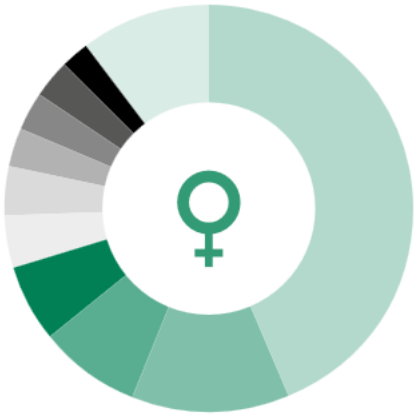
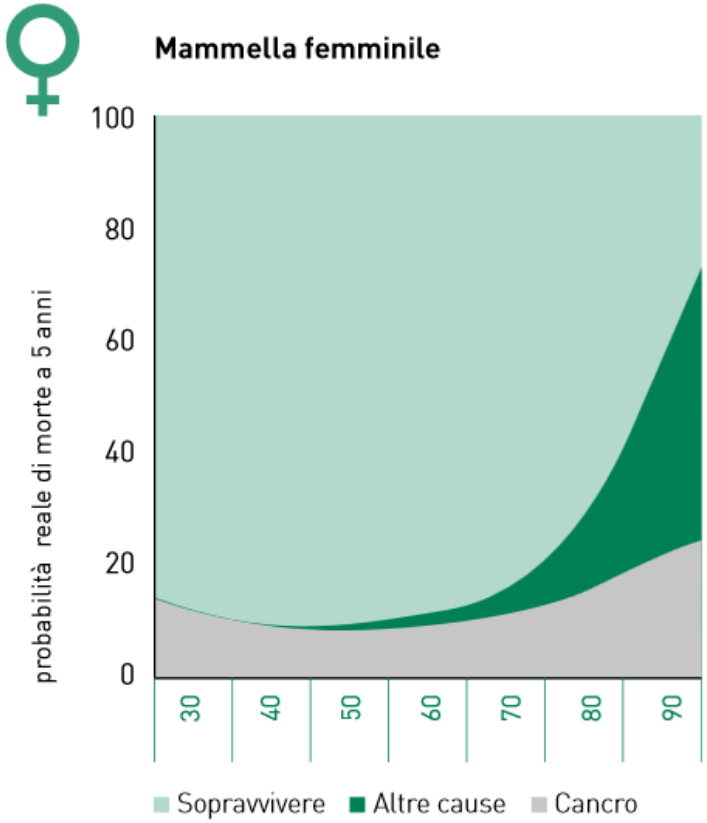
BC survivors and competing causes of death



Tumore	N.	%
Mammella	799196	43
Colon-retto-ano	226652	12
Tiroide	155995	6
Utero corpo	114485	5
Cute (melanomi)	82066	4
Linfoma n. H.	67681	4
Vescica	57196	3
Utero cervice	56063	3
Ovaio	50032	3
Rene, vie urinarie	43858	2
Altri	184185	10

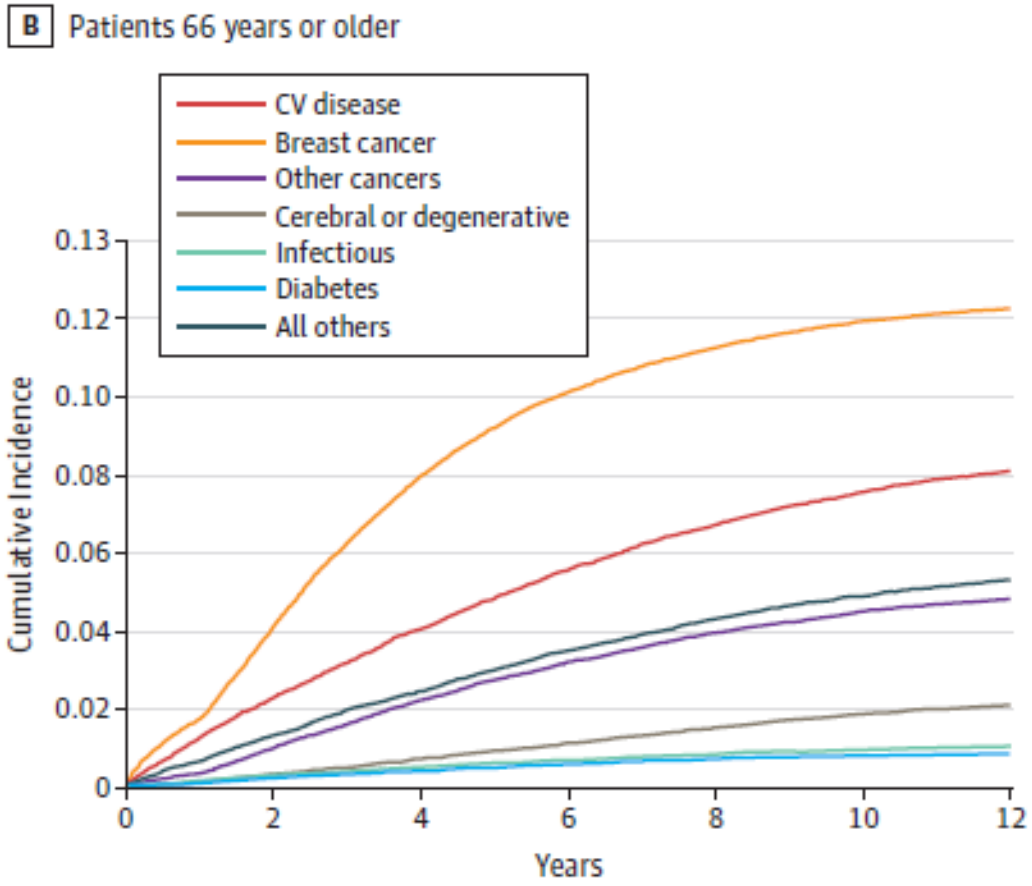


I numeri del cancro in Italia AIOM-AIRTUM 2018

JAMA Cardiology | Brief Report

A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer

Husam Abdel-Qadir, MD; Peter C. Austin, PhD; Douglas S. Lee, MD, PhD; Eitan Amir, MB, ChB, PhD; Jack V. Tu, MD, PhD; Paaladinesh Thavendiranathan, MD, MSc; Kinwah Fung, MSc; Geoffrey M. Anderson, MD, PhD



Cardiotoxicity induced by BC treatments

Table 1 Major cardiotoxicities associated with breast cancer therapy

Cancer therapy	Major cardiovascular toxicity
Anthracyclines	Cardiomyopathy
HER-2 antagonists	Cardiomyopathy
Radiation	Coronary artery disease
Cyclophosphamide	Hemorrhagic myocarditis
Taxanes	Bradycardia, ischemia
Fluoropyrimidines	Vasospasm and ischemia
Tamoxifen	Thromboembolism
Aromatase inhibitors	Hyperlipidemia, hypertension, ischemia
Cyclin dependent kinase 4/6 inhibitors	QTc prolongation

