Cardiovascular Complications of Cancer Treatment

Focus on Early Detection

Aaron L Sverdlov

MBBS, PhD, FRACP, FCSANZ, FESC, FHFA, FACC

Heart Foundation Future Leader Fellow

A/Prof & Director of Heart Failure

Co-Director, Cancer and the Heart Program

University of Newcastle, HMRI, HNELHD, John Hunter Hospital, Calvary Mater Newcastle

Why discuss heart disease and cancer? Let's consider…

- **These are by far the two most common disease conditions in the developed world**
- Cardiac disease may pre-exist cancer therapy or may be caused/exacerbated by it
- Cancer therapy is more effective than ever before at treating cancer, but has a price...
- Therapeutic choices for both cardiology and oncology have significant overlap

Cancer and the heart

- Cancer in the Heart
  - Primary Cardiac Tumours: benign and malignant
  - Metastases from other tumours

- ***Cardiovascular complications of cancer therapy (termed cardio-oncology)***
  - *Survivors of cancer years ago*
  - *Active Cancer Treatment and Heart Disease*
    - ***Medical therapy***
    - ***Radiotherapy***

Not a new problem…

DAUNOMYCIN, AN ANTITUMOR ANTIBIOTIC, IN THE TREATMENT OF NEOPLASTIC DISEASE

Clinical Evaluation with Special Reference to Childhood Leukemia

CHARLOTTE TAN, MD, HIDEKO TASAKA, MD, KOU-PING YU, MD, M. LOIS MURPHY, MD, AND DAVID A. KARNOFSKY, MD

Daunomycin is a new antibiotic in the anthracycline group obtained from Streptomyces peucetius. It consists of a pigmented aglycone (daunomycinone) in glycoside linkage with an amino sugar (daunosamine). Differences in the biological effects of daunomycin, which reacts with DNA, and actinomycin D which complexes with DNA in a different manner to inhibit RNA production, are discussed. The toxic effects of daunomycin are a severe local reaction if the drug extravasates, bone marrow depression resulting in leucopenia, anemia, thrombocytopenia and bleeding, fever, oral ulcers and alopecia. In patients receiving maintenance doses of daunomycin the development of tachypnea, tachycardia pulmonary insufficiency, heart failure and hypotension possibly is associated with daunomycin but the evidence is unclear. Sixty per cent of children with leukemia obtained brief complete or partial hematological remissions from a single course of daunomycin. The remission could be prolonged by maintenance therapy. Daunomycin is temporarily effective in some cases of neuroblastoma, reticulum cell sarcoma and rhabdomyosarcoma.

Cancer 1967

How to deal with the “collateral damage” caused by oncologists & haematologists

“We’ve found a mass. The good news is we have weapons of mass destruction.”

Cardio-oncology – new field

1st International Conference on Cancer and the Heart, Houston, Texas, 2010

Patient comment

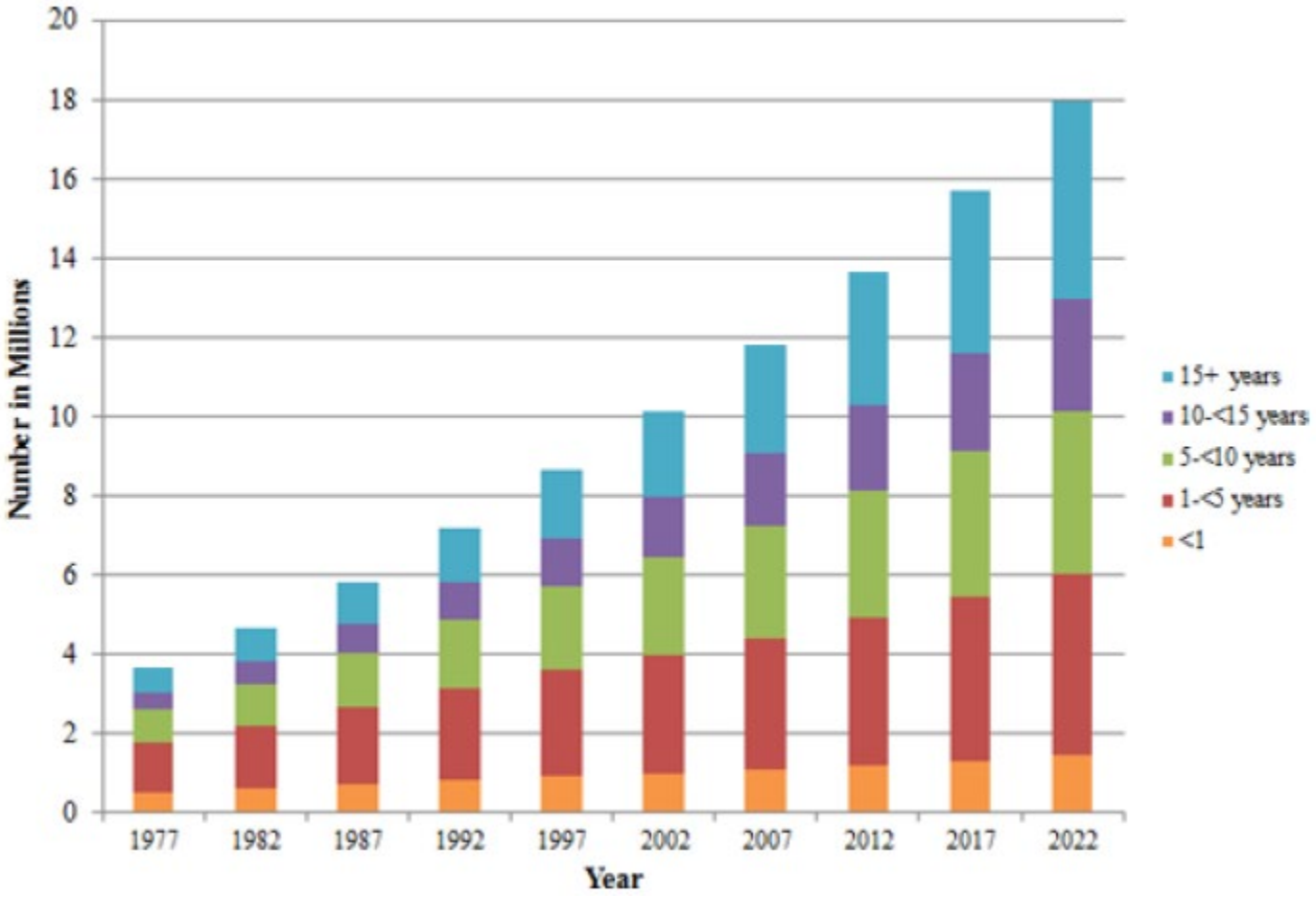
"When I was diagnosed with cancer I felt I could cope and was very positive, but when they said my heart was failing as well, this was too much to bear."

Improvements in longevity after cancer

Site	1975 (%)	2007 (%)	% increase
Overall	50	67	17
Childhood	30	79	49
Prostate	67	99	32
Breast	75	90	15
Colon	51	65	14
Lung	12	16	4

- Dramatic improvements in early detection and adjuvant therapy → significant survival gains
- Approx 30 million cancer survivors worldwide
- Increased risk of the late-effects of cancer therapy
- Commonest childhood cancer - acute lymphoblastic leukaemia
  - 5 year survival in 1983 < 10%
  - 2012 > 80%

Estimated and projected cancer survivors in USA



de Moor JS et al, Cancer Epidemiol Biomarkers Prev 2013

Changing paradigm - Cancer survival to cancer survivorship

Estimated number of new cancer cases diagnosed in 2018

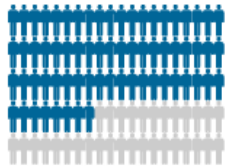
138,321 = 74,644 males + 63,676 females

Estimated number of deaths from cancer in 2018

48,586 = **27,552 males + 21,034 females**

Chance of surviving at least 5 years (2009–2013)

68%



People living with cancer at the end of 2012 (diagnosed in the 5 year period 2008 to 2012)

410,530

Estimated number of new cases of lymphoma diagnosed in 2018

6,403 = **3,681 males + 2,722 females**

Estimated % of all new cancer cases diagnosed in 2017

4.6%

Estimated number of deaths from lymphoma in 2018

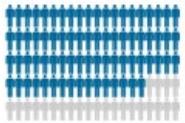
1,489 = **871 males + 617 females**

Estimated % of all deaths from cancer in 2017

3.1%

Chance of surviving at least 5 years (2010–2014)

