Prevention & Reduction of Cardiotoxicity in Childhood Cancer Therapy

Hong Kong College of Cardiology, 28th Annual Scientific Congress

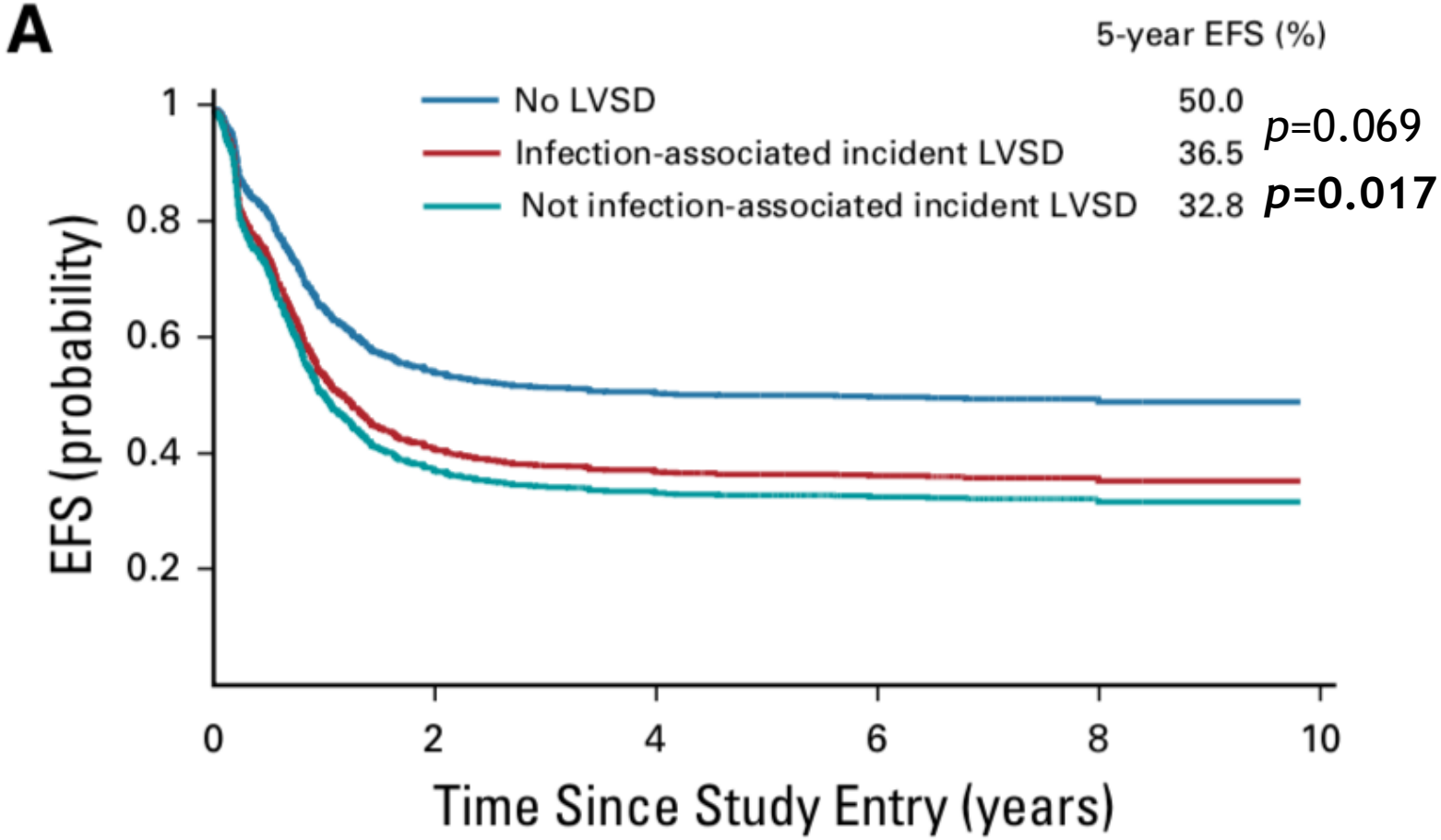
Pediatric Cardiology Program

July 2020

Importance of cardio-oncology

- Improved survival
  - SEER data in 1970s: 5-year survival rate of malignancy diagnosed before 15 years old <60%
  - Improved to 83% in 2010
- Survival implication
  - CVS-related disease: leading cause of morbidity and mortality after cancer recurrence and secondary malignancies
  - Once diagnosed with congestive heart failure: 5-year overall survival <50%