Caron J, Nohria A. Curr Rep Cancer 2018

Cardiotoxicity definition

Classification system	Grade I	Grade II	Grade III	Grade IV
NYHA	No limitation of activities	Mild limitation of activity	Marked limitation of activity	Confined to bed or chair
American College of Cardiology/American Heart Association	Stage A; at high risk but without structural heart disease or symptoms	Stage B; structural heart disease but without signs or symptoms	Stage C; Structural heart disease with prior or current symptoms	Stage D; Refractory CHF requiring specialized interventions
Clinical Toxicity Criteria version 2.0	Asymptomatic decline of resting EF ≥10% but <20% of baseline value	Asymptomatic but resting EF less than LLN for laboratory or decline of resting EF of ≥20% of baseline value; <24% SF	CHF responsive to treatment	Severe or refractory CHF or requiring intubation
Common Terminology Criteria for Adverse Events version 4.03	**EJECTION FRACTION DECREASE**			
	-	Resting EF 50-40%; 10-19% drop from baseline	Resting EF 39-20%; >20% drop from baseline	Resting EF <20%
	LEFT VENTRICULAR SYSTOLIC DYSFUNCTION			
	-	-	Symptomatic due to drop in EF responsive to intervention	Refractory or poorly controlled due to drop in EF; intervention such as ventricular assist device, IV vasopressor support or heart transplant indicated
Cardiac review and evaluation committee	Any of: 1. Cardiomyopathy characterized by a decrease in LVEF globally or more severe in the septum 2. Signs and symptoms of HF 3. Decline of EF ≥5% to final ejection fraction < 55% with symptoms of congestive HF 4. Asymptomatic decline of LVEF ≥ 10% to final ejection fraction < 55%			

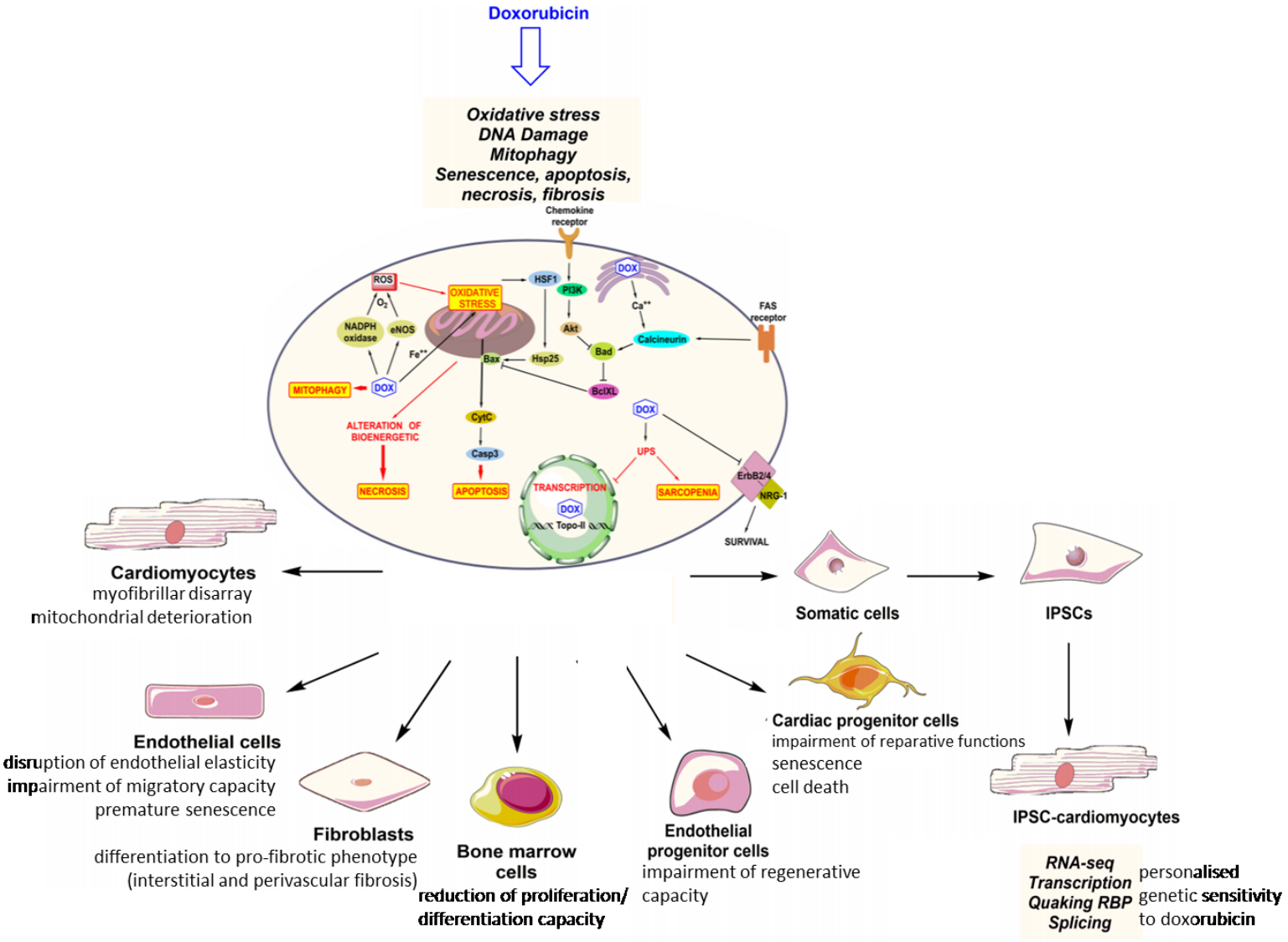
Modified from Bird and Swain, 2008 Clinical Cancer Research

Two types of treatment-related cardiac dysfunction

TYPE I: *e.g.* anthracyclines	TYPE II: *e.g.* trastuzumab
Cellular death (damage starts with the first administration)	Cellular dysfunction (mitochondrial and protein alterations)
Biopsy changes	No typical anthracycline-like biopsy changes
Cumulative-dose related	No cumulative-dose related
Time to presentation: weeks to decades	Time to presentation: weeks
Nonreversible (myocyte death)	Predominantly reversible (myocyte dysfunction)
Risk factors: combination CT, RT, age, previous cardiac disease, hypertension	Risk factors: prior/concomitant anthracyclines, age, previous cardiac disease, obesity

Suter TM, Ewer MS, Eur Heart Journal 2013

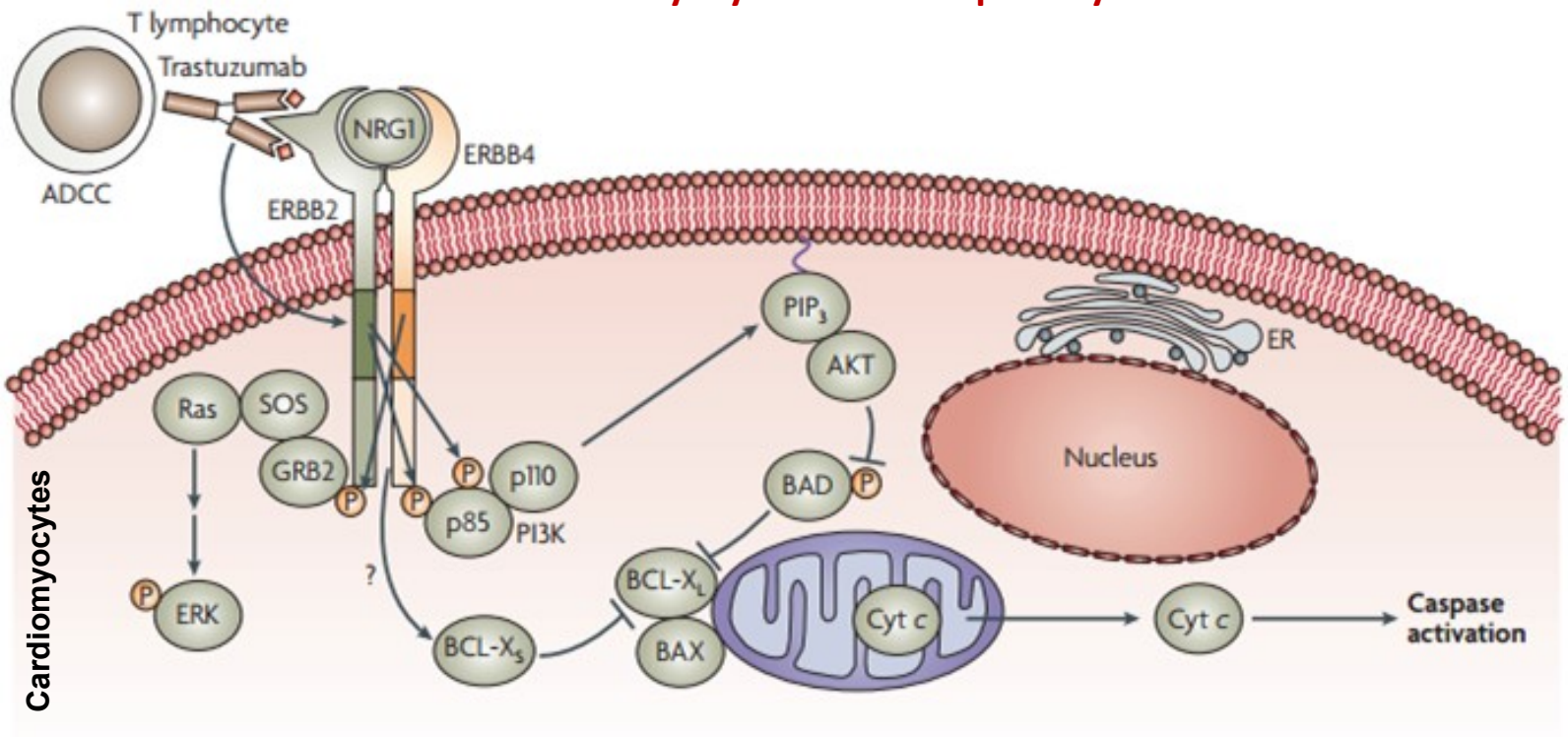
Anthracycline-related TYPE I cardiotoxicity