76%



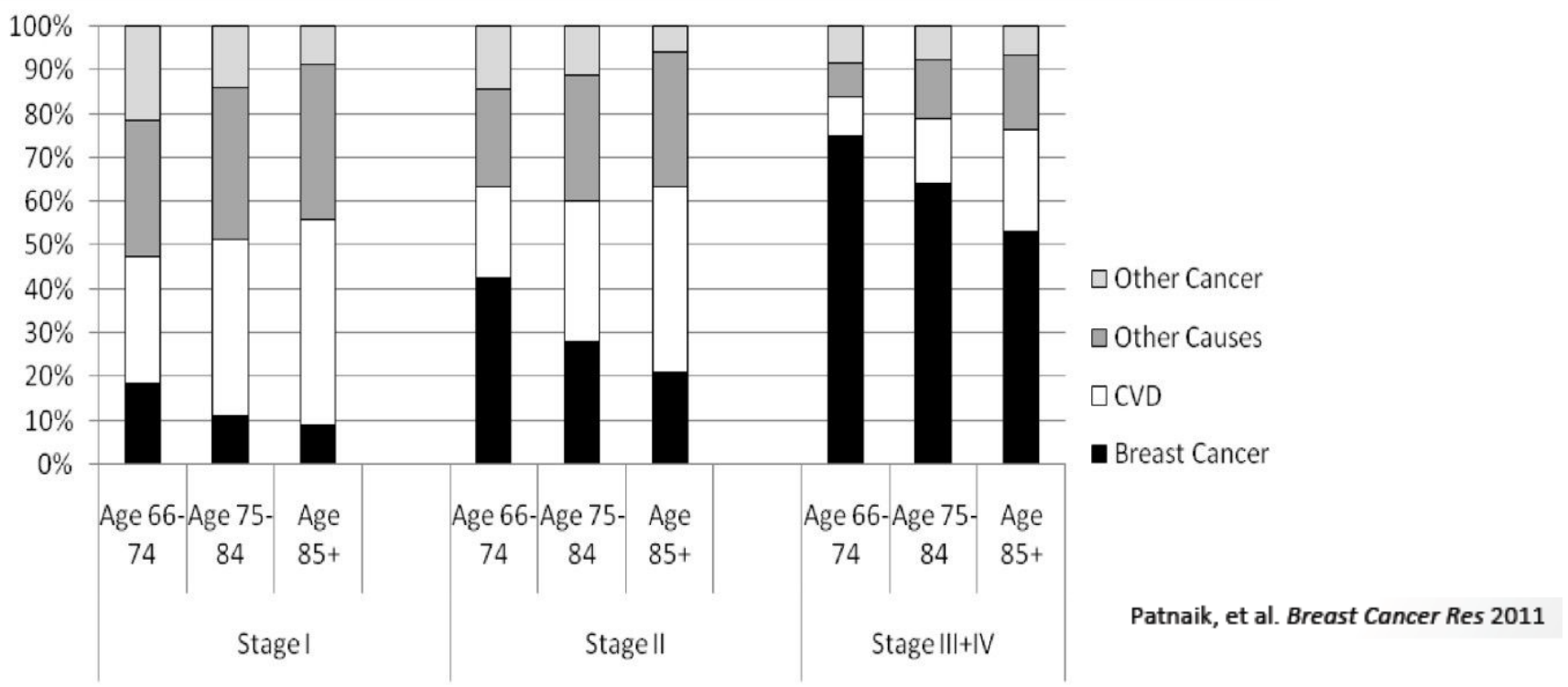
People living with lymphoma at the end of 2013 (diagnosed in the 5 year period 2009 to 2013)

21,103

https://canceraustralia.gov.au/affected-cancer/what-cancer/cancer-australia-statistics

Is there a problem?

Among 63566 breast cancer patients, CVD was the leading cause of death, followed by breast cancer



Patnaik, et al. *Breast Cancer Res* 2011

Among women who died as a result of CVD, only 25% were also categorized as having CVD as a co-morbid condition at the time of breast CA diagnosis

Risk of developing severe health conditions among cancer survivors vs siblings

Condition	Survivors (N = 10,397)	Siblings (N = 3034)	Relative Risk (95% CI)
	percent		
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)

Table 1. Risk of cardiac disease and cardiac risk factors in long-term survivors of childhood cancer vs healthy siblings (Childhood Cancer Survivor Study)

	CAD[9]	Heart failure[9]	Hypertension[10]	Diabetes[10]	Dyslipidemia[10]
RR (95% CI)	10.4 (4.1-25.9)	15.1 (4.8-47.9)	1.9 (1.6-2.2)	1.7 (1.2-2.3)	1.6 (1.3-2.0)
n	10,397	10,397	8599	8599	8599

CAD, coronary artery disease; CI, confidence interval; RR, relative risk.

Oeffinger et al, N Engl J Med 2006; 355:1572-82

Cancer Treatment and Heart Failure Mortality

3-fold worse outcome than ICM

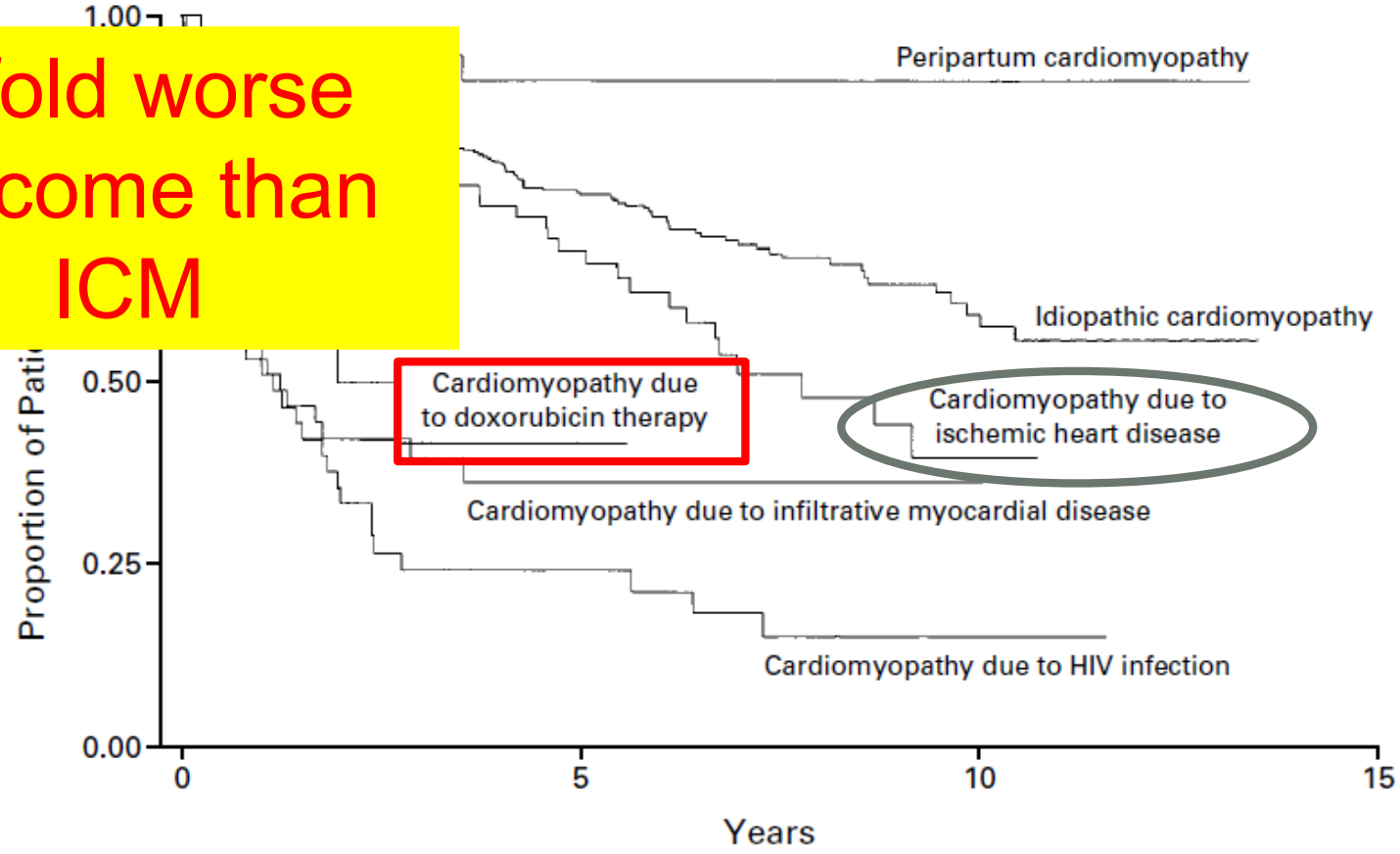
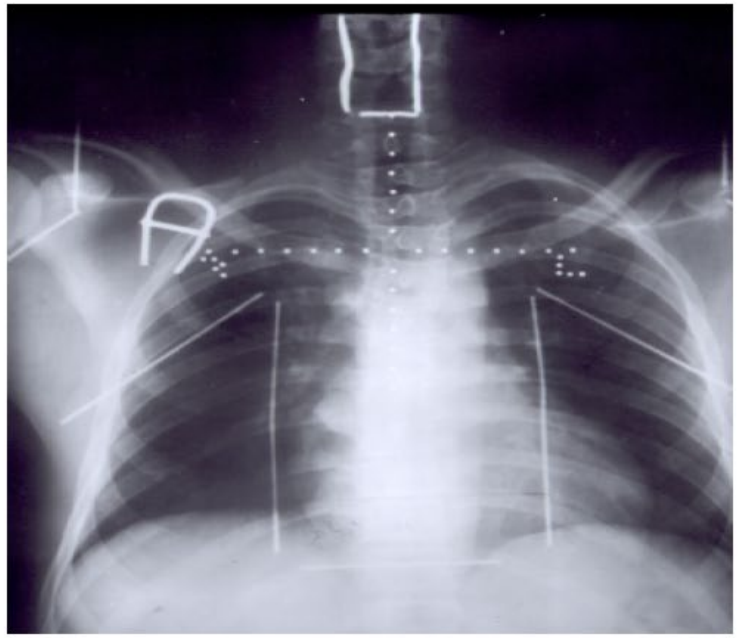


Figure 1. Adjusted Kaplan–Meier Estimates of Survival According to the Underlying Cause of Cardiomyopathy. Only idiopathic cardiomyopathy and cardiomyopathy due to causes for which survival was significantly different from that in patients with idiopathic cardiomyopathy are shown.