Children's Oncology Group trial AAML0531



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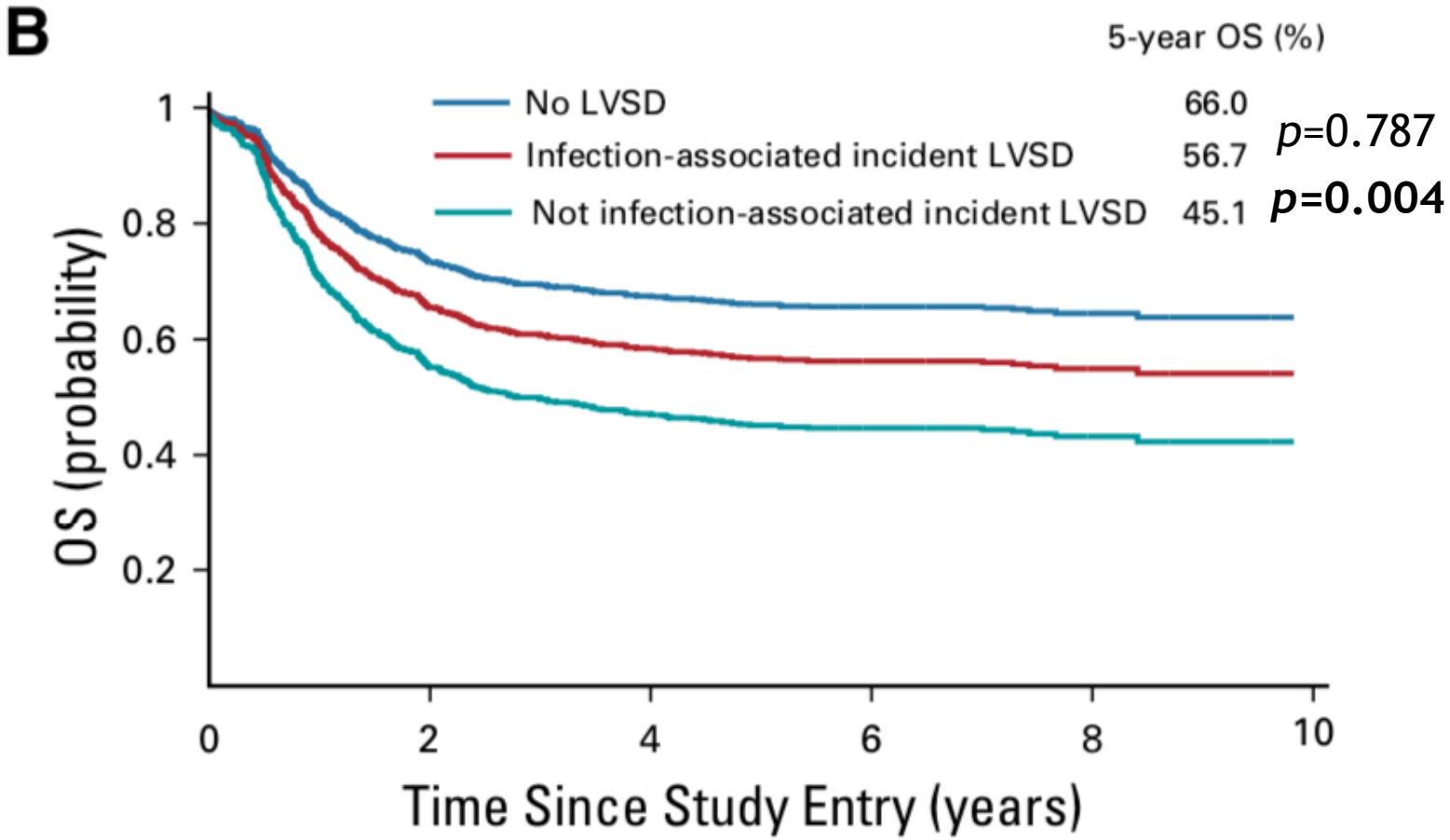


Importance of cardio-oncology

- More common than we thought
  - Cumulative incidence of coronary artery disease, heart failure, valvular disease and arrhythmia among survivors: 5 times higher than healthy siblings
  - Up to half of all survivors: cardiac dysfunction within 20 years after treatment

What is cardiotoxicity

- Acute and early onset: during and within 1 year of commencement of treatment
- Chronic
- Cardiovascular comorbidities