Modified from Nebigil, 2018, Frontiers in Pharmacology

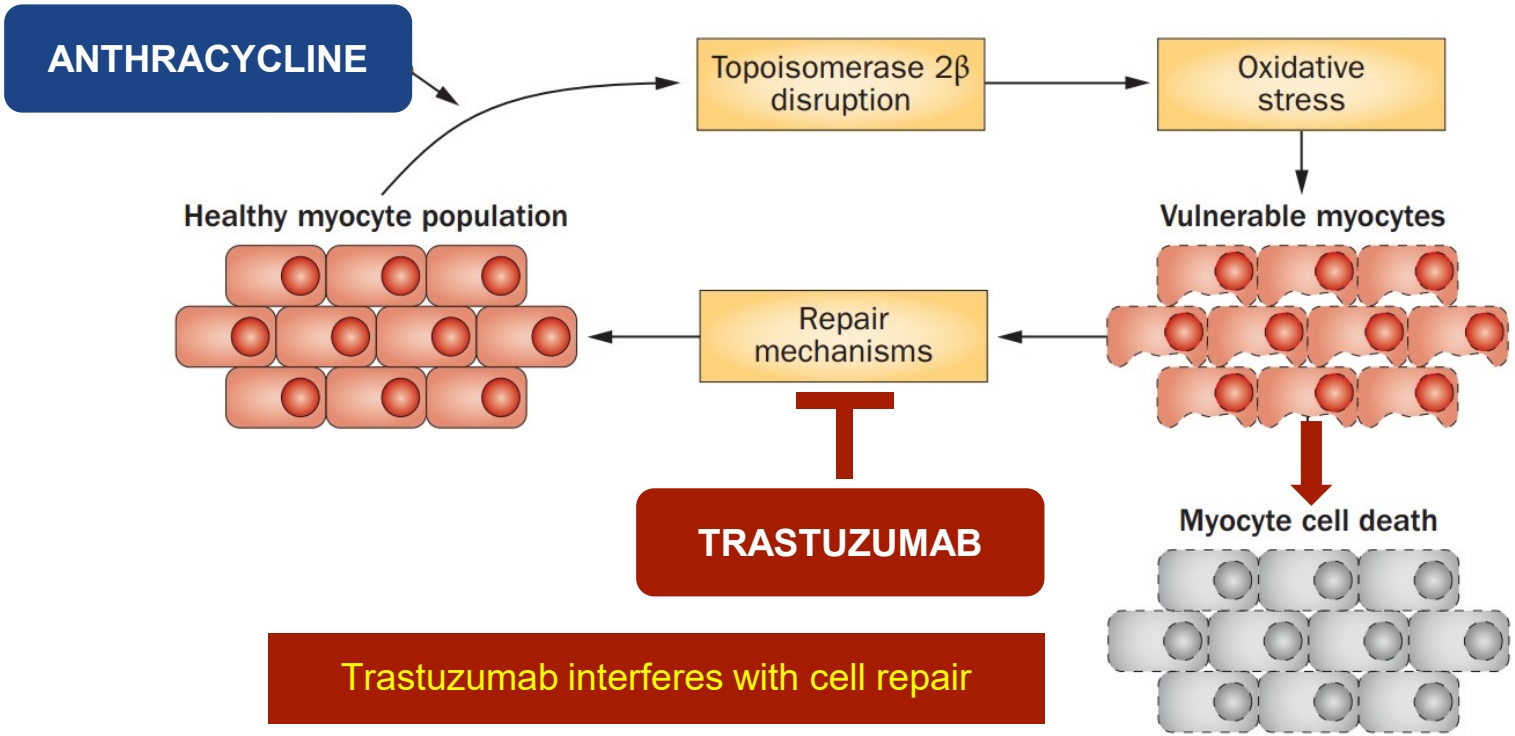
Trastuzumab-related TYPE II cardiotoxicity

Signalling in cardiomyocytes through the HER2– HER4 heterodimers is essential for development during embryogenesis and cardiomyocyte survival especially in situations of stress



modified from Force, 2007, Nature Reviews Cancer

Anthracycline + Trastuzumab



Ewer, 2015, Nature Reviews Cardiology

Cardiotoxicity from adjuvant anthracycline and trastuzumab for BC: Clinical considerations

- **Prevalence and risk factors**
- **Strategies to minimize cardiac risk**
  - Can we avoid anthracyclines?
  - De-escalated trastuzumab-containing regimens
  - Cardioprotection/biomarkers (next presentations)
- **What do guidelines say on monitoring and baseline assessment**