Felker et al, N Engl J Med 2000

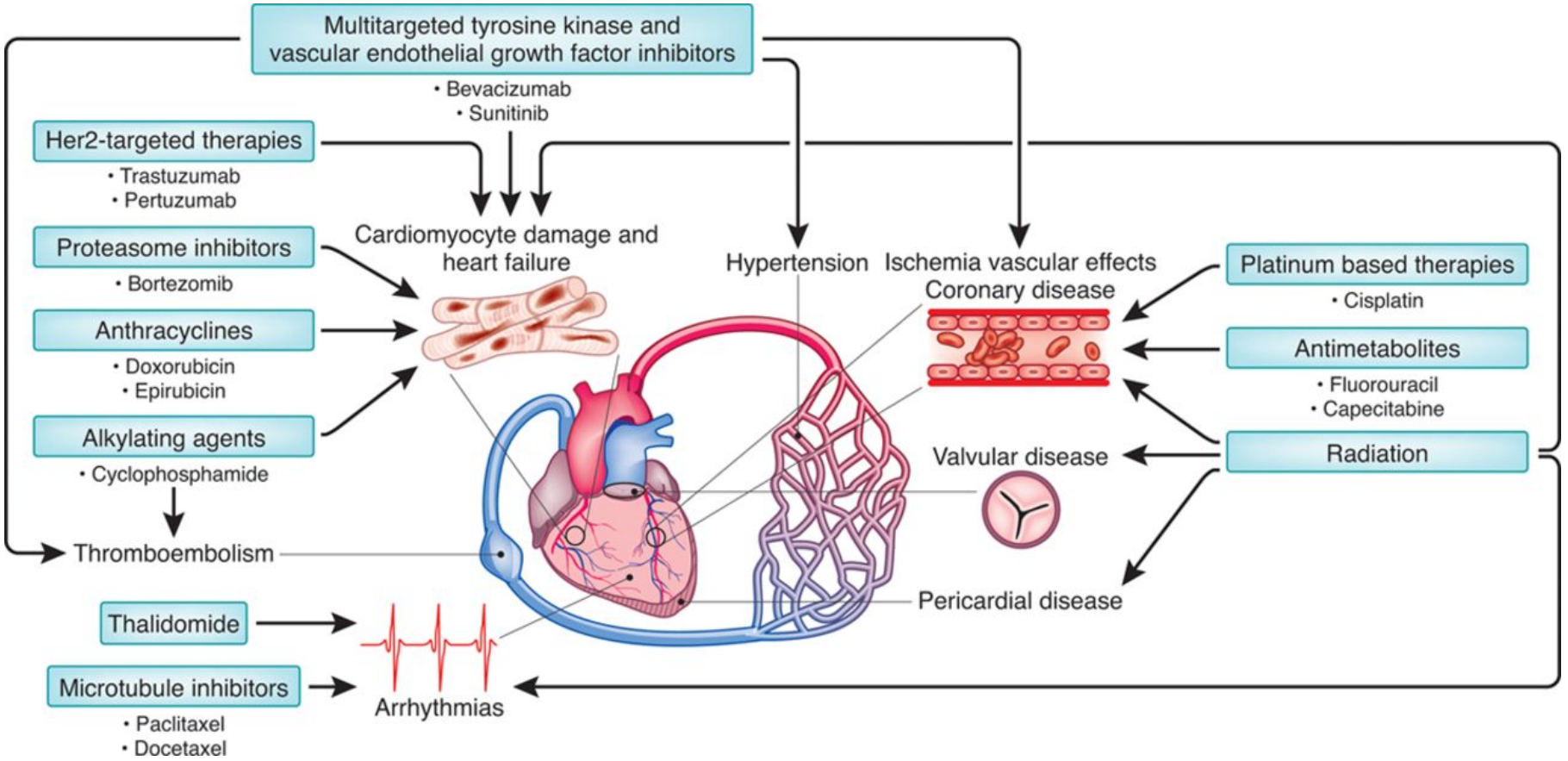
Chemotherapy-induced cardiomyopathy

Anthracycline Cardiomyopathy



Mantle Radiotherapy

Which drugs are the culprits?



Lenneman and Sawyer Circ Res. 2016;118:1008-1020

Cardiotoxicity of Antineoplastics

Antitumour antibiotics Eg Anthracycline	• Cardiomyopathy, arrhythmias, CHF • Cumulative dose
Microtubule targeting agents Eg Taxanes	• Bradycardia, arrhythmias, CHF, MI • Typically reversible, may potentiate anthracycline toxicity
Alkylating agents Eg Cisplatin, Cyclophosphamide	• Arrhythmias, heart block, CHF • Mechanism: Electrolyte abnormalities ; endothelial capillary damage
Antimetabolites Eg Fluorouracil	• Cardiac failure, MI • Likely Mechanism: Coronary vasospasm

Floyd JD et al. JCO 2005;23:7685-7696

How serious is the problem? Δ LVEF

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m² 550 mg/m² 700 mg/m²	 3–5 7–26 18–48
Idarubicin (>90 mg/m²)	5–18
Epirubicin (>900 mg/m²)	0.9–11.4
Mitoxanthone >120 mg/m²	2.6
Liposomal anthracyclines (>900 mg/m²)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide <10 g/m² 12.5–16 g/m²	 0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1

Chemotherapy agents	Incidence (%)
Monoclonal antibodies	
Trastuzumab	1.7–20.1
Bevacizumab	
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib	
Pazopanib	
Sorafenib	4–8
Dasatinib	2–4
Imatinib mesylate	0.2–2.7
Lapatinib	0.2–1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11–25
Bortezomib	2–5
Miscellanous	
Everolimus	<1
Temsirolimus	<1