Acute and early onset cardiotoxicity

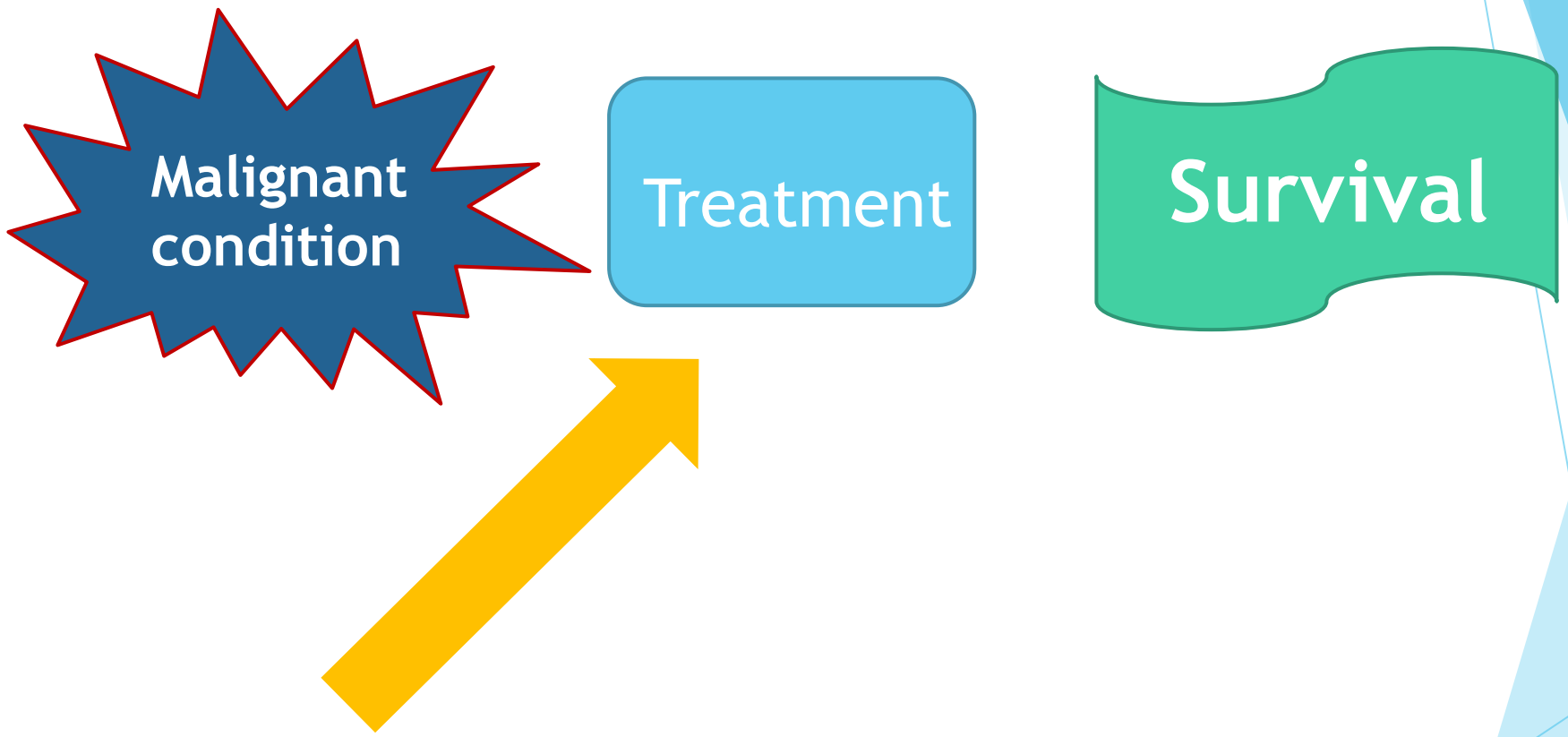
- Arrhythmia
  - Usually transient and subclinical
  - Seen in up to 24% of adults within 24 hours of infusion
  - Prevalence in paedi unknown
- Myocardial injury, with subclinical troponin elevation
  - in ~50% in children receiving moderate dose anthracycline for ALL
- Transient or progressive left ventricular systolic dysfunction (LVSD)
  - COG: cumulative LVSD incidence of 12% within 18 months of therapy
  - Those having LVSD during protocol showed a 12-fold increased risk for LVSD after therapy
- Myocarditis
- Pericarditis

Chronic cardiotoxicity

- Late cardiomyopathy
  - Reported prevalence varied
  - Different definition, screening methodologies, study designs
- Anthracycline-exposed survivors
  - Symptomatic cardiac dysfunction: up to 16%
  - Subclinical disease >50%
- Premature coronary artery disease