Classification of anthracycline-induced cardiotoxicity

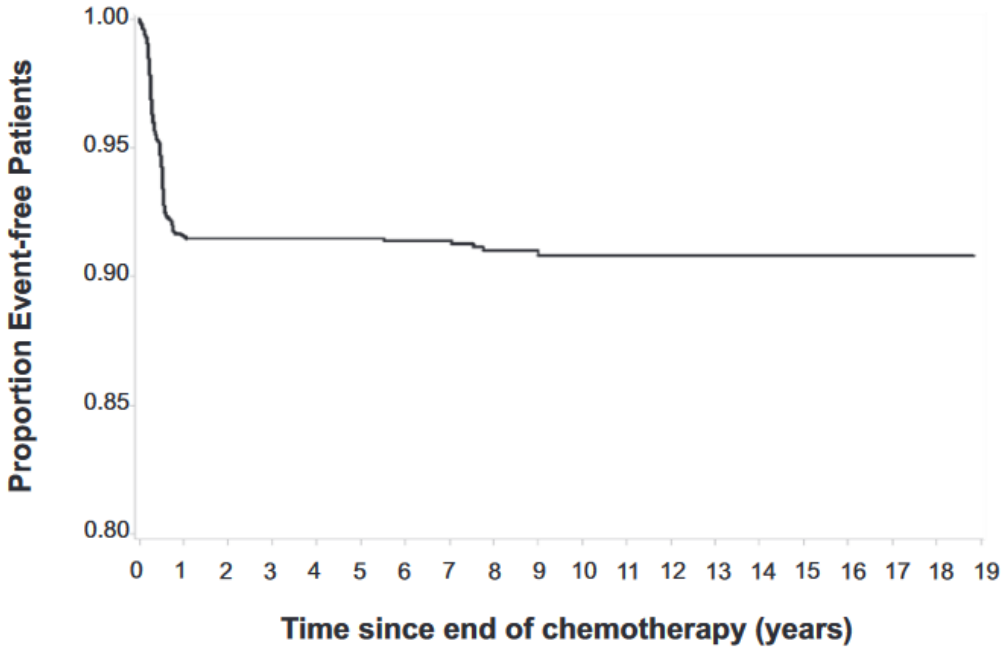
Definition	Incidence	Timing	Clinical manifestation
Acute	<1%	Immediately after infusion	Acute, transiet decline in myocaridal contractility
Early-onset chronic progressive	1.6-2.1%	During or <1y from end of treatment	Dilated CMP
Late-onset chronic progressive	1.6%-5%	>1y from the end of treatment (may become clinically evident 10-20y from end of treatment)	Dilated CMP

Old classification (1990s), based on retrospective small studies

Curigliano G, Ann Oncol 2012

Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

Daniela Cardinale, MD, PhD, FESC; Alessandro Colombo, MD; Giulia Bacchiani, MD; Ines Tedeschi, MSc; Carlo A. Meroni, MD; Fabrizio Veglia, PhD; Maurizio Civelli, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Giuseppe Curigliano, MD, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD



N tot=2625 cancer pts treated with anthracyclines

Prospective LVEF monitoring

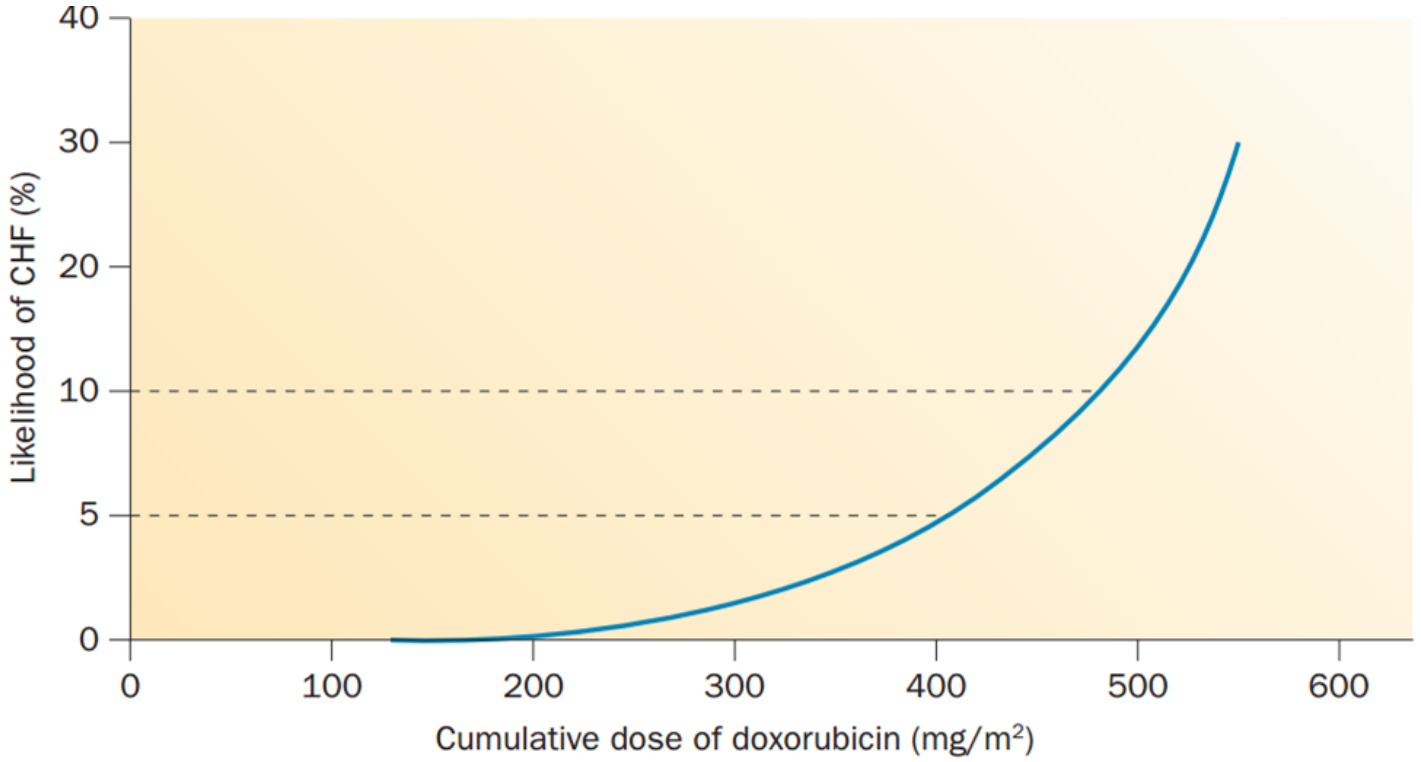
Cardiac tox definition: reduction in LVEF >10 percentage points from baseline and <50%

N=226 pts (9%) had cardiac toxicity, 98% within 1st year from end of CT

Cum Doxo dose 359±172 (tox) vs 299±144 (no tox) , p<0.001

Circulation, 2015

Cumulative doxorubicin dose and risk of congestive heart failure



	Cumulative life-time dose	Usual max dose in adjuvant BC treatment regimens
Doxorubicin	400-550 mg/mq	240 mg/mq
Epirubicin	900 mg/mq	360-540 mg/mq

Ewer, 2015, Nature Reviews Cardiology

Trastuzumab containing regimens for early breast cancer

Lorenzo Moja[1], Ludovica Tagliabue[2], Sara Balduzzi[3], Elena Parmelli[4], Vanna Pistotti[5], Valentina Guarneri[4], Roberto D'Amico[3]