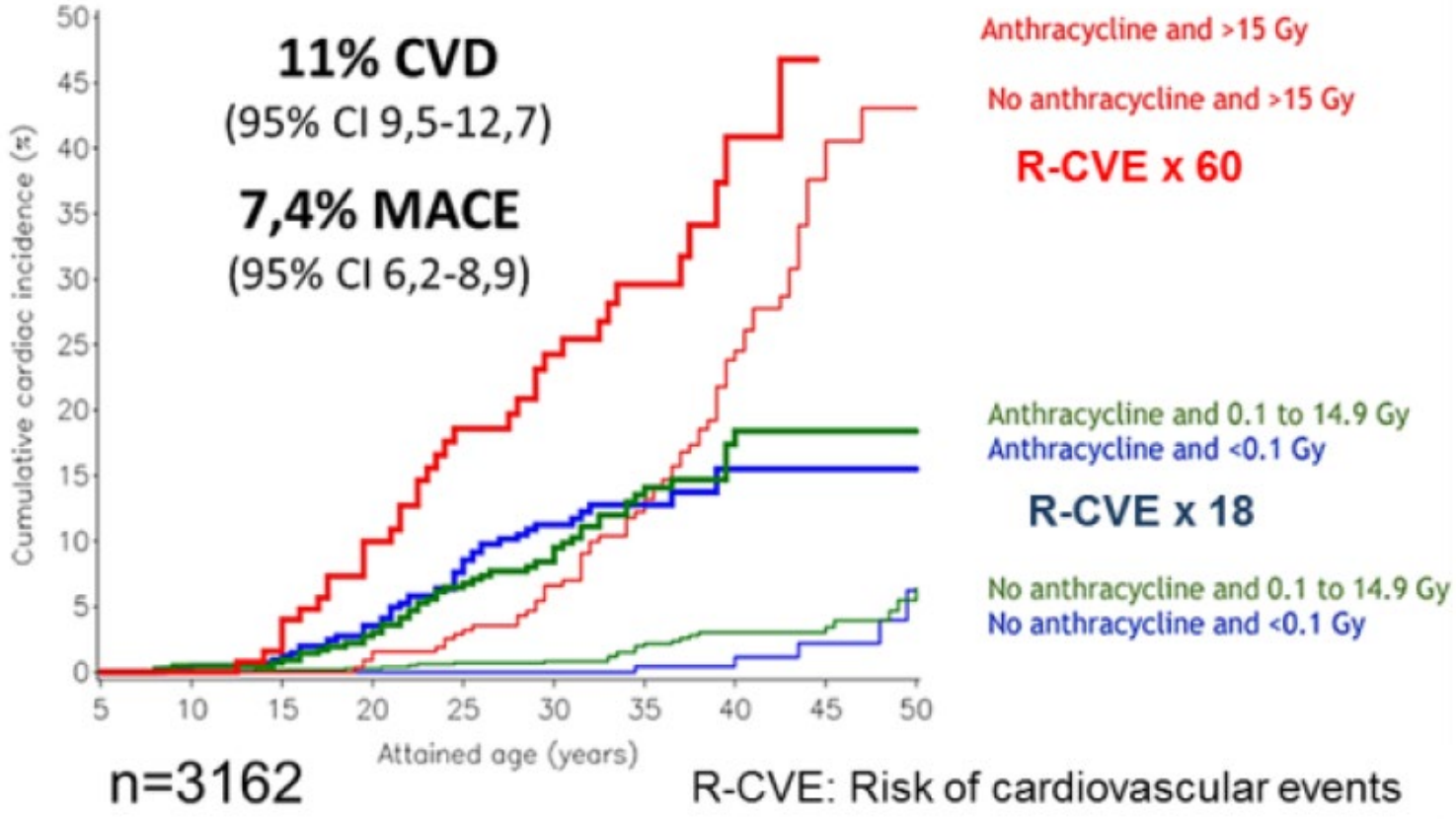
30% incidence of HT

28% incidence of ↓ LVEF
Over 40% incidence of HT

www.escardio.org/guidelines

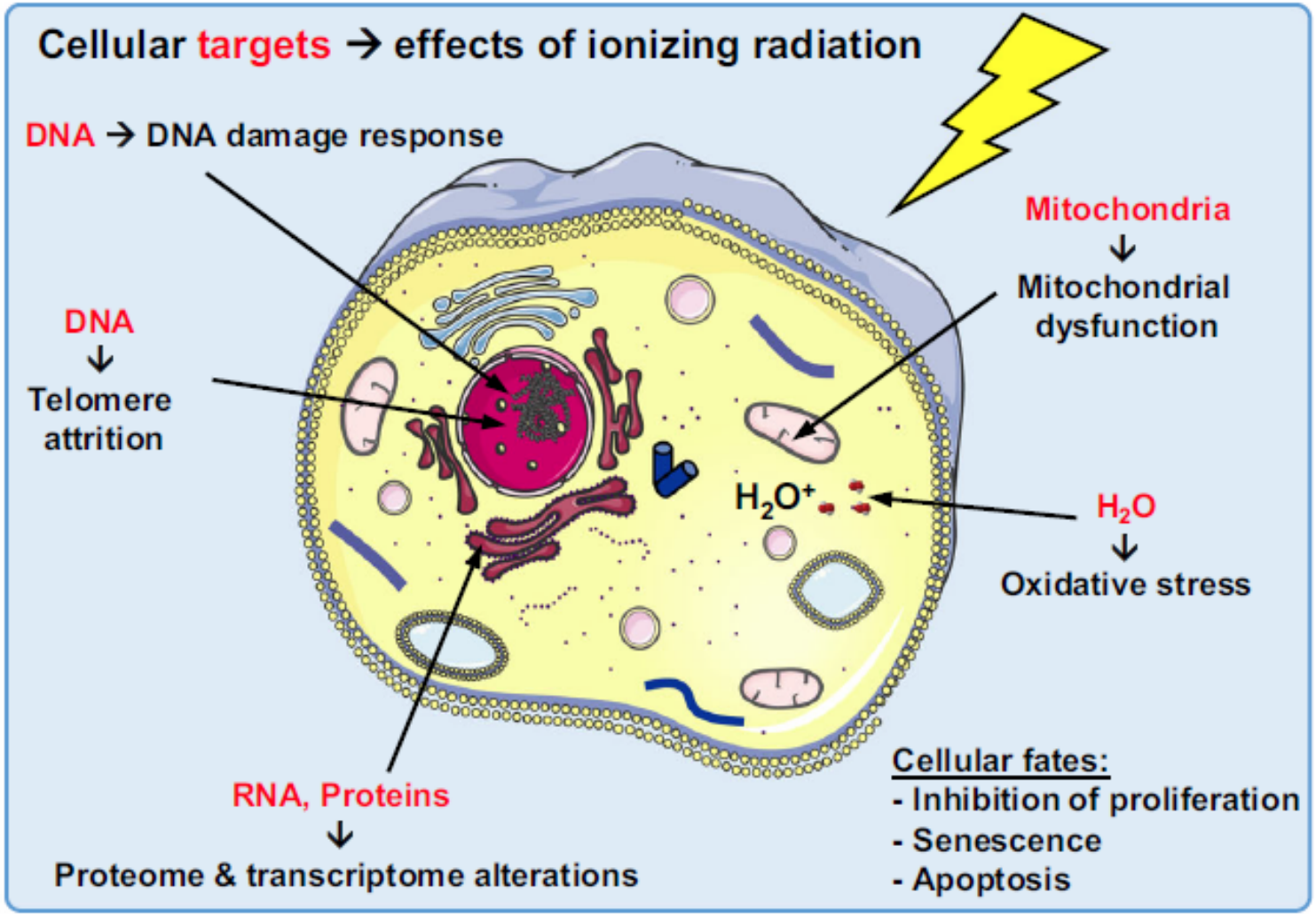
European Heart Journal doi:10.1093/eurheartj/ehw211 - EHJ 2016;37:2768-2801

Is it just the drugs?



CA Cancer J Clin 2016;66:271–2891 J Clin Oncol 32:1218-1227. © 2014 Circulation. 2016;133:31-38

Compound effects: RTx and CTx, esp anthracyclines



Spetz et al., Curr Treat Options Cardio Med (2018) 20: 31

It's getting even more complex

HER2 targeted therapies
- Trastuzumab
- Pertuzumab
- T-DM1
- Lapatinib

VEGF-tyrosine kinase inhibitors
- Bevacizumab
- Sunitinib
- Sorafenib
- Pazopanib
- Axitinib
- Regorafanib
- Cabozantinib

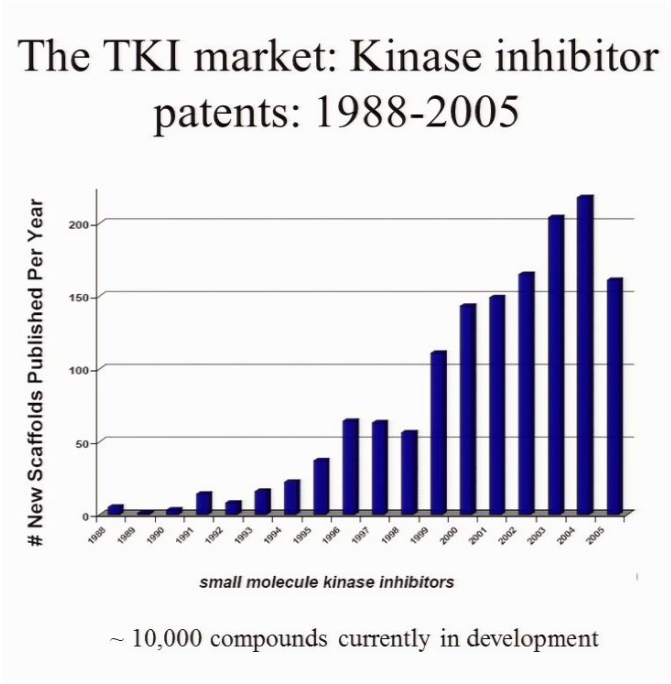
Raf-MEK pathway inhibitors
- Debrafanib
- Vemurafenib
- Trametinib

Proteosomal inhibitors
- Bortezomib
- Carfilzomib
- Ixazomib

BCR-Abl inhibitors
- Imatinib
- Nilotinib
- Dasatanib
- Bosutinib
- Ponatanib

BTK inhibitors
- Ibrutinib

CDK 4/6 inhibitors
- Palbociclib
- Ribociclib



Data courtesy of HFSA

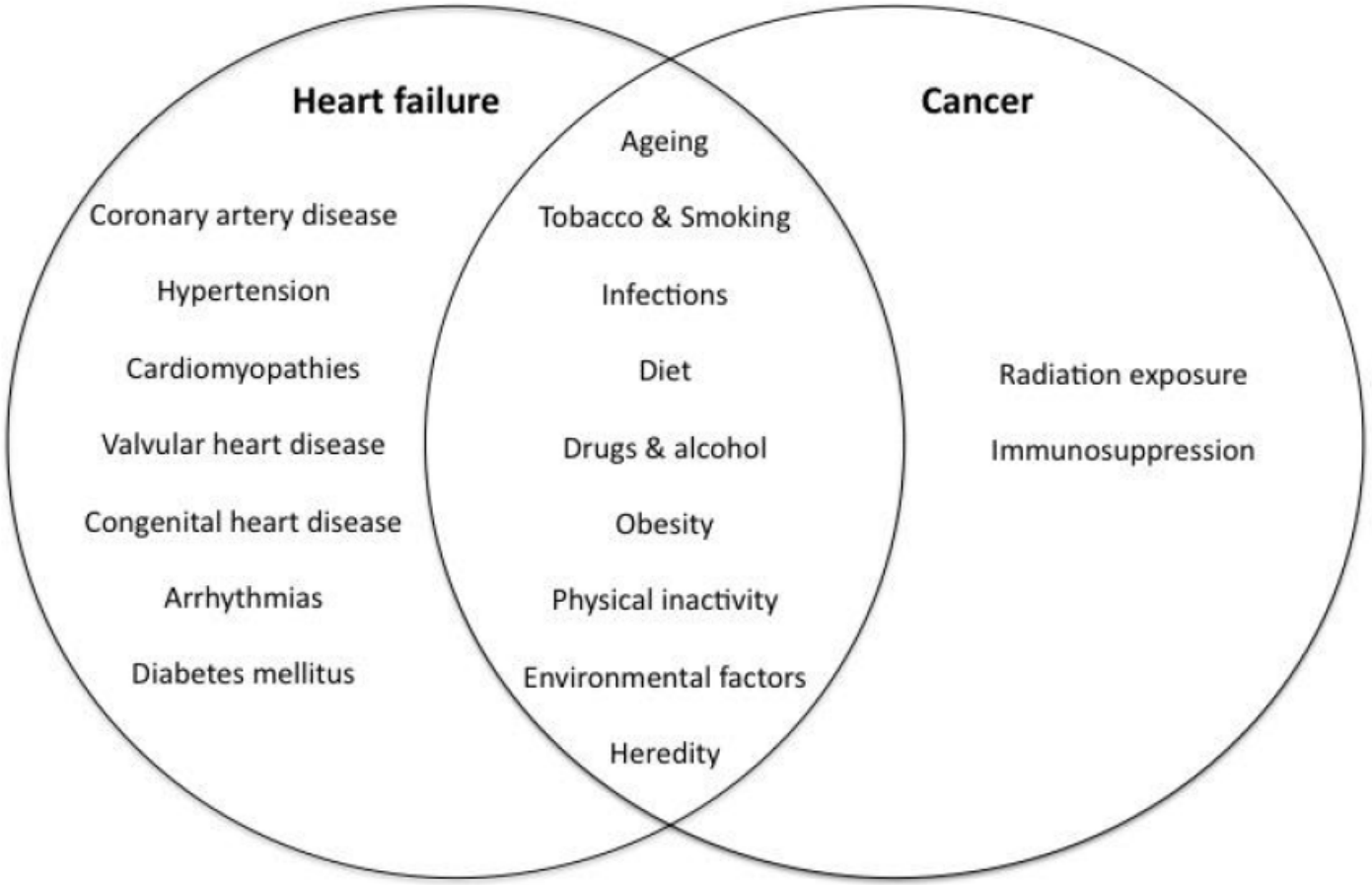
Immunotherapies
- Nivolumab
- Ipilumimab
- Pembrolizumab
- Atezolizumab
- Durvalumab
- Avelumab