CVS comorbidities

- Hypertension
- Dyslipidaemia
- Obesity


Malignant condition
Treatment
Survival

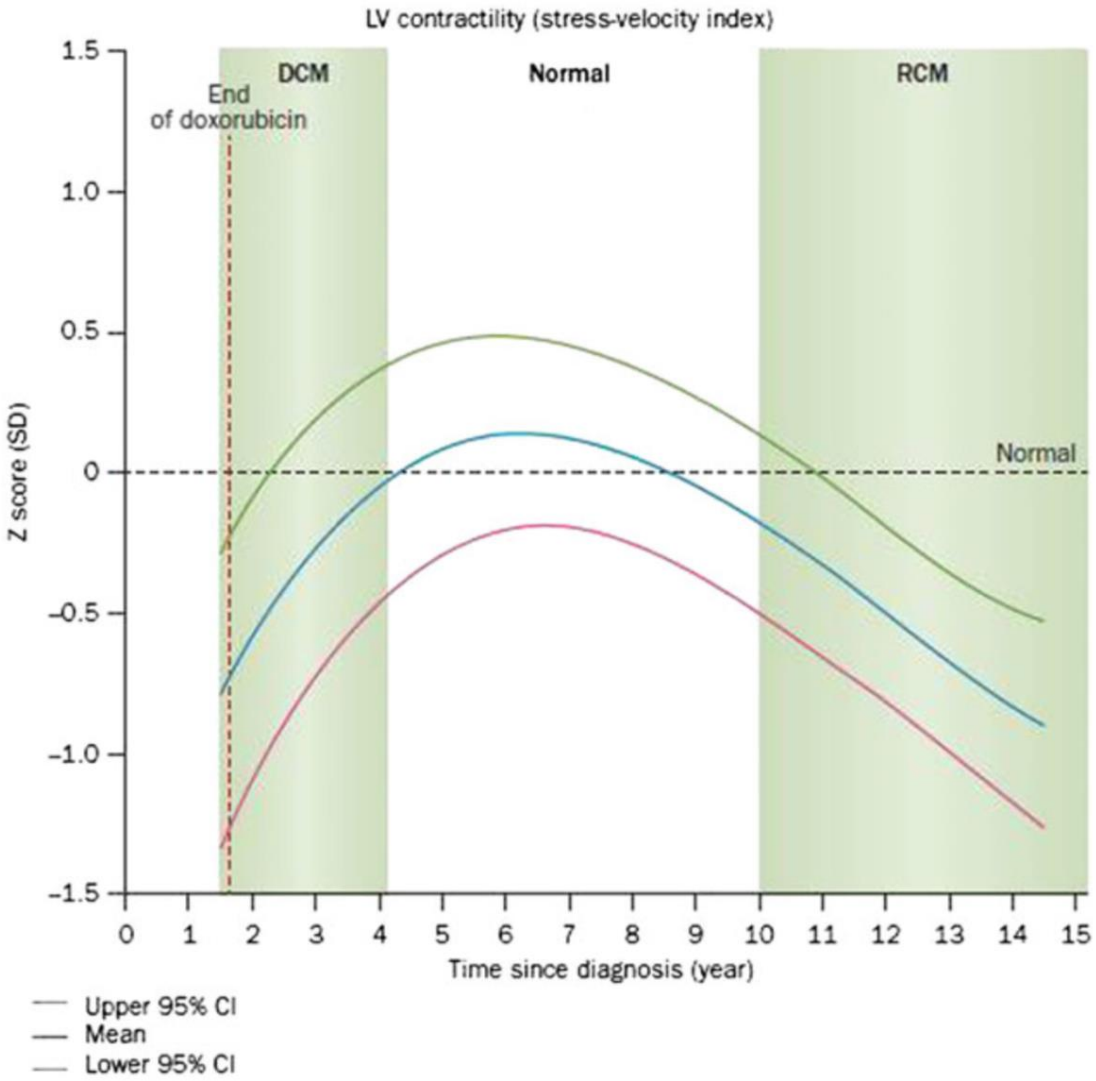
What causes cardiotoxicity

- Traditional chemotherapy
  - Anthracycline
  - Alkylating agents
  - Platinums
  - Anti-metabolites
- Radiation
- Novel agents
  - Targeted therapy
  - Differentiating agents: arsenic, tretinoin
  - Tyrosine kinase inhibitors
  - Immune checkpoint inhibitors

Anthracycline: the most studied

- Doxorubicin, daunorubicin, epirubicin and idarubicin
- Anti-cancer mechanism
  - Inhibits **topoisomerase-II (Top2)** activity → disrupts DNA uncoiling
    - Top2α isoform: overexpressed in tumor cells
    - Top2β isoform: cardiomyocytes
  - DNA basepair intercalation → prevents cell replication
- Backbone of regimen
  - Haemic malignancies: ALL, AML, Hogdkin lymphoma
  - Solid tumors: Ewing sarcoma, osteosarcoma, neuroblastoma, hepatoblastoma