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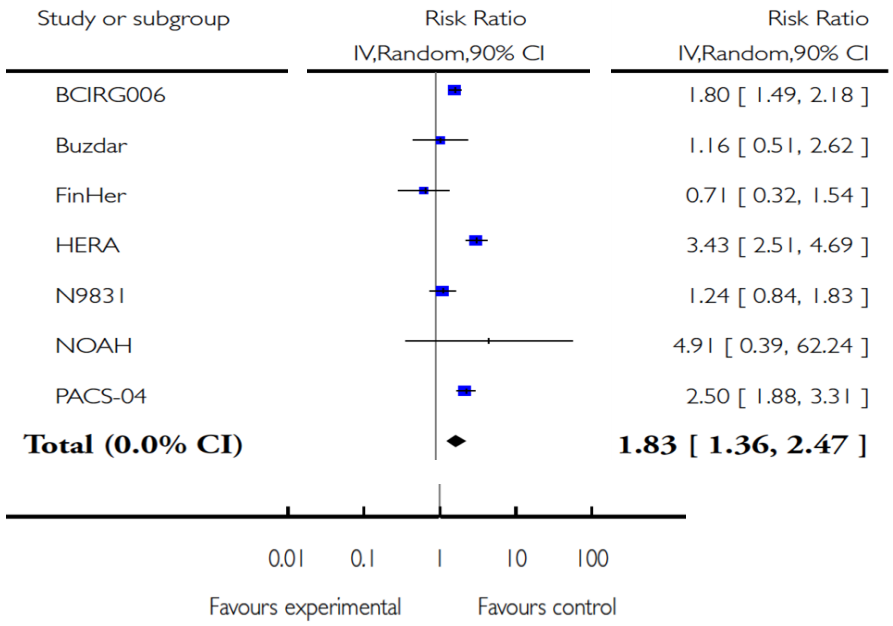
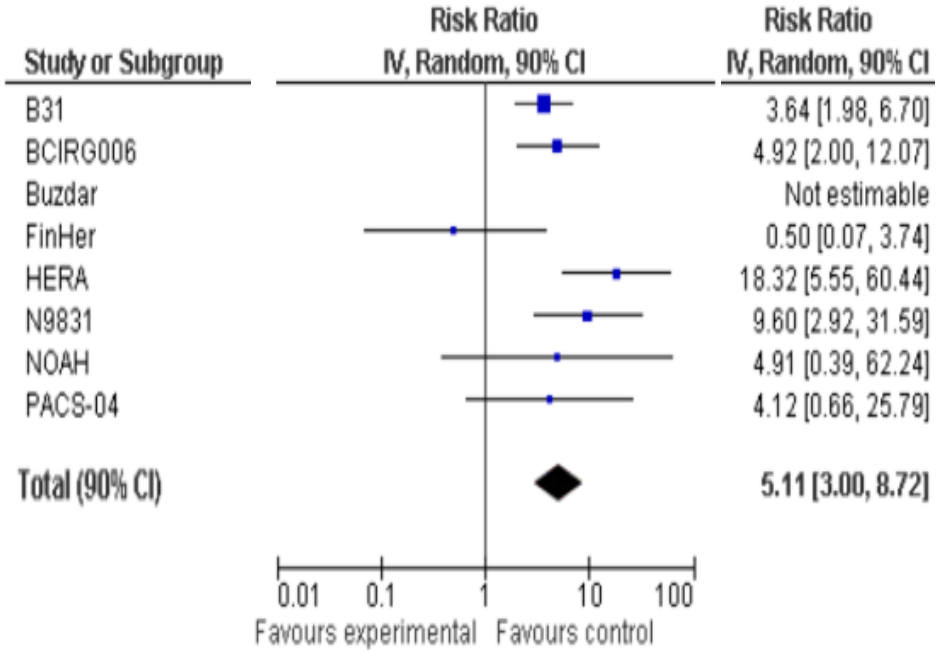
LVEF decline



Congestive heart failure



Total events 135 20

Heterogeneity: Tau² = 0.20; Chi² = 8.32, df = 6 (P = 0.22); I² = 28%

Test for overall effect: Z = 5.02 (P < 0.00001)

Moja,2012 The Cochrane Library

Cardiotoxicity related to anthracycline and trastuzumab containing treatment

Trial		Reported incidence in CHF (%)	Reported incidence of LV dysfunction (%)	Reversibility reported	Reported cardiac deaths (n)
NSABP B-31		4.0	-	Yes	1
NCCTG N9831	Arm B (AC→T→H)	2.8	7.8	Yes	1
	Arm C (AC→TH→H)	3.3	10.4	Yes	0
BCIRG-006	Anthracycline arm	2.0	18.6	Yes	0
FNCLCC-PACCS		1.5	11.1*	-	0

*severe LVEF decline

adapted from Ewer, 2015, Nature Reviews Cardiology

Recovery from trastuzumab-related cardiac toxicity in the HERA trial

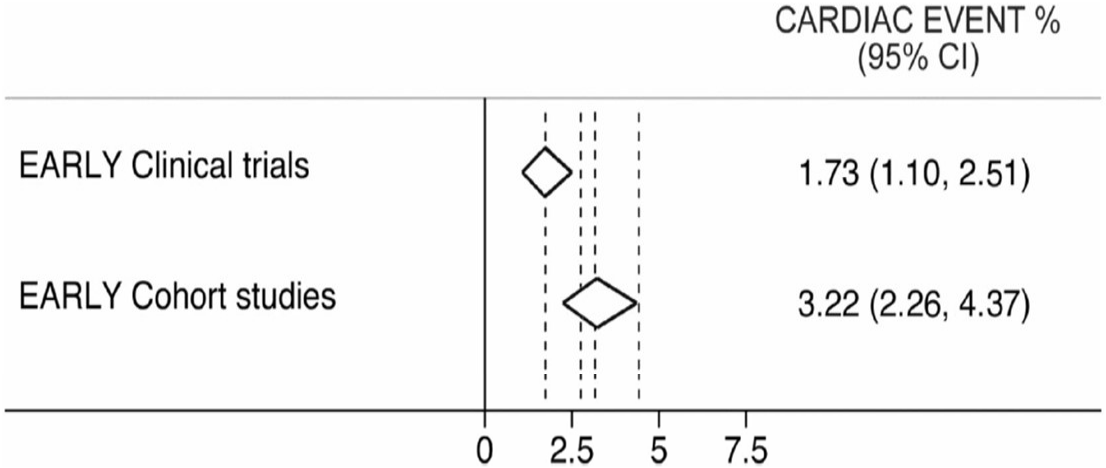
Table 4. Summary of Acute Recovery in the Trastuzumab Arms

Variable	1 Year of Trastuzumab				2 Years of Trastuzumab			
	No.	%	Median (months)*	Range (months)†	No.	%	Median (months)*	Range (months)†
Severe CHF	14				13			
Reached acute recovery	10	71.4			11	84.6		
Time to acute recovery			9.7	2.3-61.0			5.8	1.0-58.1
Occurrence of LVEF decrease < 50% after acute recovery	4	40.0			4	36.4		
Time to LVEF decrease < 50% after acute recovery			34.8	6.9-34.8			—	17.5-52.6
Confirmed significant LVEF decrease	69				120			
Reached acute recovery	56	81.2			105	87.5		
Time to acute recovery			6.3	0.7-31.3			8.3	0.5-71.7
Occurrence of LVEF decrease < 50% after acute recovery	21	37.5			36	34.3		
Time to LVEF decrease < 50% after acute recovery			87.8	6.0-87.8			—	2.8-67.8
Any cardiac end point	83				133‡			
Reached acute recovery	66	79.5			116	87.2		
Time to acute recovery			6.6	0.7-61.0			7.2	0.5-71.7
Occurrence of LVEF decrease < 50% after acute recovery	25	37.9			40	34.5		
Time to LVEF decrease < 50% after acute recovery			87.8	6.0-87.8			—	2.8-67.8

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction.
*Kaplan-Meier estimate of median.
†Range excluding censored values.
‡Three patients who experienced cardiac death were excluded.

