



Cardiovascular complications to new anti-cancer drugs

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Chemotherapy and cardiotoxicity

Problem size

Specific treatments

- Anthracyclines

- Tyrosine kinase inhibitors

 - small molecule based

 - antibody based

- Antimetabolites

Cardiac toxicity

- Heart failure

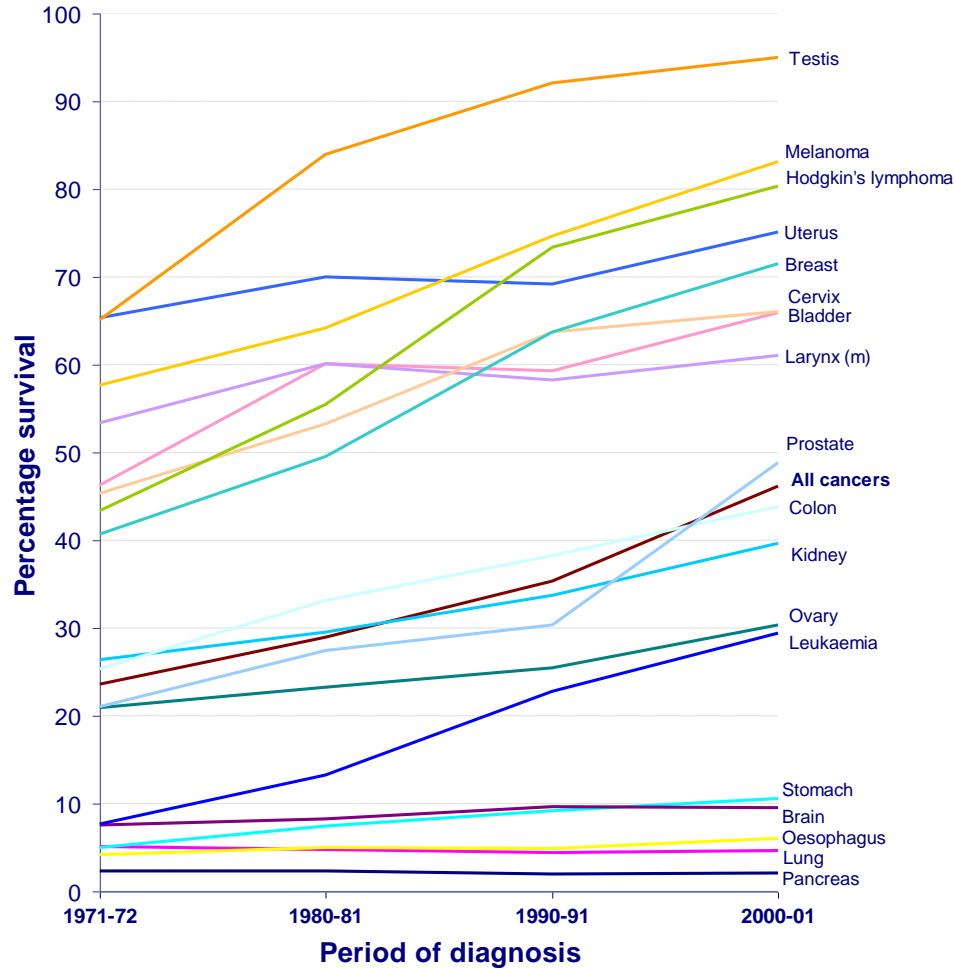
- Coronary disease

- SCD

Prevention and management

Cancer survival

Figure 1.2: Ten year relative survival of adults* diagnosed with cancer in England and Wales, 1971-2001



Childhood cancer

80% of children with cancer become long-term survivors.

In 2010 1 in 500 individuals between 21-40 years have had a childhood cancer.

Long-term survivors of childhood cancer: comparison with siblings

Condition	Survivors (N=10,397) <i>percent</i>	Siblings (N=3034) <i>percent</i>	Relative Risk (95% CI)
Major joint replacement*	1.61	0.03	54.0 (7.6–386.3)
<u>Congestive heart failure</u>	1.24	0.10	15.1 (4.8–47.9)
Second malignant neoplasm†	2.38	0.33	14.8 (7.2–30.4)
Cognitive dysfunction, severe	0.65	0.10	10.5 (2.6–43.0)
<u>Coronary artery disease</u>	1.11	0.20	10.4 (4.1–25.9)
<u>Cerebrovascular accident</u>	1.56	0.20	9.3 (4.1–21.2)
Renal failure or dialysis	0.52	0.07	8.9 (2.2–36.6)
Hearing loss not corrected by aid	1.96	0.36	6.3 (3.3–11.8)
Legally blind or loss of an eye	2.92	0.69	5.8 (3.5–9.5)
Ovarian failure‡	2.79	0.99	3.5 (2.7–5.2)