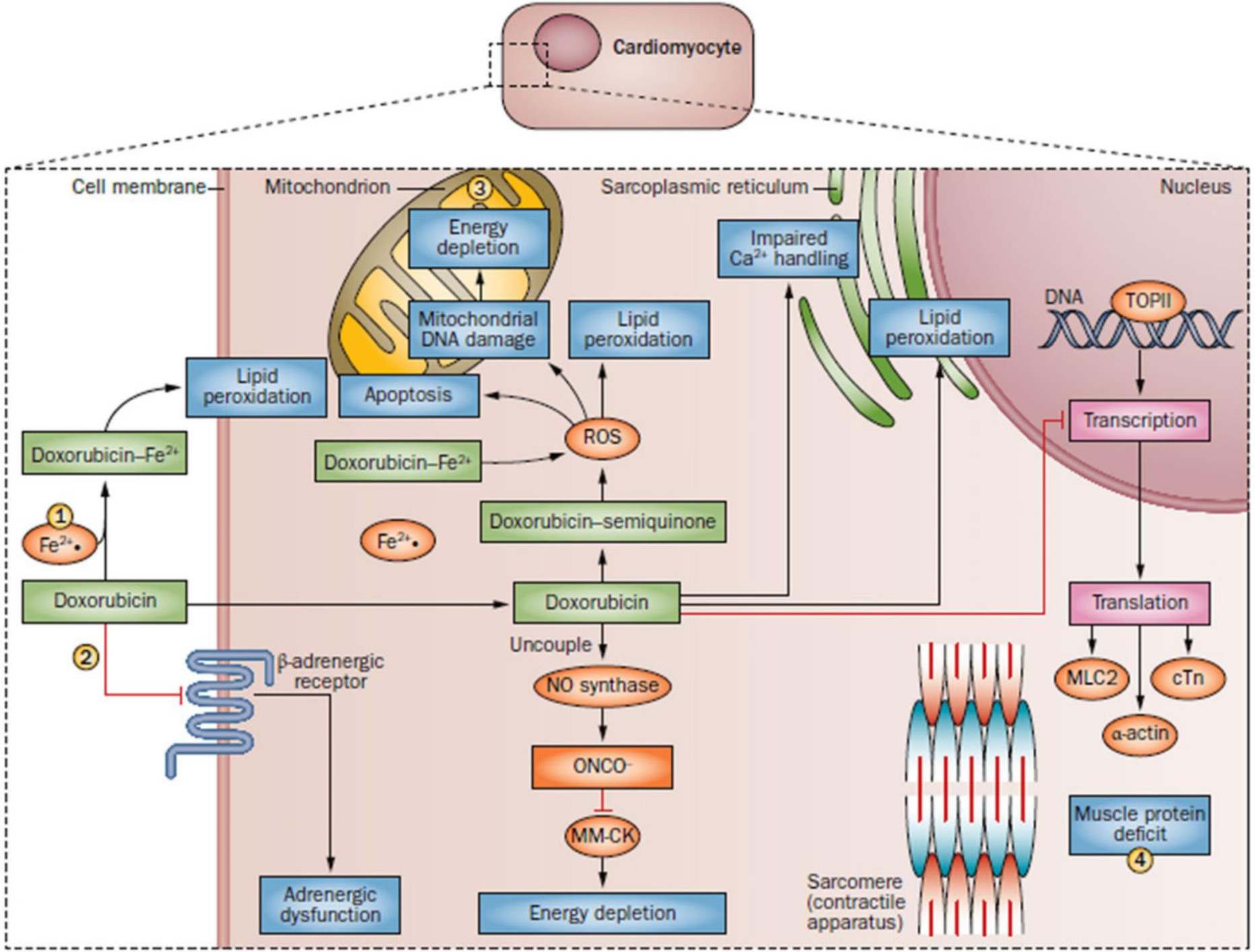
Dana-Farber Cancer Institute data



- Long-term survivors of ALL
- Initially: asymptomatic dilated cardiomyopathy
  - Reduction in LV fractional shortening and contractility
  - LV dilation
- Transient normalized with time
- Years later, progressed to restrictive cardiomyopathy
  - Significantly reduced LV wall thickness, fractional shortening, contractility
  - Normal to reduced LV dimension

Mechanism of anthracycline-cardiotoxicity

- Many proposed pathways
- Dose-dependent cardiotoxicity


Cardiomyocyte
Cell membrane
Mitochondrion
3
Energy depletion
Mitochondrial DNA damage
Lipid peroxidation
Apoptosis
Lipid peroxidation
Doxorubicin–Fe2+
ROS
Doxorubicin–Fe2+
Doxorubicin–semiquinone
1
Fe2+•
Fe2+•
Doxorubicin
Doxorubicin
2
β-adrenergic receptor
Uncouple
NO synthase
ONCO-
MM-CK
Adrenergic dysfunction
Energy depletion
Sarcoplasmic reticulum
Impaired Ca2+ handling
Lipid peroxidation
Nucleus
DNA
TOPII
Transcription
Translation
MLC2
cTn
α-actin
Muscle protein deficit
4
Sarcomere (contractile apparatus)

Risk factors for anthracycline-related cardiotoxicities

- Non-modifiable
- Treatment-related
- Modifiable

Non-modifiable risk factors

- Genetic predisposition
  - Not all children with the same treatment have features of cardiac dysfunction
  - RARG S427L variant: increases Top2β → highly associated with anthracycline-induced cardiotoxicity
  - Genetic variation in UGT1A6*4 haplotype: drug glucuronidation → reduce elimination of anthracyclines and metabolites
  - Hereditary haemochromatosis: mutation of *Hfe* gene → interferes with iron metabolism, causing iron overload
  - Trisomy-21: even for patients without congenital heart disease

Genetic predisposition

Table 3 Published genetic associations for anthracycline-related cardiomyopathy in cancer survivors, adapted from Chow *et al.*[17]

Gene, alphabetical[a,b]	First author, alphabetical (PMID)[c,d]
ABCB1, *ABCB4*, *ABCC1*[a], *ABCC2*, *ABCC5*[a]	Armenian (23927520)
CAT	Aminkeng (26237429)[d]
CBR3[a]	Blanco (18457324 and 22124095)[d]
CELF4[a,b]	Cascales (23576480)
CYBA	Hertz (26799497)
FMO2	Krajinovic (26345518)[d]
HAS3[a,b]	Leger (26968791)
HFE[a]	Lipshultz (23861158)[d]
HNMT	Rajic (19863340)[d]
NCF4[a]	Rossi (19448608)
NOS3	Schneider (27993963)
PRDM2[a]	Semsei (21929509)[d]
RAC2	Visscher (21900104, 23441093, and 26230641)[d]
RARG[a,b]	Vulsteke (26017071)
SLC10A2	Wang (24470002 and 26811534)[d]
SLC22A17[a], *SLC22A7*[a], *SLC28A3*[a]	Wells (28542097)
SPG7	Wojnowski (16330681)
UGT1A6[a]	
rs28714259 (intergenic)[a]	

Studies based on human samples as identified from PubMed as of 1 October 2018; studies based only on cell lines or drug pharmacokinetics are not listed.