De Azambuja E, J Clin Oncol 2014

Anthracycline and trastuzumab-related cardiotoxicity: REAL WORLD



Severe cardiac events at 2 yrs:
- CHF
- myocardial infarction
- cardiac dysrhythmia
- LVEF decline ≤40%
- grade III/IV cardiac toxicity
- grade II cardiac toxicities requiring specific pharmacological treatment

Cardiovascular risk factors	Number of studies	Number of patients	Cases	Proportion, % (95 % CI)
Age ≥60	7	3526	139	4.91 (3.22–6.94)
History of cardiac diseases	2	92	17	19.12 (11.85–27.63)
Hypertension	6	1503	74	5.47 (3.40–7.99)
Diabetes	4	167	11	6.19 (0.85–15.93)
Dyslipidemia	3	357	15	4.43 (2.54–6.78)
Body mass index (BMI) ≥25	4	898	36	6.49 (2.34–12.51)
Smoking	2	343	16	5.31 (2.15–9.75)

Mantarro, 2016 Int Emerg Med

Cardiotoxicity from adjuvant anthracycline and trastuzumab for BC: Clinical considerations

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- **Strategies to minimize cardiac risk**
  - Who can be spared anthracyclines?
  - De-escalated trastuzumab-containing regimens
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Avoid overtreatment: de-escalated strategies

- Sparing chemotherapy for low-risk HR+/HER2- early breast cancer patients:
  - Clinicopathological factors
  - Multigene assays (LoE1A for Mammaprint[1] and Oncotype DX[2])

- Avoid anthracyclines for patients candidate to adjuvant chemotherapy
  - recent data from joint analysis of RCTs suggest that taxane-based anthracycline-free CT may be an option especially for HR+ N0[3]

- Liposomal anthracycline formulations (MBC)

- Reduce the burden of treatment for HER2+ patients candidate to adjuvant chemotherapy and trastuzumab

Clinical decision must be taken based on an accurate comorbidities assessment

[1]Cardoso F, NEJM 2016; [2]Sparano J, NEJM 2015 & 2018; [3]Blum JL, J Clin Oncol 2017

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[1]Cardoso F, NEJM 2016; [2]Sparano J, NEJM 2015 & 2018; [3]Blum JL, J Clin Oncol 2017

CURRENT OPINION

Escalation and de-escalation in HER2 positive early breast cancer

2018

Maria Vittoria Dieci[a,b], *Grazia Vernaci*[a], *and Valentina Guarneri*[a,b]

Randomized noninferiority trials of short vs. 1 year adjuvant trastuzumab

Study	N	Median FU (years)	Treatment arms	Efficacy		Cardiac events (according to protocol definition)	
				% DFS	HR 95% CI	% events	P
PERSEPHONE [30▪▪]	4088	4.9	CT (Center's choice) + H for 6 m CT (Center's choice) + H for 12 m	4 yrs 89.4% 4 yrs 89.8%	1.07 (0.93–1.24) [a]	4% [f] 8% [f]	<0.0001 [f]
PHARE [31,32]	3380	3.5	CT → H (6 m) CT → H (12 m)	2 yrs 91.1% 2 yrs 93.8%	1.28 (1.05–1.56) [b]	4.0% 6.6%	<0.001
SOLD [33▪]	2174	5.2	TH (9 w) →FEC TH (9 w) →FEC → H (up to 12 m)	5 yrs 88.0% 5 yrs 90.5%	1.39 (1.12–1.72) [c]	2% 4%	0.01
ShortHER [34▪]	1253	5.2	3 wT + wH (9 w) → FEC AC → 3 wTH →H (up to 12 m)	5 yrs 85.4% 5 yrs 87.5%	1.15 (0.91–1.46) [d]	5.2% 14.4%	<0.0001 [g]
HORG [35]	481	3.9–4.25	ddFEC → ddT + H (6 m) ddFEC → ddT + H (12 m)	3 yrs 93.3% 3 yrs 95.7%	1.57 (0.086–2.10) [e]	0.8% 0%	NA

Earl HM, ASCO 2018; Pivot X, Lancet Oncol 2013; Joensuu H, JAMA Oncol 2018; Conte P, Ann Oncol 2018; Mavroudis D, Ann Oncol 2015

Cardiac Outcomes of Patients Receiving Adjuvant Weekly Paclitaxel and Trastuzumab for Node-Negative, ERBB2-Positive Breast Cancer

APT trial

- HER2 (+)
- Node (-)
  - micro-mets allowed
- Size ≤ 3.0 cm

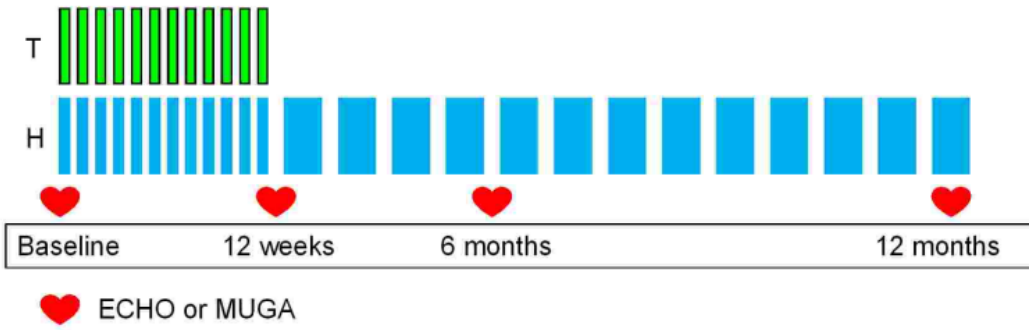

Table 3. Summary of LVEF at Protocol-Specified Time Points and Changes From Baseline Values

Characteristic	No. (%) Baseline	12 weeks	6 mo	1 y
LVEF reduction from baseline				
<10%		343 (84)	325 (80)	302 (74)
10%-15%		29 (7)	36 (9)	35 (9)
≥16%		2 (<1)	5 (1)	7 (2)

- 2 patients (0.5%) developed grade 3 LVSD.
- 13 patients (3.2%) had significant asymptomatic LVEF decline, 11 of whom completed study treatment.

Dang 2016 JAMA

Cardiotoxicity from adjuvant anthracycline and trastuzumab for BC: Clinical considerations

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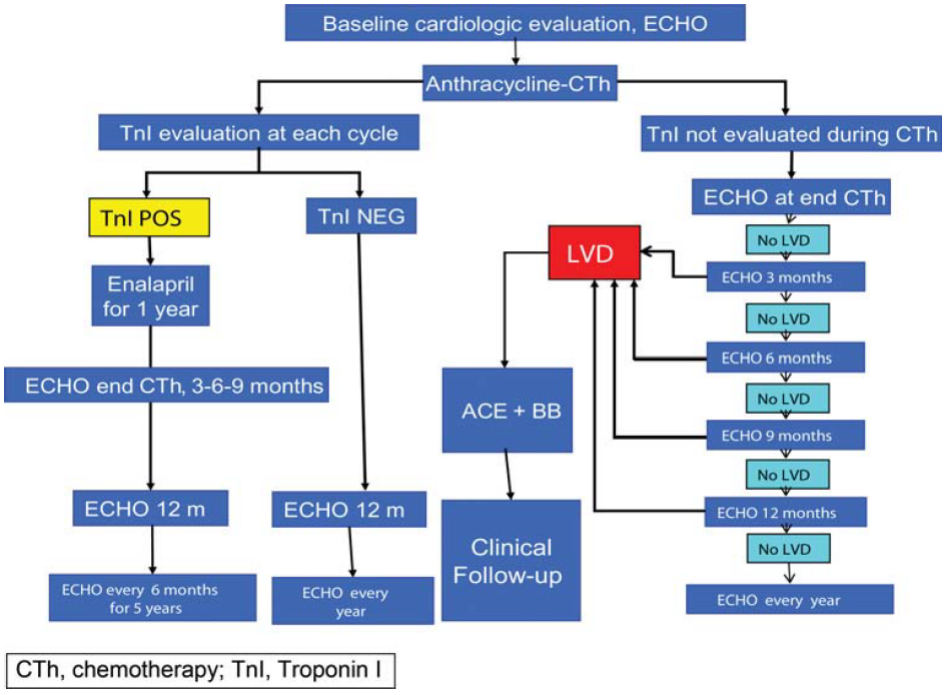
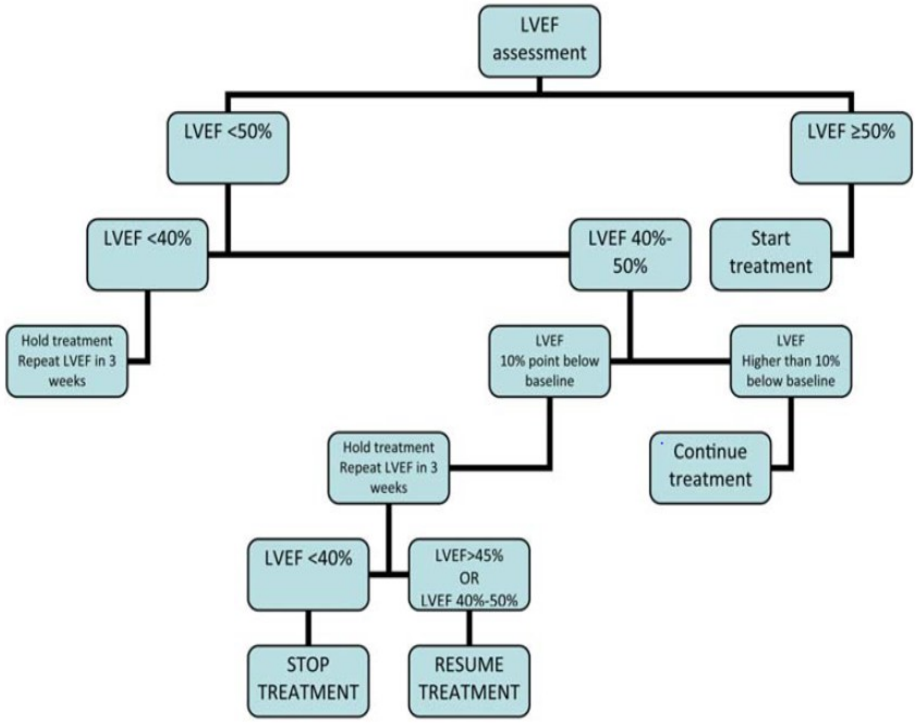
Baseline cardiac function assessment as screening procedure: ESMO guidelines