Specific treatment groups

Anthracyclines: cardiotoxicity

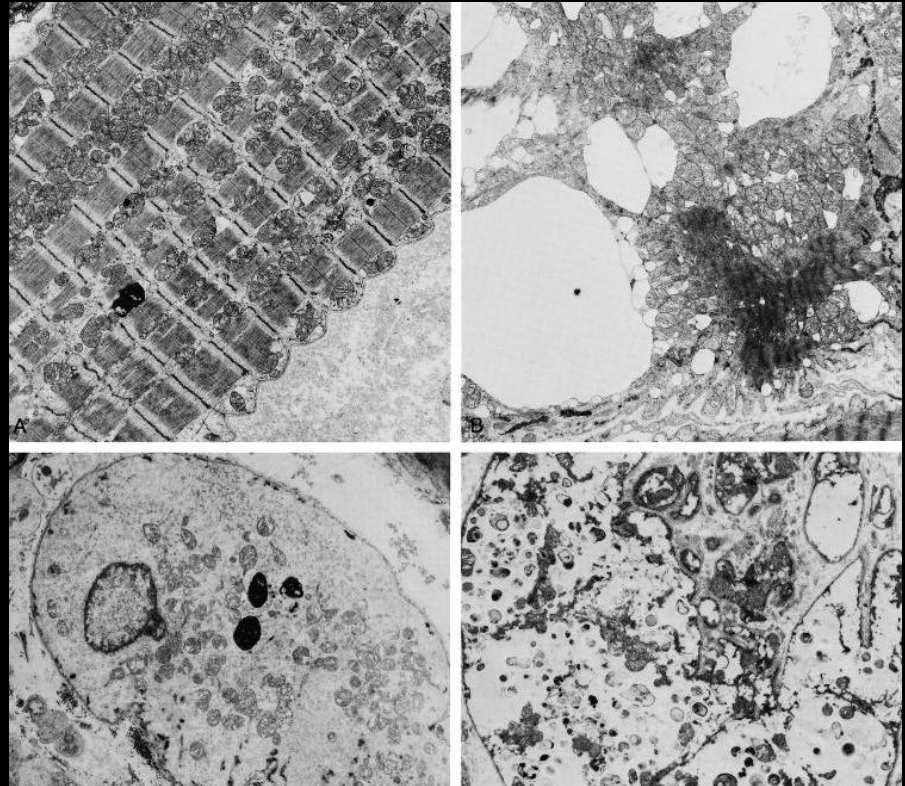
Acute

Chronic, progressive

Dose-dependent

Free radicals involved

Specific histologic picture



Anthracyclines

Cumulated dose dependency:

Doxorubicin-induced HF:

3-5% at 400 mg/m²

7-26% at 550 mg/m²

18-48% at 700 mg/m²

Maximum lifetime cumulated dose for doxorubicin: 400-550 mg/m²

Risc for cardiotoxicity increased by:

IV bolus

Previous radiation

Concomitant use of other cardiotox drugs
(cyclofosfamide, trastuzumab, paclitaxel)

Female

Previous cardiac disease

Age

Time from treatment

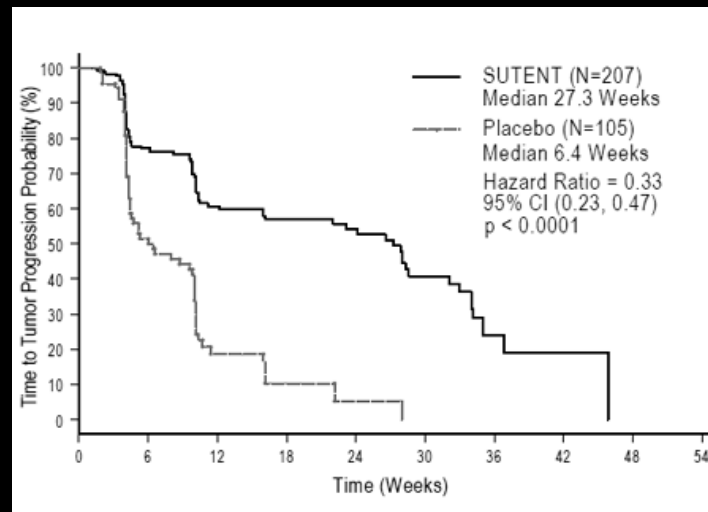
Anthracyclines

Despite this knowledge heart failure after anthracycline treatment remains a considerable clinical problem.