[a]Polymorphism in the gene has been associated with the phenotype in at least one separate sample/population.

[b]Evidence for an association from in vitro (i.e. functional) experiments.

[c]Includes studies that reported null findings.

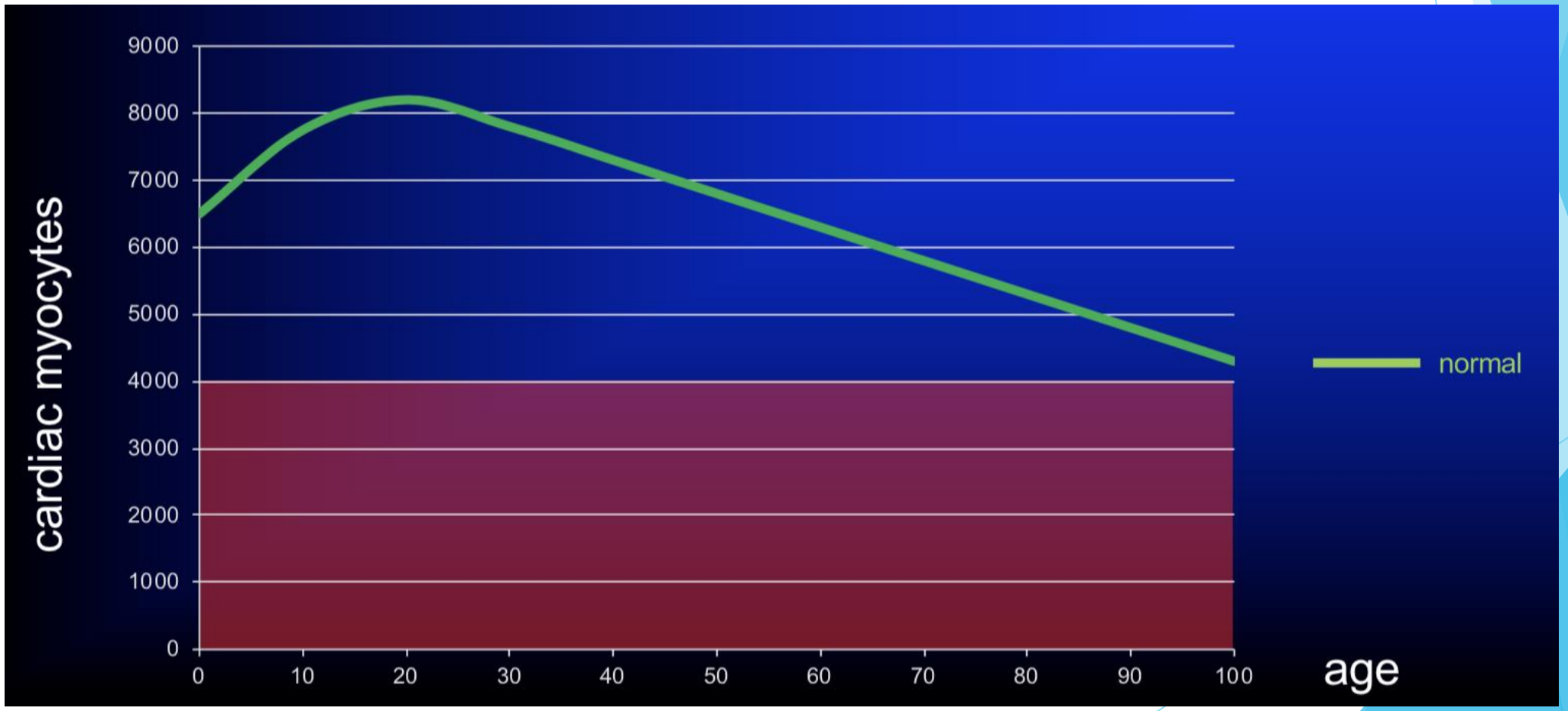
[d]Studies where the population was >50% survivors of childhood cancer.