Targets of TKIs

Imatinib Nilotinib	Dasatinib		
ABL	ABL	TXK	LIMK2
ARG	ARG	DDR1	MYT1
BCR-ABL	BCR-ABL	DDR2	PTK6/Brk
KIT	KIT	ACK	QIK
PDGFR	PDGFR	ACTR2B	QSK
DDR1	SRC	ACVR2	RAF1
NQO2	YES	BRAF	RET
	FYN	EGFR/ERBB1	RIPK2
	LYN	EPHA2	SLK
	HCK	EPHA3	STK36/ULK
	LCK	EPHA4	SYK
	FGR	EPHA5	TA03
	BLK	FAK	TESK2
	FRK	GAK	TYK2
	CSK	GCK	ZAK
	BTK	HH498/TNNI3K	
	TEC	ILK	
	BMX	LIMK1	

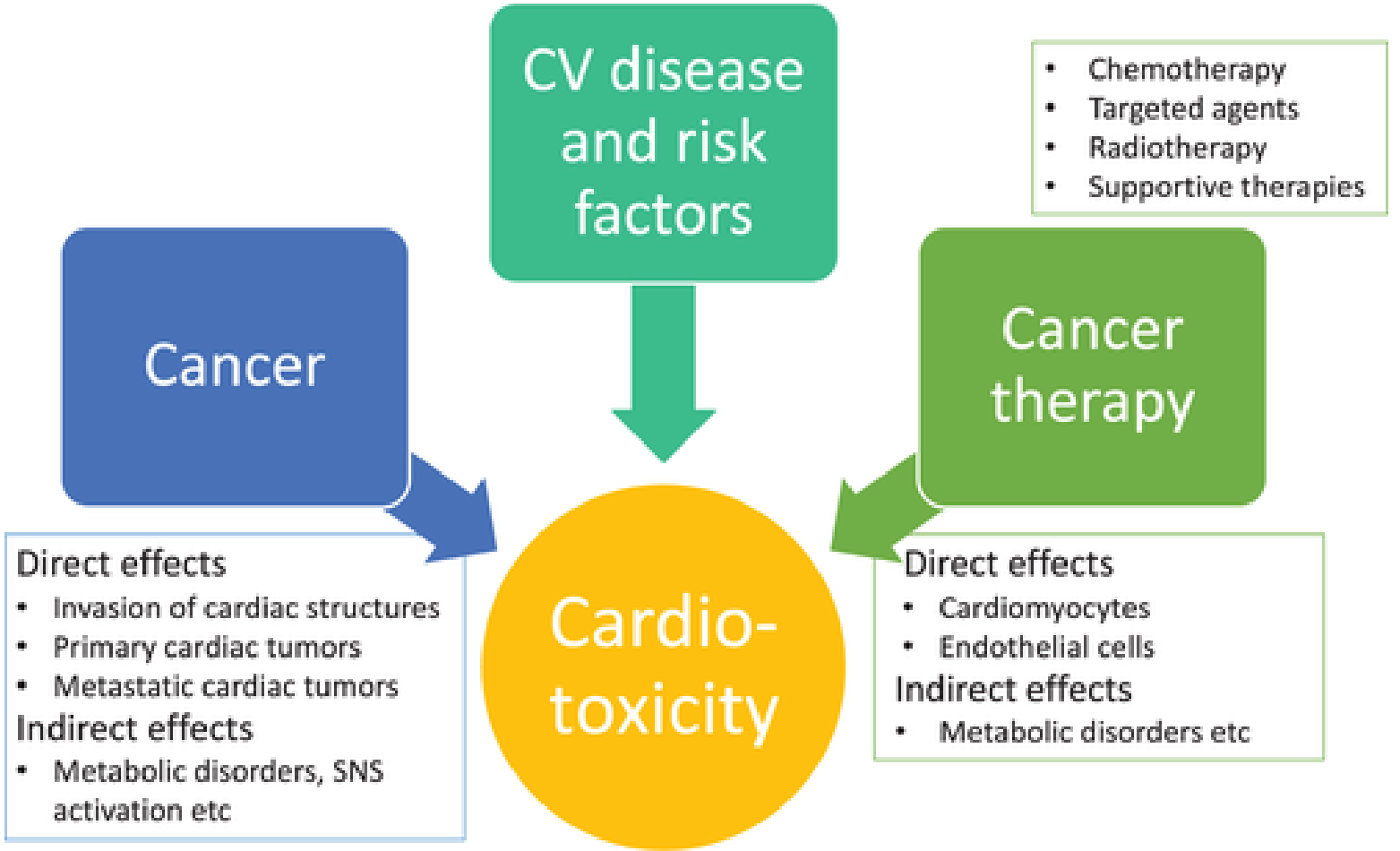
Plus a number of non kinase targets have now been identified

Common risk factors in HF & cancer



Farmakis et al, Int J Cardiol 2016

Why is there a problem?



Farmakis et al. Eur J Heart Fail 2018

Cancer and the Heart - elusive balance

CANCER

Cell division

Increased cell number

Angiogenesis

Increased metabolic activity

Drug/toxin resistance

HEART DISEASE

Failure of cell division/ tissue repair
Cell loss

Ischaemia

Impaired/decreased energetic efficiency

Increased sensitivity to toxins

Summary

- Advancement in diagnostic tools and therapies have dramatically improved cancer survival
- Adverse cardiac effects of conventional therapies remain
- Newer adjuvant therapies interfere with molecular pathways crucial to normal cardiovascular health
  - Numerous more drugs in the pipeline
- The cancer survivor population is aging with a higher prevalence of traditional CVD risk factors
- If there trends continue, further improvements in cancer-specific and overall survival may be offset by increased therapy-associated CV mortality

What can we do as physicians?

What can we do about the problem?

Early:

- Identification of patients at greatest risk
- Prevention
- Early detection and treatment

Ongoing:

- Improved service delivery
- More dedicated service
- Long-term survivorship clinics

Definition of Cardiotoxicity

- **Lack of consensus**
- **Most current definitions incorporate some/all of the following:**
  - Cardiomyopathy in terms of a reduction in LVEF
  - Symptoms associated with HF
  - Signs associated with HF, such as S3 gallop, tachycardia, or both
  - Reduction in LVEF from baseline
    - in the range of ≤ 5% to < 55% with signs or symptoms of HF