Anthracycline



Trastuzumab



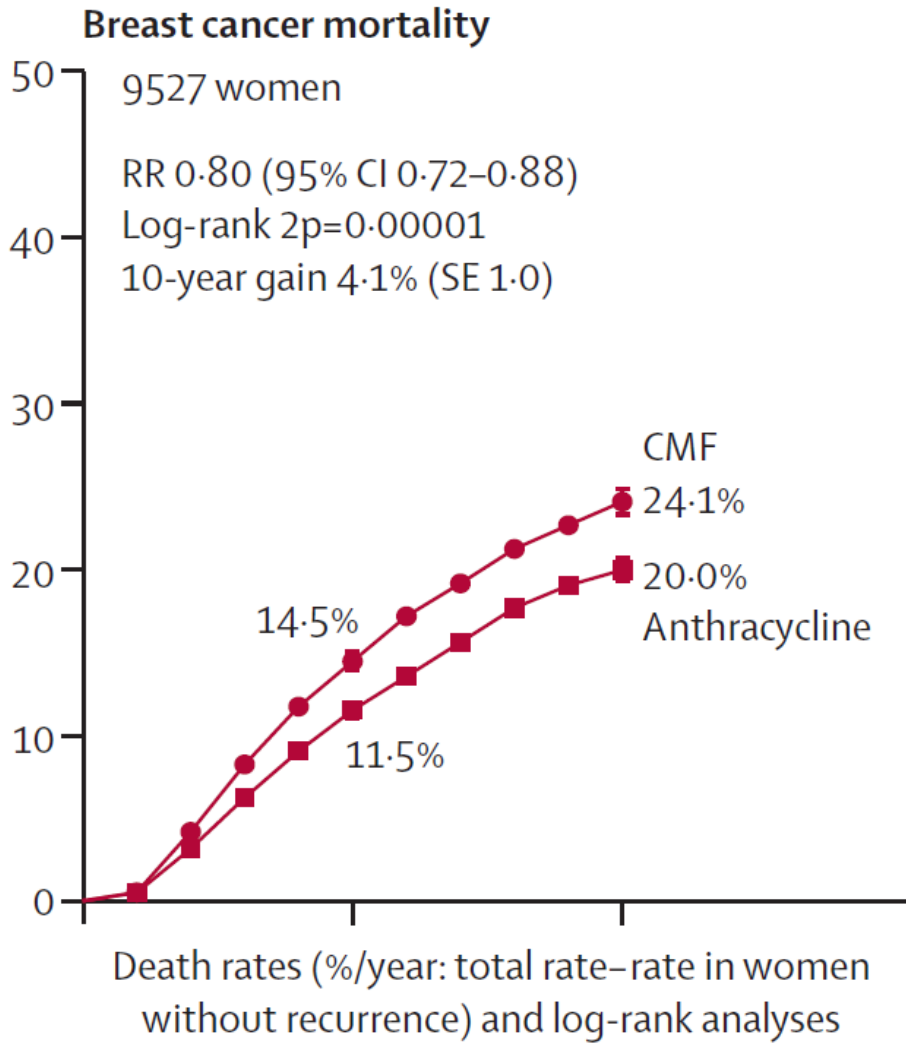
LoE III-B for TnI & other biomarkers

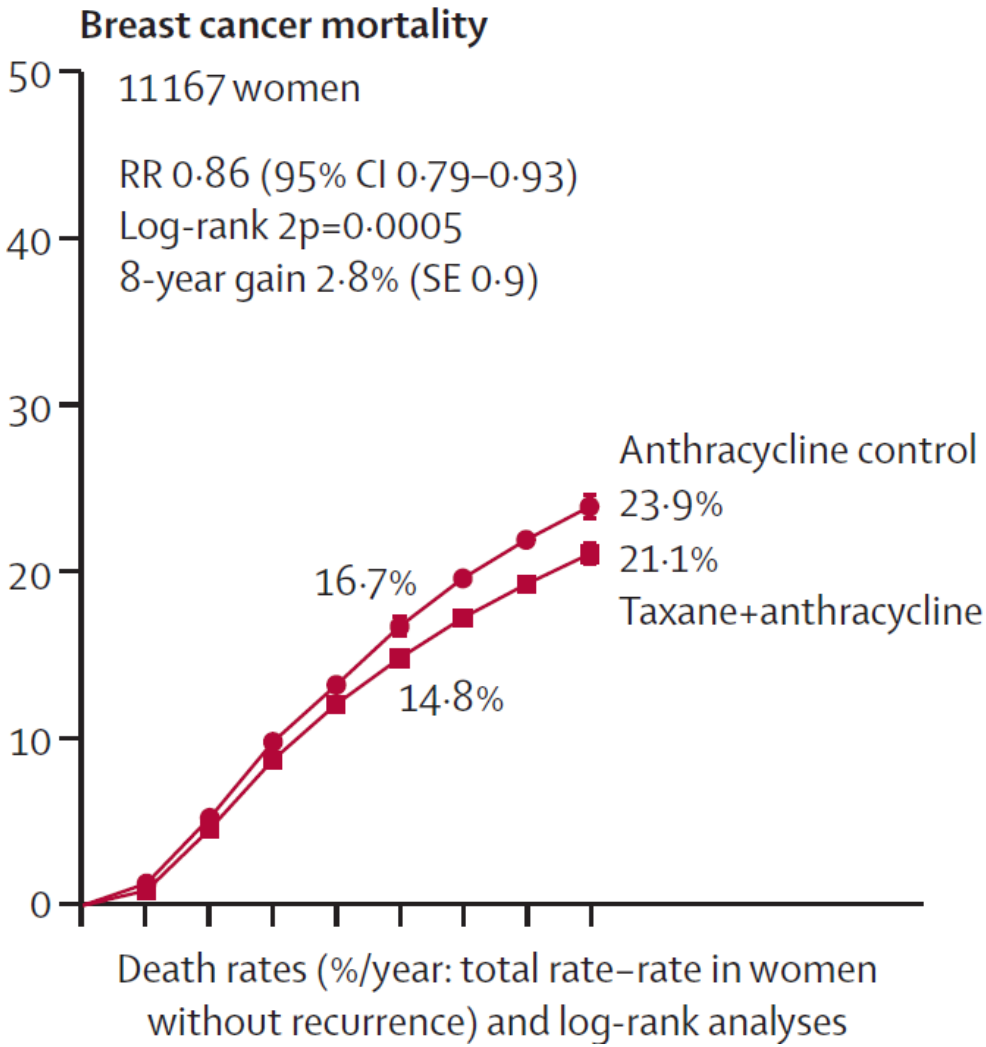
Curigliano, 2012 Annals of Oncology

Conclusions

- Advances in screening and adjuvant treatments has led to an improvement in BC survival.
- Anthracycline-based and trastuzumab-containing regimens have become the standard of care for EBC based on a survival advantage, but at the price of increased risk of cardiotoxicity.
- Real-world patients present more frequently with older age and comorbidites as compared to patients in clinical trials.
- De-escalated therapeutic options are now available, allowing for treatment modulation based on baseline risk of relapse and toxicity.