Tyrosine kinase inhibitors

Sunitinib (Sutent) (small molecule TKI)

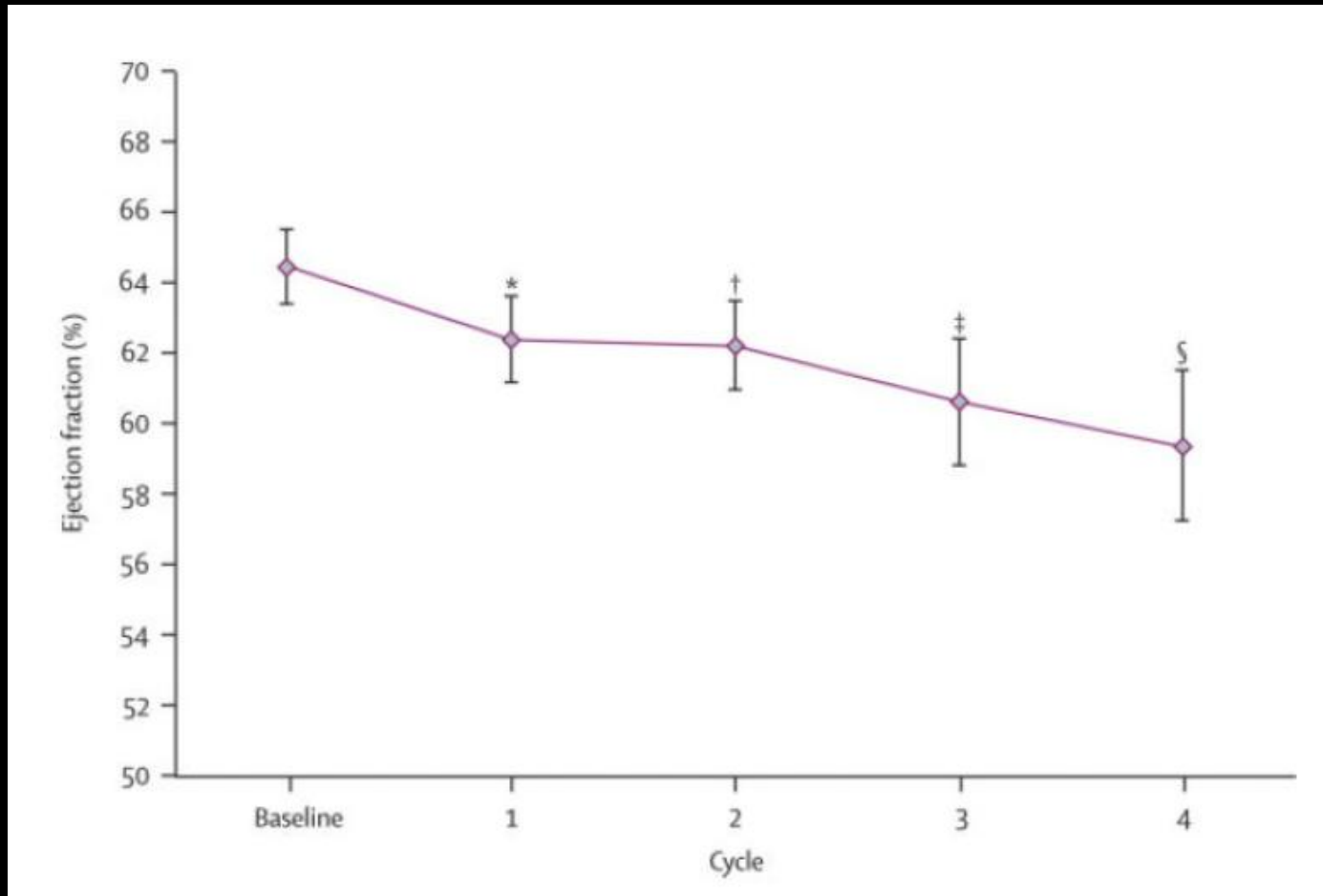
Sunitinib is used in the treatment for advanced renal cell carcinoma, chronic myeloid leucemia and certain GI cancers.