      or
    - in the range of ≥ 10% to < 55% without signs or symptoms of HF

- **National Cancer Institute (Singapore)**

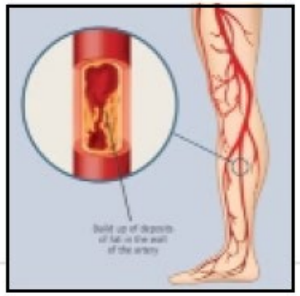
Toxicity that affects the heart

Not just Heart Failure

HF

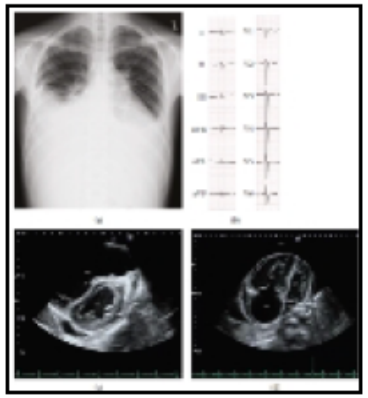
HT

Ischaemia

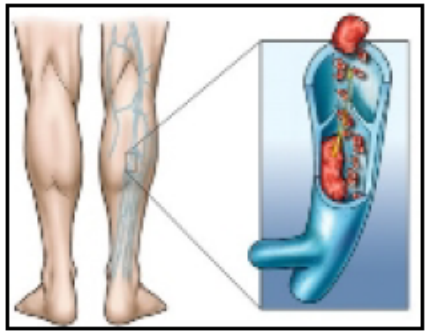


PAD

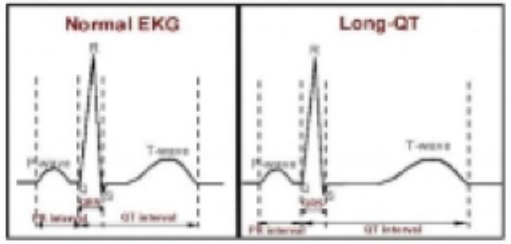
PHT



VTE



QT prolongation
Arrhythmias



Prevention of cardiotoxicity

Table 1 Characteristics of randomised trials

Study	Exp. drug	Median age		No. of patients		Malignancy (%)	Anthracycline	Definition of LV dysfunction	Definition of cardiac events*	Baseline LVEF, % (SD)		N (%)				F/U (month)
		Exp	Ctrl	Exp	Ctrl					Exp	Ctrl	Radiation†	HTN	HLD	DM	
Kalay *et al* 2006[27]	Carvedilol	46.8	49.0	25	25	Breast cancer 34 (68) Lymphoma 9 (18) Others 7 (14)	Doxorubicin Epirubicin‡	LVEF <50%	Heart failure	70.6 (8.0)	69.7 (7.3)	0 (0)	NR	NR	NR	6
Cardinale *et al* 2006[28]	Enalapril	47	44	56	58	Acute leukaemia15 (13) Breast cancer 29 (25) Ewing's sarcoma 4 (4) Hodgkin lymphoma 10 (9) Non-Hodgkin lymphoma 39 (34) Multiple myeloma 17 (15)	Epirubicin Idarubicin Daunorubicin§	LVEF <50% and >10% LVEF reduction	Sudden death Cardiac death Heart failure Acute pulmonary oedema, Arrhythmia requiring treatment	61.1 (3.2)	61.8 (4.3)	37 (32)	7 (6)	4 (4)	2 (2)	12
Georgakopoulos *et al* 2010[29]	Metoprolol	51.0	49.1	42	40	Hodgkin lymphoma 60 (48) Non-Hodgkin Lymphoma 65 (52) Within metoprolol group Hodgkin lymphoma 21 (50) Non-Hodgkin lymphoma 21 (50)	Doxorubicin¶	LVEF <50% and >10% LVEF reduction	Sudden death Cardiac death Heart failure Bradycardia Arrhythmia requiring treatment	65.7 (5.0)**	67.6 (7.1)**	26 (21)	30 (24)	35 (28)	19 (15)	12
	Enalarpril	47.4	49.1	43	40	Hodgkin lymphoma 60 (48) Non-Hodgkin lymphoma 65 (52) Within enalarpril group Hodgkin lymphoma 19 (44) Non-Hodgkin lymphoma 24 (56)	Doxorubicin¶	LVEF <50% and >10% LVEF reduction	Sudden death Cardiac death Heart failure Bradycardia Arrhythmia requiring treatment	65.2 (7.1)**	67.6 (7.1)**	26 (21)	30 (24)	35 (28)	19 (15)	12
Bosch *et al* 2013[30]	Carvediloland Enalapril	49.7	50.9	45	45	Acute leukaemia 36 (40) Hodgkin lymphoma 9 (10) Non-Hodgkin lymphoma 23 (26) Multiple myeloma 22 (24)	Idarubicin Daunorubicin††	LVEF <45% or ≥10% LVEF reduction	Death‡‡ Heart failure‡‡ Final LVEF <45%	61.7 (5.1)	62.6 (5.4)	16 (18)	14 (16)	10 (11)	4 (4)	6
Kaya *et al* 2013[31]	Nebivolol	51.4	50.5	27	18	Breast cancer 45 (100)	Doxorubicin Epirubicin §§	NR	Cardiac death Bradycardia Heart failure requiring hospitalisation	63.8 (3.9)	66.6 (5.5)	12 (27)	10 (22)	0 (0)	4 (9)	6
Dessi *et al* 2013[32]	Telmisartan	52.9	53	25	24	Breast cancer 18 (37) Endometrium cancer 21 (43) Non-Hodgkin lymphoma 3 (6) Non-small cell lung cancer 1 (2) Ovarian cancer 5 (10) Salivary gland cancer 1 (2)	Epirubicin ¶¶	NR	NR***	66.0 (7.0)	66.0 (5.0)	0 (0)	0 (0)	NR	0 (0)	12

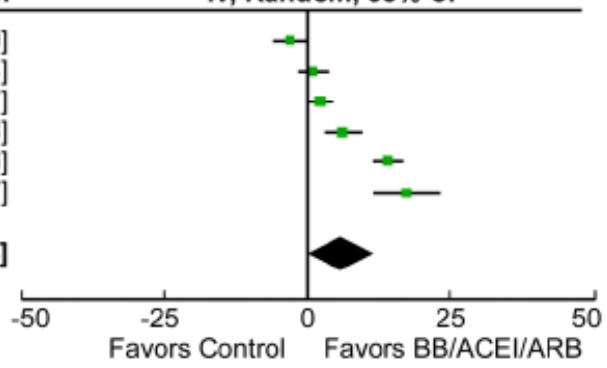
Yun et al, Postgrad Med J 2015;91:627-33

Prevention of cardiotoxicity

LVEF

Study or Subgroup	BB/ACEI/ARB Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95%CI
1 Georgakopoulos 2010	63.6	7.45	85	66.6	6.70	40	17.1%	-3.00 [-5.61, -0.39]
2 Dessi 2013	68.0	4.00	25	67.0	5.00	24	17.1%	1.00 [-1.54, 3.54]
3 Bosch 2013	61.5	6.30	42	59.3	3.30	37	17.2%	2.19 [0.01, 4.37]
4 Kaya 2013	63.8	3.90	27	57.5	5.60	18	16.9%	6.30 [3.32, 9.28]
5 Cardinale 2006	62.4	3.50	56	48.3	9.30	58	17.1%	14.10 [11.54, 16.66]
6 Kalay 2006	69.7	6.00	25	52.3	14.00	25	14.7%	17.40 [11.43, 23.37]
Total (95% CI)			**260**			**202**	100.0%	**6.06 [0.54, 11.58]**

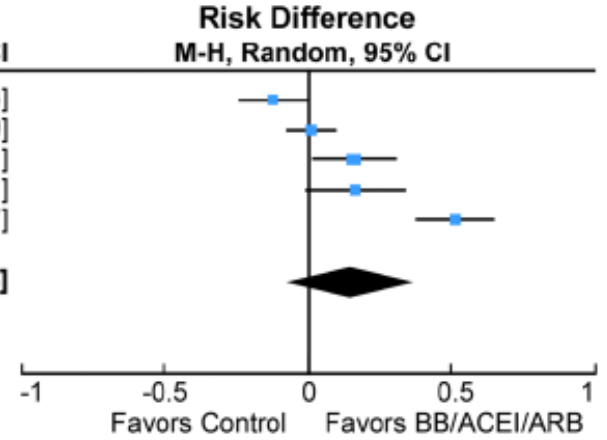
Heterogeneity: $Tau^2 = 44.80$; $Chi^2 = 116.46$, df = 5 ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: Z = 2.15 (P = 0.03)



Cardiac events

Study or Subgroup	BB/ACEI/ARB Events	Total	Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1 Georgakopoulos 2010	17	85	3	40	20.3%	0.13 [0.01, 0.24]
2 Kaya 2013	0	27	0	18	20.9%	0.00 [-0.09, 0.09]
3 Bosch 2013	3	45	10	45	19.8%	-0.16 [-0.30, -0.01]
4 Kalay 2006	1	25	5	25	19.0%	-0.16 [-0.33, 0.01]
5 Cardinale 2006	1	56	30	58	20.0%	-0.50 [-0.63, -0.37]
Total (95% CI)		**238**		**186**	**100.0%**	**-0.14 [-0.35, 0.08]**
Total events	22		48			

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 60.52$, df = 4 ($P < 0.00001$); $I^2 = 93\%$
Test for overall effect: Z = 1.22 (P = 0.22)



Yun et al, Postgrad Med J 2015;91:627-33

Trials of cardioprotection

- OVERCOME
  - Haemato-oncological pts receiving ACs
  - 1° prevention carvedilol and enalapril
    - Prevented LVEF reduction
- PRADA
  - Breast cancer receiving epirubicin (HER2-)
  - Candesartan prevented small LVEF fall
  - Metoprolol no benefit
- CECCY trial
  - Breast cancer receiving anthracyclines (HER2-)
  - Carvedilol – no benefit on LVEF reduction (1° endpoint)
  - Carvedilol did significantly reduce troponin rise and new LV diastolic dysfunction
- MANTICORE
  - HER2+ breast cancer pts randomised to Bisoprolol, Perindopril or placebo
  - No effect on trastuzumab-induced LV remodelling (1° endpoint)
  - Both reduced LVEF decline reduction (2° endpoint)
- Kentucky study
  - HER2+ breast cancer pts randomised to Carvedilol, Lisinopril or placebo
  - No reduction in rate of cardiotoxicity in entire cohort
  - Significant reduction in cohort receiving AC followed by trastuzumab
- ICOS-ONE
  - Enalapril primary prevention vs biomarker guided

Small studies
Low risk patients
Surrogate end points

Ongoing trials

PROACT Trial

Multicentre UK trial
Primary prevention with Enalapril in breast cancer patients receiving epirubicin
ClinTrials.gov: NCT03265574
EudraCT: 2017-001094-16
Lead by Dr David Austin
James Cook University Hospital
Middlesborough, UK

SUCCOUR Trial

JACC: CARDIOVASCULAR IMAGING

PUBLISHED BY ELSEVIER

Rationale and Design of the Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes

The SUCCOUR Trial

Tomoko Negishi, MD,[a] Paaladinesh Thavendiranathan, MD, SM,[b] Kazuaki Negishi, MD, PhD,[a] Thomas H. Marwick, MBBS, PhD, MPH,[a,c] on behalf of the SUCCOUR investigators

Importance of early detection

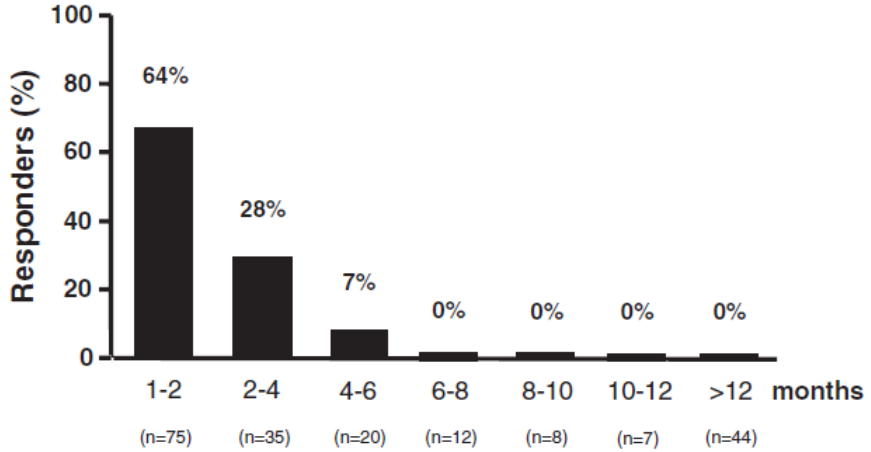
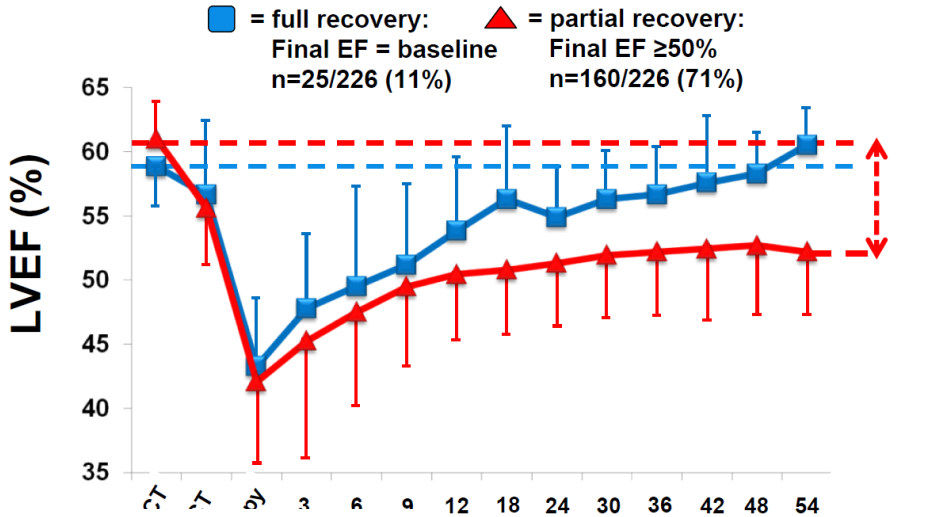
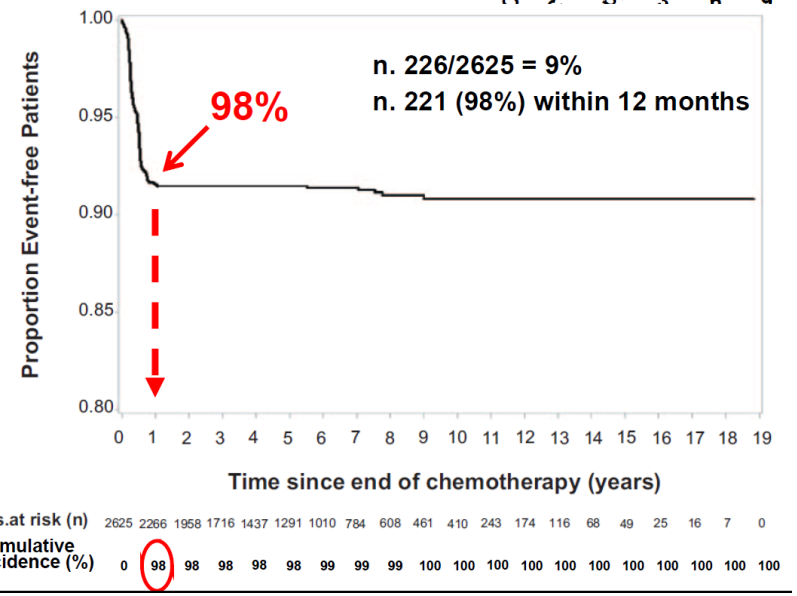