- In this evolving scenario, multidisciplinary collaboration is warranted in order to develop updated personalized monitoring and cardioprotection algorithms.

EBCTCG meta-analyses: anthracycline-based regimens

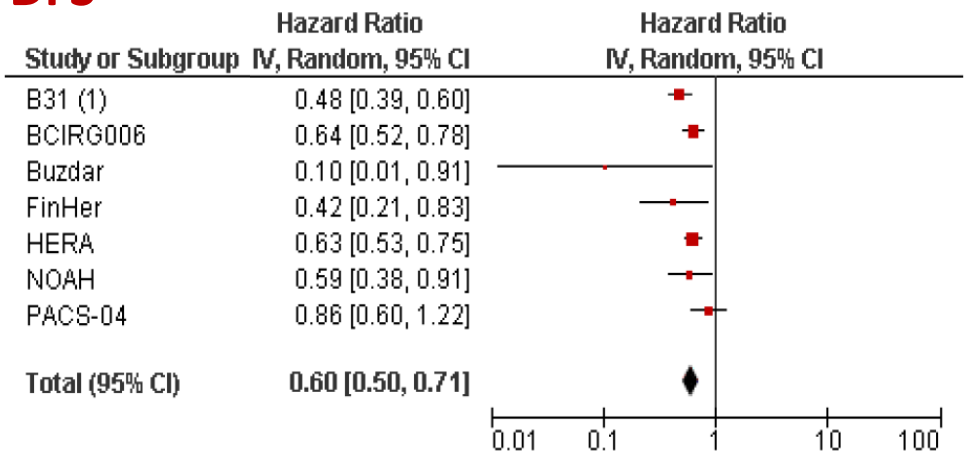




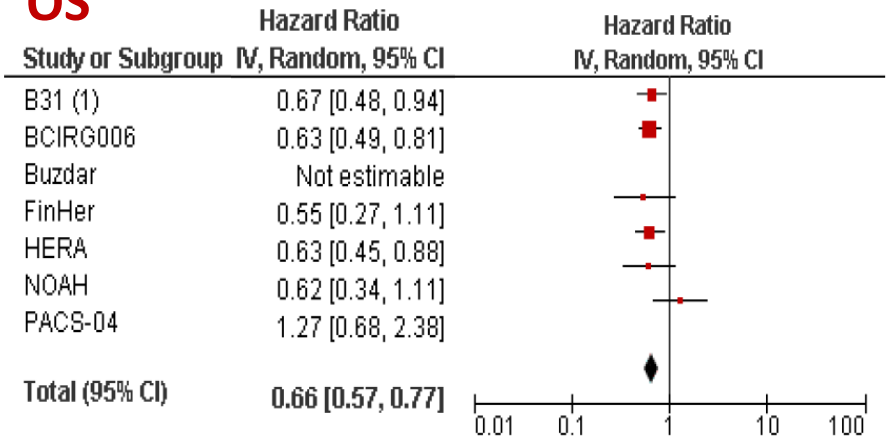
Lancet 2012

Trastuzumab for HER2+ early BC: a paradigmatic story of success

DFS



OS

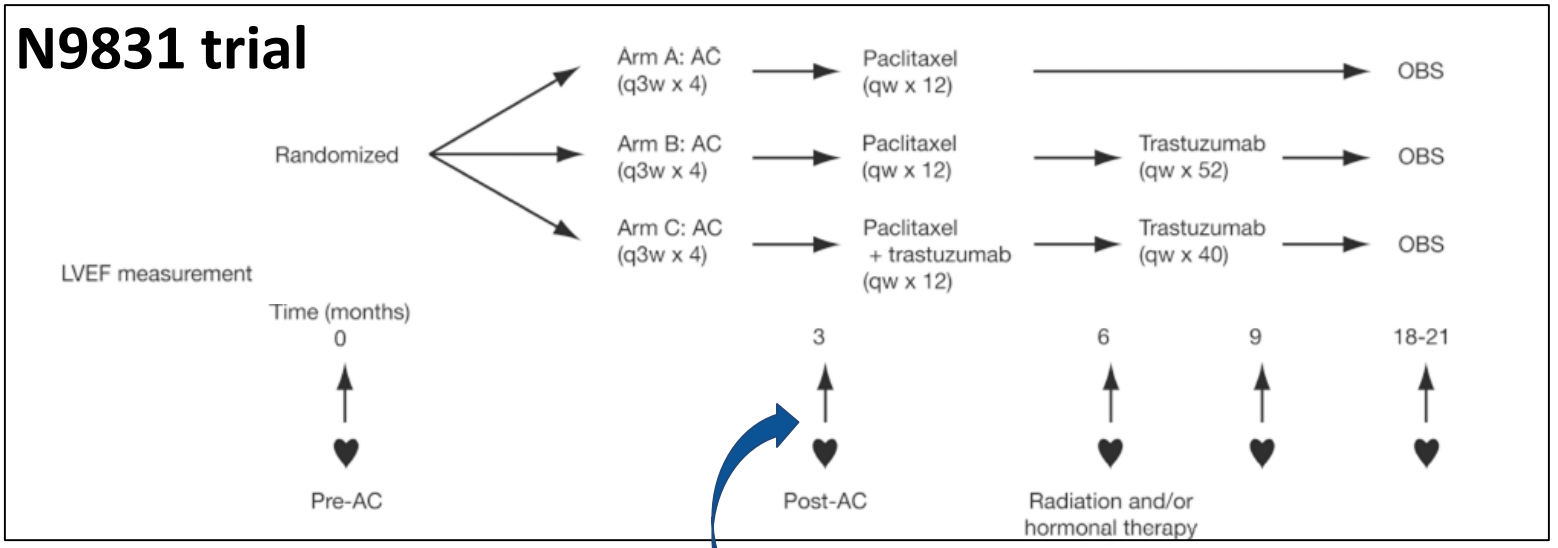


STANDARD: 1 year of trastuzumab with chemotherapy (Anthra→Tax+Trast→Trast)

THE COCHRANE COLLABORATION®

Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D'Amico R

Cardiotoxicity immediately after anthracycline-based adjuvant CT



Post-AC LVEF level

- decrease >15% in 2.6%
- ≤15% to below the LLN in 2.4%

5% of patients had post-AC LVEF decreases that did not allow the administration of trastuzumab

Perez, 2008 JCO