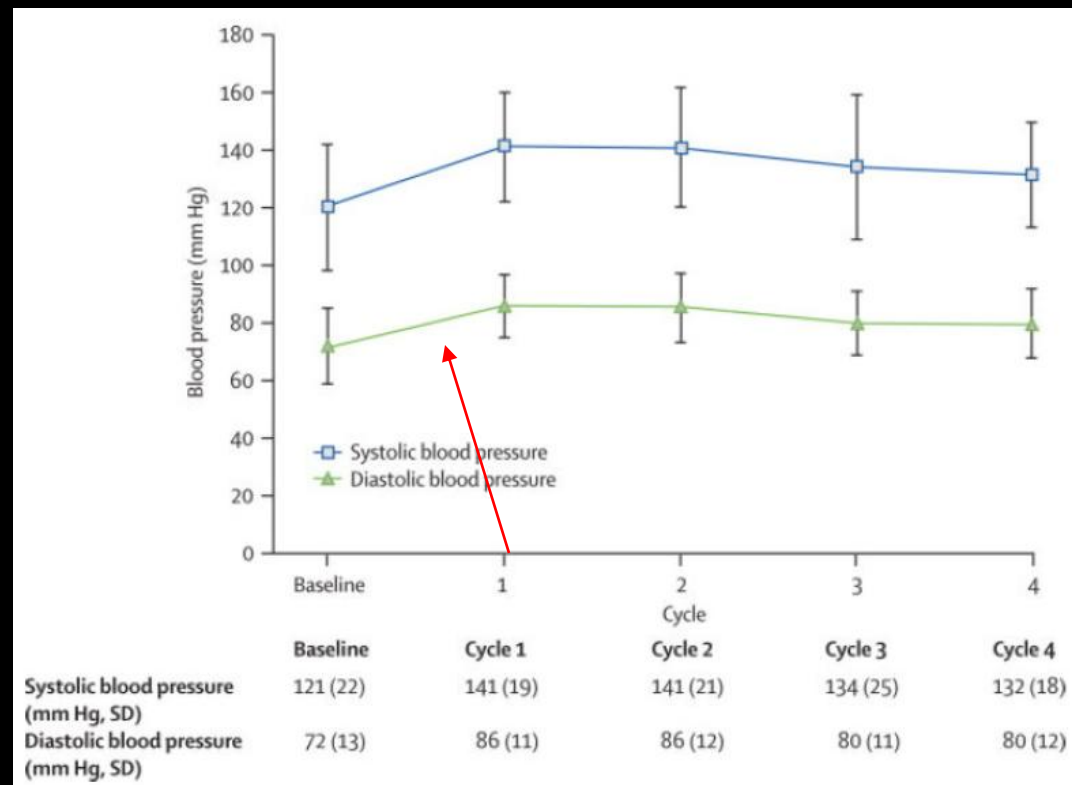
Tyrosin kinase inhibitors are designed to inhibit mutated kinases, typically produced by tumours to a large extent.