Figure 1 Percentage of Respond… Time Elapsed From AC … Start of HF Therapy



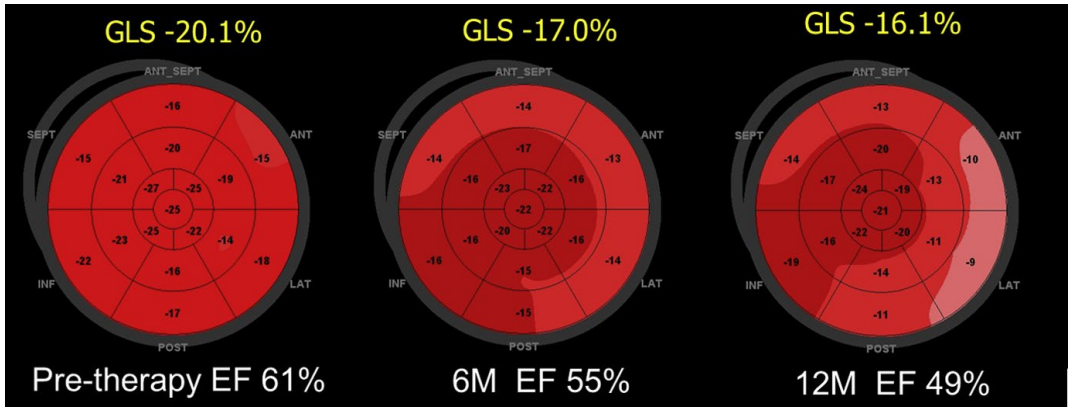


Cardinale et al., J Am Coll Cardiol 2010; 55:213–20

Cardinale et al., Circulation. 2015;131:1981-1988

Focus has been on LV systolic dysfunction/EF

- LVEF not sensitive for preclinical heart disease
- In chronic cardiotoxicity with AC: E/A ratio, DT and IVRT were all deranged in 50% of patients Rx with AC, when LVEF was still normal {*Tjeerdsma G,et al Heart 1999:81:419*}
- Novel measures (myocardial deformation) – Global longitudinal strain (GLS)
  - Predicts development of LV dysfunction after 12 months



Thavendiranathan et al, JACC 2014;63:2751-68

Cardiotoxicity Progression: heart failure cascade

Pre-existing Risk
Age
Genetic
LVH
Coronary disease
Prior ACs
Prior DXT
CV Risk Factors

Anthracyclines
Herceptin
TKI

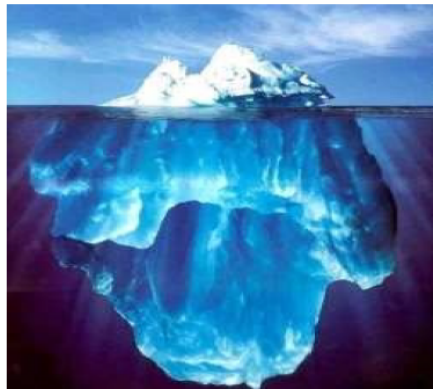
Early diastolic dysfunction
Loss of contractile reserve

Apoptosis

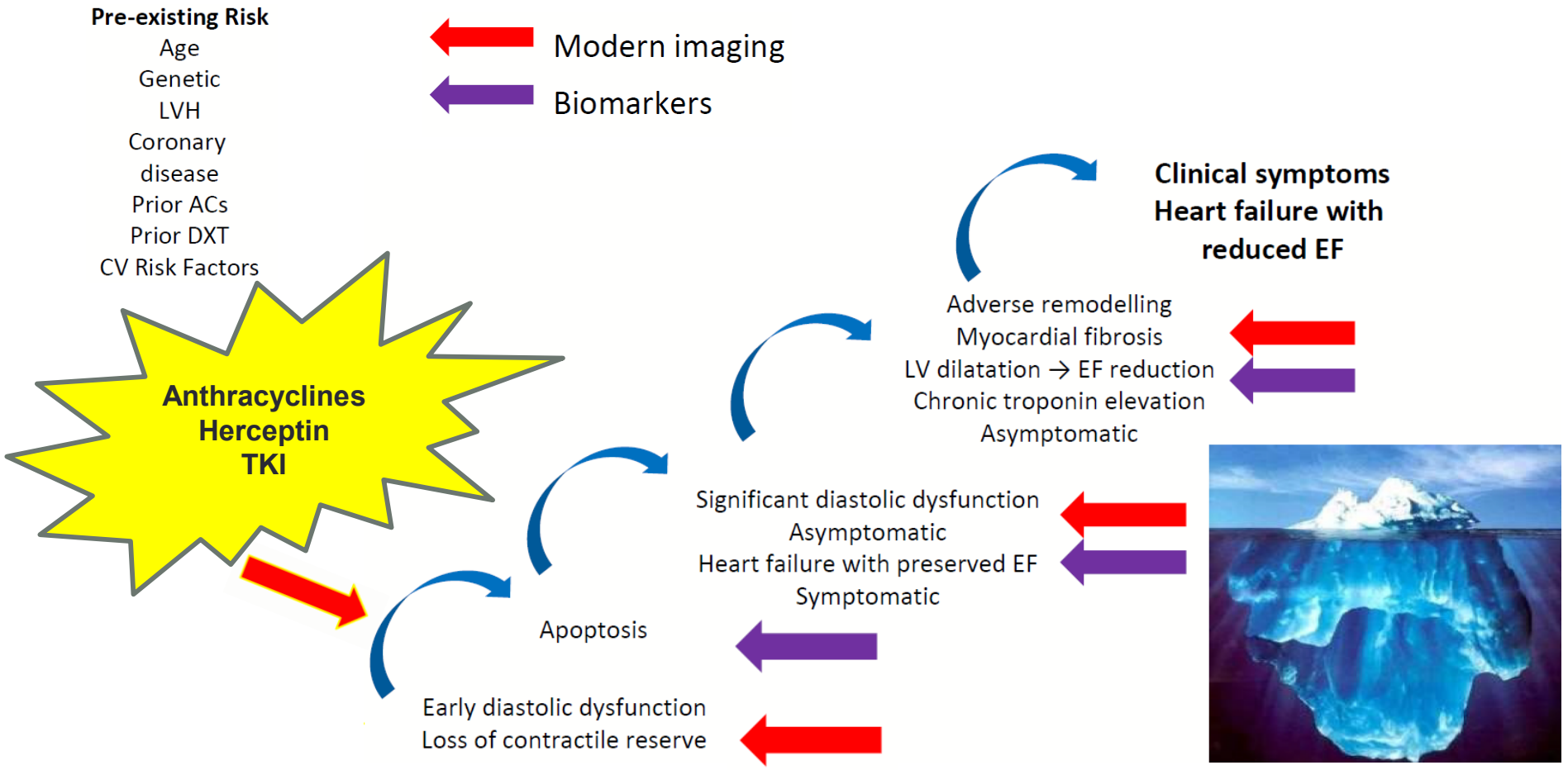
Significant diastolic dysfunction
Asymptomatic
Heart failure with preserved EF
Symptomatic

Adverse remodelling
Myocardial fibrosis
LV dilatation → EF reduction
Chronic troponin elevation
Asymptomatic

Clinical symptoms
Heart failure with reduced EF



Combining Biomarkers and Imaging



Biomarkers in chemotherapy-induced cardiotoxicity

- Most biomarker studies were done in setting of anthracycline chemotherapy only

- Troponins
  - Mixed results, although on balance increase in Trop is associated with reduction in cardiac function and/or cardiotoxicity
  - Persistent increase in Trop predicts subsequent LVEF decline
  - Downside: implies myocyte damage has already occurred

Biomarkers in chemotherapy-induced cardiotoxicity

- BNP
  - Mixed results
  - Not as robust as Trop at predicting cardiotoxicity per se
  - Good correlation with LVEF
  - But…does not always predict change in LVEF

- Other biomarkers – limited data
  - MPO (oxidative stress)
  - hs-CRP (inflammation)
  - Placental growth factor (angiogenesis)
  - Soluble Flt-1 (vascular remodelling)
  - GDF-15 (inflammation and oxidative stress)

What do guidelines tell us

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: **–3D-based LVEF** **–2D Simpson's LVEF** **–GLS**	• LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemo-dynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	• >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	• Reproducibility.	• Cumulative radiation exposure. • Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	• Accuracy, reproducibility. • Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	• Limited availability. • Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: – **Troponin I** – **High-sensitivity Troponin I** – **BNP** – **NT-proBNP**	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs futher investigation.	• Accuracy, reproducibility. • Wide availability. • High-sensitivity.	• Insufficient evidence to establish the significance of subtle rises. • Variations with different assays. • Role for routine surveillance not clearly established.