Non-modifiable risk factors

- Premorbid cardiovascular status
  - Pre-existing CVS disease
  - Family history of premature CVS disease

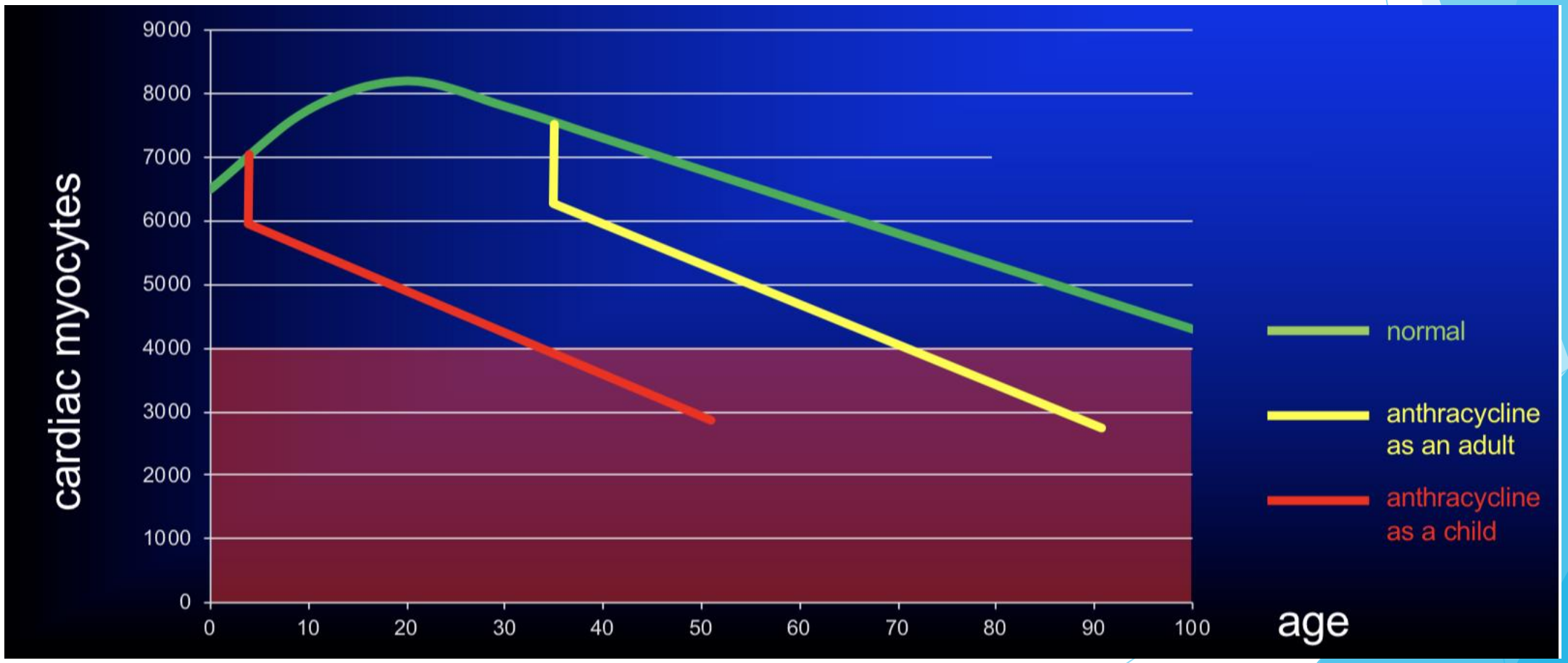
Non-modifiable risk factors

- Age



Non-modifiable risk factors

- Age



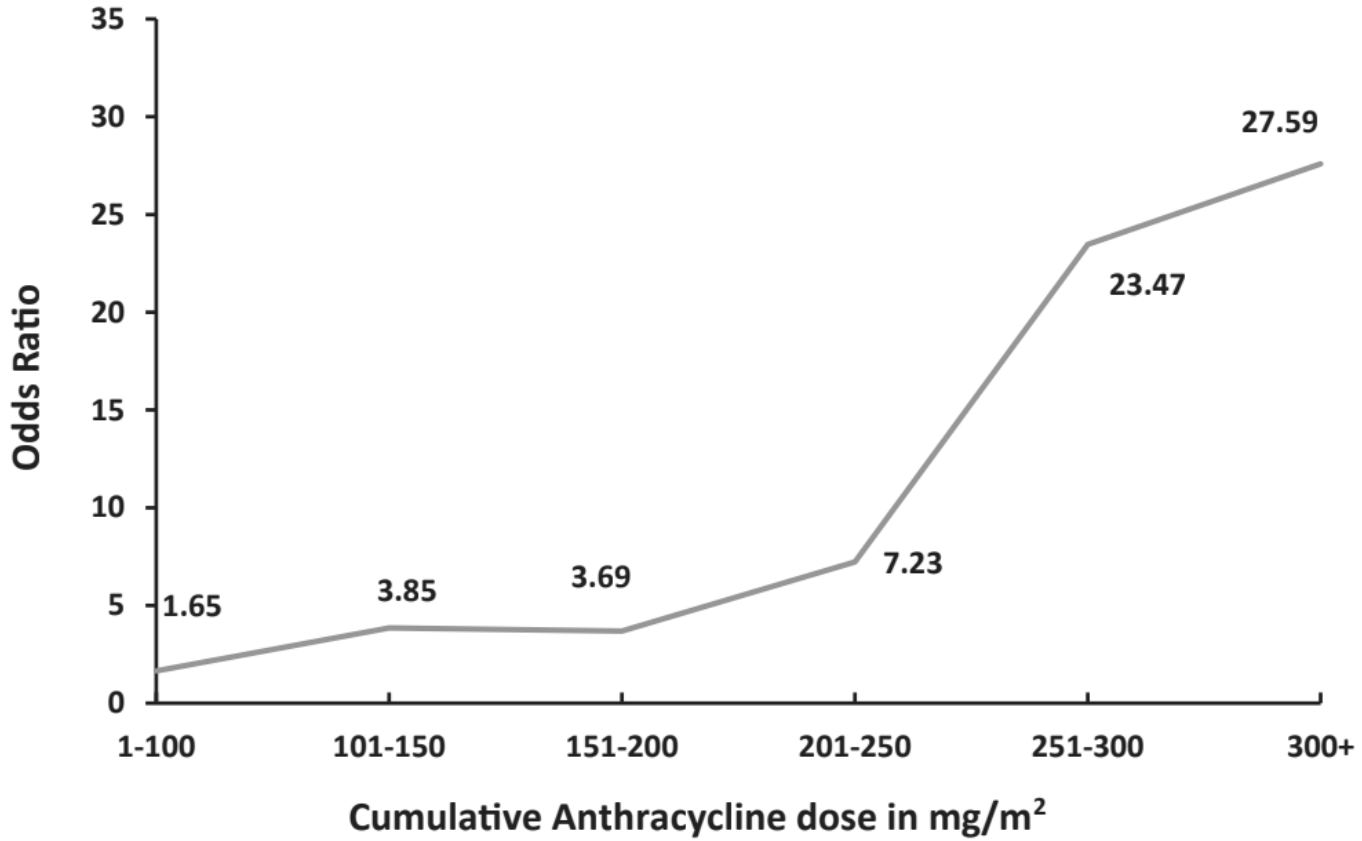
Non-modifiable risk factors

- Race
  - African-Americans
- Gender
  - Female more susceptible
  - Higher percentage of body fat
  - Anthracyclines: poorly absorbed by fat
    - Higher resultant circulating concentrations of drug

Treatment-related risk factors

- High cumulative dose of *anthracycline*
  - A cumulative doses >300mg/m^2 : carries an **11 times** risks of cardiotoxicity as that of cumulative doses < 240mg/m^2
  - Subclinical events in 30% at doses of 180-240mg/m^2
  - Subclinical echo abnormalities also found in patients with cumulative doses < 100mg/m^2
  - → essentially there is **no ”safe” dose**

FIGURE 1. Dose-Response Relationship Between Cumulative Anthracycline Exposure and Risk for Cardiomyopathy



Patients with no exposure to anthracyclines served as the reference group. Magnitude of risk is expressed as odds ratio, which was obtained using conditional logistic regression adjusting for age at diagnosis, sex, and chest radiation. Cumulative anthracycline dose is expressed as doxorubicin equivalent.

Not all anthracyclines are created equal

Anthracycline Toxicity Equivalence Ratios Used in Various Cooperative Groups and Cohort Studies for Assessment of Cardiotoxicity

Group or Study	Doxorubicin*	Daunorubicin	Idarubicin	Epirubicin	Mitoxantrone