However, they also inhibit kinases present in normal cells i.e. cardiomyocytes

Sunitinib: effect on LVEF



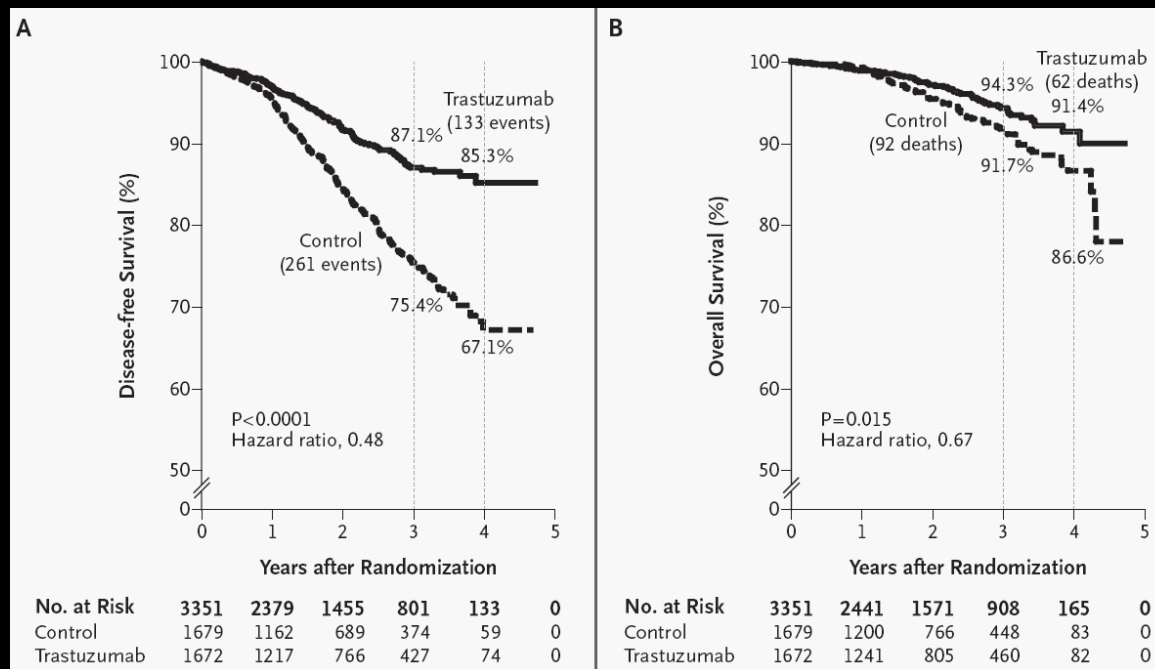
Sunitinib: development of hypertension



Hypertension may contribute to the effect on LVEF with respect to the development of clinical HF

Trastuzumab

Trastuzumab (Herceptin) – monoklonal antibody blocking human epidermal growth factor receptor-2 (HER-2 receptors)
Reduces mortality in Her-2+ breast cancer



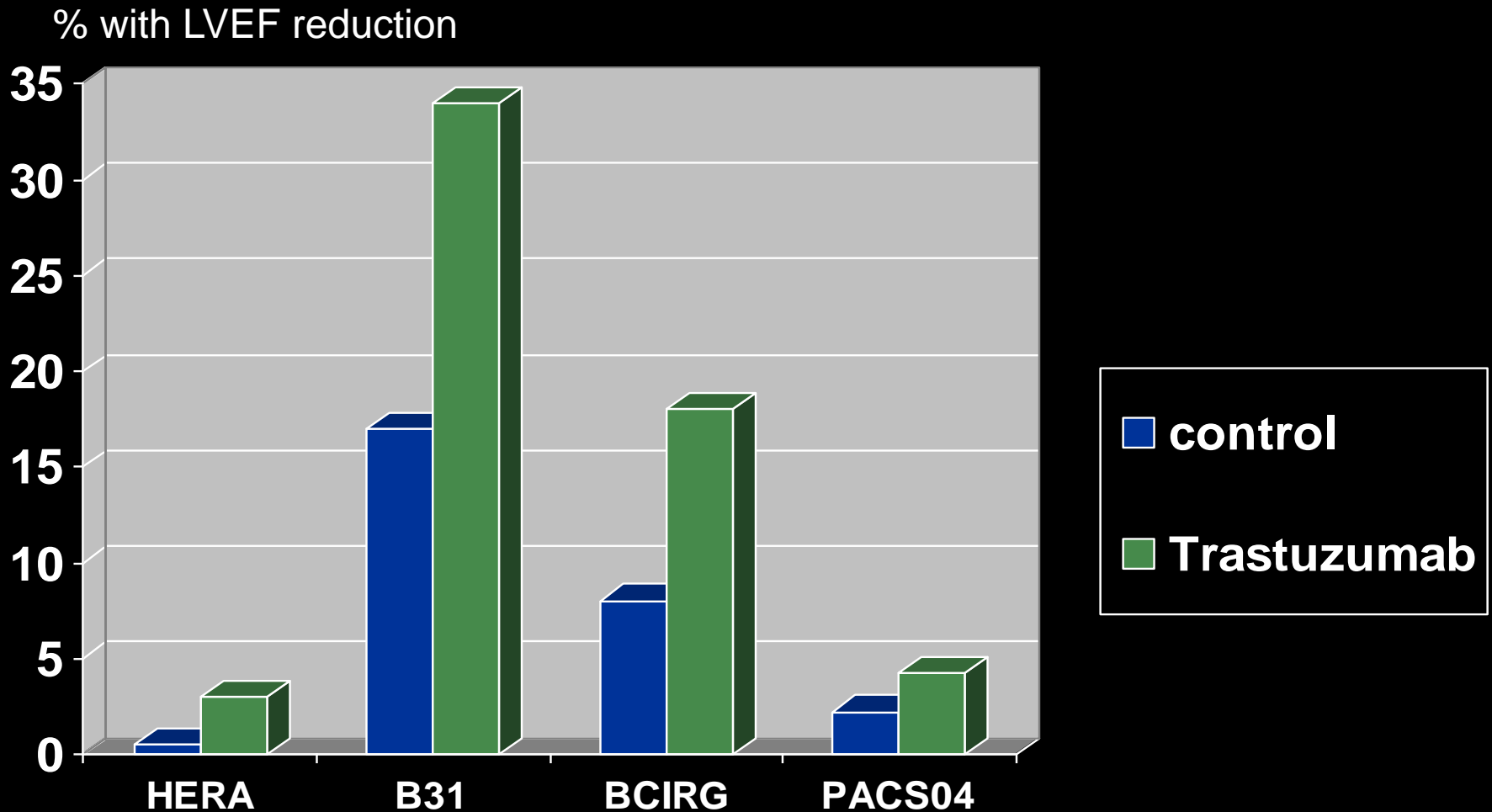
Trastuzumab (Herceptin)