Criteria for a clinically useful biomarker

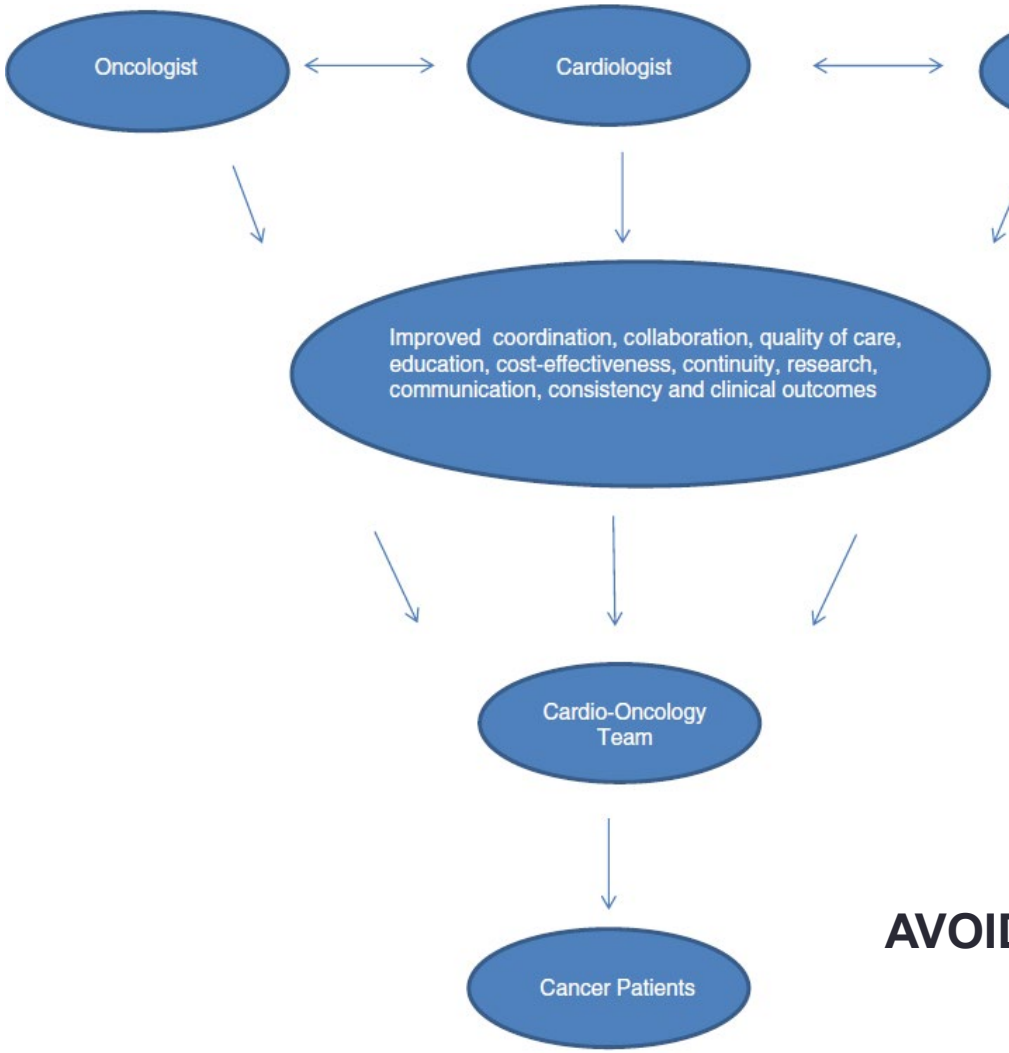
- Can the clinician measure it?
  - Accurate & reproducible
  - Fast
  - Reasonable cost
- Does it add new information?
  - Strong and consistent association with disease and/or outcomes
  - Cut-off values/ranges can be defined
- Will it help with management?

"If it costs less than 20 bucks, it's a lab test. If it costs more than 20 bucks, it's a biomarker."

Service delivery – cardio-oncology

- Dedicated sub-service as part of heart failure program
- Multidisciplinary clinic – even more important than with other programs – heart is seldom the only organ affected!
- Need to be ready/anticipate progressive increase in service utilization

Why dedicated cardio-oncology service?

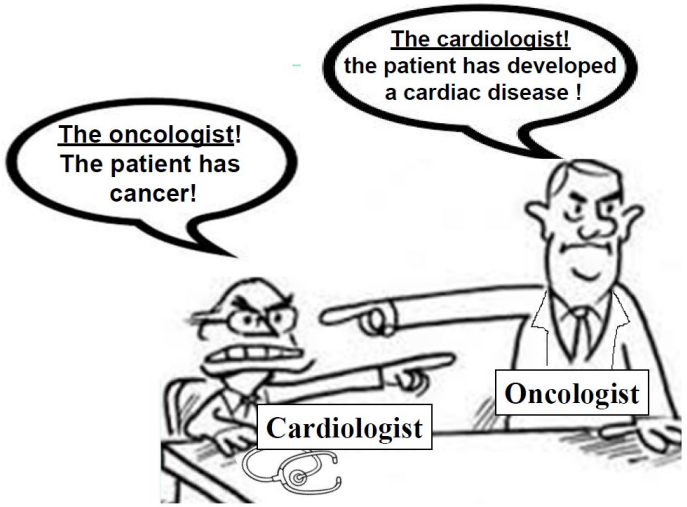


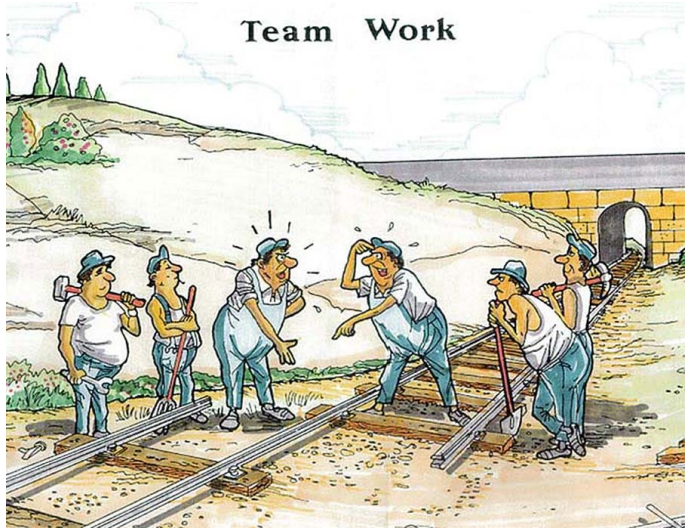
- Increasing referrals from haematology & oncology to cardiology
- Many patients receiving cardiotoxic agents
- Older population requiring chemotherapy
- Otherwise seen by various cardiology services → delays in referrals and drug titration

Overall aim:
AVOID DELAYS TO CANCER TREATMENT

Challenges in cardio-oncology

- Patient priorities – treatment of cancer vs cardio protection
- Lack of formal training/guidelines
- New treatment modalities with wide ranging forms of cardiovascular toxicities
- Lack of mechanistic studies for new treatment modalities
- A team approach





Gaps in evidence

Our Cancer & the Heart Program

- Combined clinical and research program
- First full bench-to-bedside program in HNE and in Australia

- **In vitro** – cell lines – to assess mechanisms of cardiovascular toxicities of chemotherapy
- **Exosomes**: Identify early exosomal biomarkers in response to chemotherapy released from human cardiovascular cell lines.
- **Animals** – effects of cancer therapies on development of cardiotoxicity
- **Humans** –novel + established biomarkers +/- new imaging for prediction and early detection of cardiotoxicity
- **Humans** – does heart failure engender increased cancer risk?
- **Service improvements** in delivery of care

Our Program

- Research support from
  - Heart Foundation
  - NSW Ministry of Health
  - University of Newcastle
- Support from Administration and Executive
  - HNELHD
  - Cancer Network HNE
  - Cancer Clinicians & Cardiologists
  - Psycho-oncology Co-operative Research Group

We are looking for new collaborators

Acknowledgements

University of Newcastle:

A/Prof Doan Ngo

Ms Rossana Untaru

Ms Kelly Chen

Ms Amanda Croft

Prof Andrew Boyle and his lab

Adelaide:

Prof John Horowitz

Prof Robyn Clark

Dr Saifei Liu

USA:

Prof Doug Sawyer

Prof Wilson Colucci

UK:

Dr Alex Lyon

Cancer Network:

Dr Tony Proietto

Dr Craig Gedye

Dr Nick Zdenkowski

Dr Ina Nordman

Prof Philip Rowlings

Dr Wojt Jankowski

A/Prof Jarad Martin

Prof Rodney Scott

Prof Steven Ackland

Prof Jennifer Martin

CMN Cardiology:

Dr Angela Worthington

Dr Stuart Murch

PoCoG:

Prof Brian Kelly

Dr Joanne Shaw

Mayo cardio-oncology clinic model