HER-2 is essential in cardiac embryogenesis and adult myocardium expresses HER-2 receptors.

HER-2 cardiac knock-out mice develop a severe cardiomyopathy.

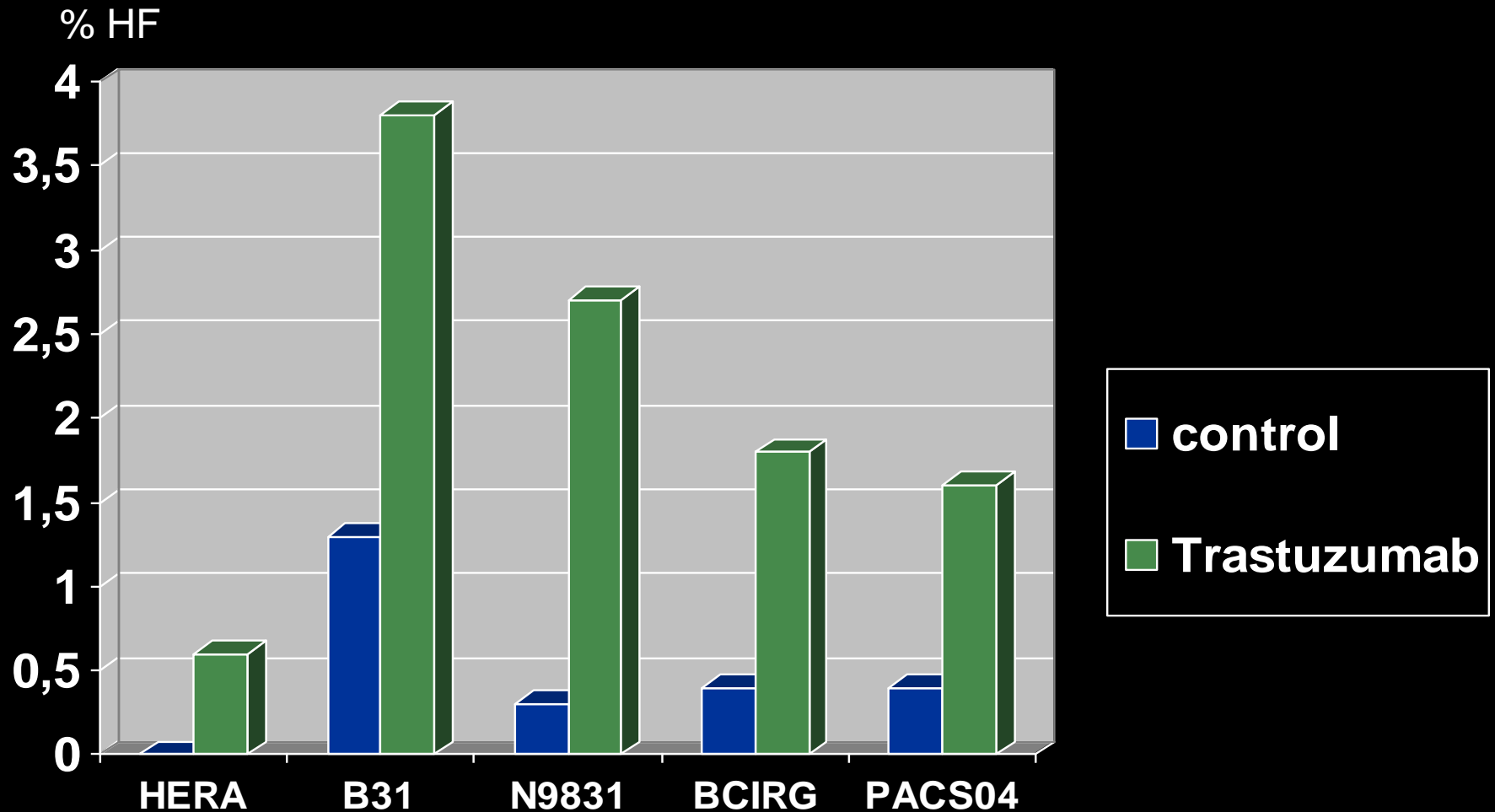
Decline in LVEF

Def: drop greater than 10% or LVEF < 45%



Development of HF

1-3 yr. Follow-up



Herceptin HF-risks

- General: approximately 3%
 - in conjunction with anthracyclines: up to 27%
- Cardiotoxicity most often is reversible.
- As for anthracyclines serial monitoring of cardiac function is recommended

Monitoring of cardiac function

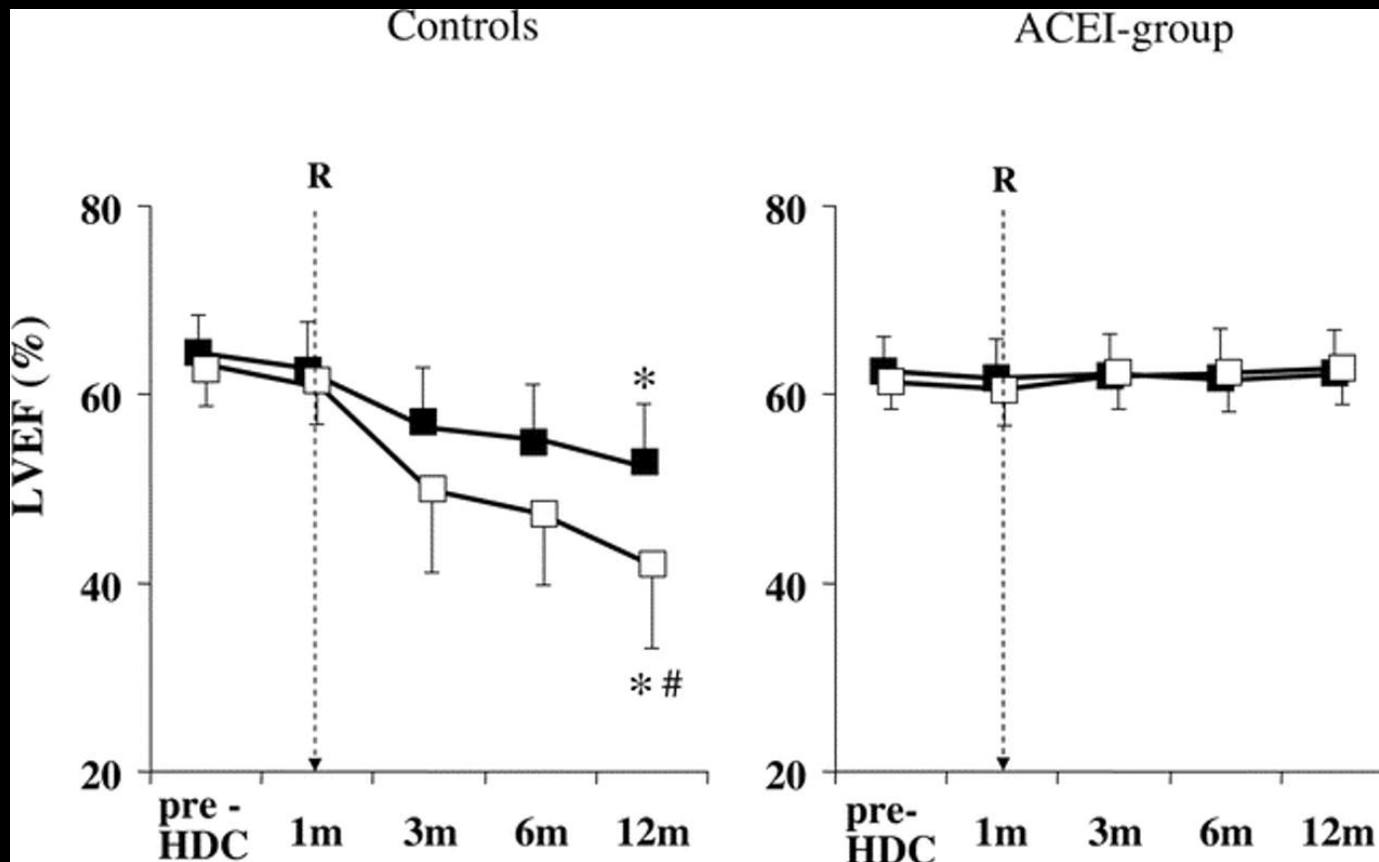
- Echo
- MUGA / RNA (gold standard in oncology?)
- Troponin T
- NTproBNP or BNP
- (MRI)

Proposed monitoring in patients treated with Herceptin

LVEF evaluated before treatment initiation (Echo or MUGA / RNA scan).

LVEF evaluation every 3 months until treatment termination and subsequently every 6 months for 2 years.

Prevention of post anthracycline LV dysfunction by prophylactic ACE-I



Management of LV dysfunction due to chemotherapy

- Prevent! –monitor dose, use lower risk regimens
- Once developed: ACE-inhibitors and beta blockers (ACC/AHA/ESC guidelines)
- Transplantation ?
- Left ventricular assist devices.

Antimetabolites

Flourouracil - 5FU

Used for breast and colonic cancer

Cardiotoxicity:

Most often angina, but sometimes VT, SCD, HF.

Mechanism most often coronary vasospasm and/or thrombosis.

Cardiotoxicity seen in 1-68% of patients.

Risk factors: High dose (>800 mg/m²) and continuous infusion.

Flourouracil - 5FU

Antianginal prevention and treatment

No.	Chemotherapy	Appearance of cardiotoxicity course (day)	Subsequent chemotherapy at minimum dose		Anti-angina therapy			
			Dose (%) baseline	Courses	Prevention		Intervention	
	First line Second line Third line					Efficacy		Efficacy
26	5-FU	2 (4)	100	4	None		None	
27	5-FU	4 (7)	100	2	None		None	
17	5-FU	1 (6)	100	5	None		None	
6	5-FU	1 (4)	100	5	BB	No	NTG	Yes
21	5-FU	1 (4)	100	5	None		NTG	Yes
2	5-FU	3 (3)	80	–	CCA	No	NTG	Yes
1	5-FU	1 (6)	75	4	CCA, nitrate	No	NTG	Yes
14	5-FU	5 (5)	70	1	None		None	
22	5-FU	2 (5)	70	4	None		NTG	Yes
23	5-FU	5 (6)	50	1	None		None	
4	5-FU	5 (5)	50	1	CCA	Yes	NTG	Yes
3	5-FU	1 (4)	–		BB	No	–	
5	5-FU	2 (6)	–	0	None		None	
7	5-FU	1 (3)	–	0	CCA, nitrate	–	NTG	Yes
9	5-FU	5 (6)	–	0	–		–	
11	5-FU	2 (5)	–	0	None		None	
29	5-FU	3 (6)	100	3	None		None	

Myocardial ischemia

Chemotherapy Agents	Incidence (%)	Frequency of Use
Antimetabolites		
Capecitabine (Xeloda) (71,74,83-85)	3-9	+++
Fluorouracil (Aducci) (8,70,71,73-79)	1-68*	+++
Antimicrotubule agents		
Paclitaxel (Taxol) (90,91)	<1-5	+++
Docetaxel (Taxotere) (10,92)	1.7	++
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab (Avastin) (10,93,94)	0.6-1.5	++
Small molecule tyrosine kinase inhibitors		
Erlotinib (Tarceva) (10)	2.3	+++
Sorafenib (Nexavar) (10,96)	2.7-3	+++

Management of ischemia w/ 5-FU or Xeloda

- Angiogram as needed- treat stenoses
- Nitrates or CCB
- Antiplatelets
- Admission and monitoring during 5FU infusions in high risk patients.

Chemotherapy and hypertension

Chemotherapy Agents	Incidence	Frequency of Use
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab (Avastin) (18,19,107-112)	4-35	++
Small molecule tyrosine kinase Inhibitors		
Sorafenib (Nexavar) (96,113-116)	17-43	+++
Sunitinib (Sutent) (37,118-122)	5-47	+++

Conclusions (1)

- More cancer survivors = more patients with post-chemo cardiac disease.
- New agents are responsible for development of HF in addition to classic agents such as anthracyclines
- Monitoring, prevention and aggressive early treatment of LV dysfunction is necessary

Conclusions (2)

Antimetabolites induce myocardial ischemia which seems to be an increasing problem

Optimal strategies to deal with this issue are not available- further research needed

With the already existing problems and given the number of new drugs in development close collaboration between oncologists and cardiologists, is necessary and ongoing systematic evaluation of the process and guideline development is warranted.