Children's Oncology Group[10–12]	1	1†	5	0.67	4
Bristol Royal Hospital for Sick Children[13]	1	1		1	
AML Collaborative Group[14]	1	1	5		5
Kyushu University, Fukuoka, Japan[15]	1	1	1	1	1
Taiwan Pediatric Oncology Group[16]	1		3		2
Childhood Cancer Survivor Study[2]	1	1	3		
Dutch Childhood Oncology Group LATER[3]	1	1		0.67	
Sookmyung Women's University, Seoul, Korea[17‡]	1	0.5	2	0.5	2.2

Abbreviations: AML, acute myelocytic leukemia; LATER, Longterm Effects of Childhood Cancer (Lange Termijn Effecten Kinderkanker).

*Reference value (except AML Collaborative Group, which used daunorubicin ratio of 1 as the reference value).

†Ratio of 1 reported in the current Children's Oncology Group guidelines, version 4, October 2013; previous versions used a ratio of 0.83.

‡All ratios listed are based on hematologic toxicity equivalence rather than cardiotoxicity with the exception of Sookmyung Women's University, which uses ratios that are based on the ratio proposed by Keefe.[18]

Treatment-related risk factors

- Concomitant irradiation
  - Mediastinal (e.g. Hodgkin lymphoma)
  - Cranial
    - Associated with decreased LV mass
    - Hypothesis: affected hypothalamic and pituitary glands, causing GH deficiency
    - Additive or synergistic effect with anthracycline: uncertain

Modifiable risk factors

- ”Usual” CVS risk factors
  - Sedentary lifestyle, hypertension, diabetes, obesity
  - Among survivors
    - 10-year accumulative incidence of diabetes = 18%
    - Among 248 childhood diabetes: 4% had hyperinsulinaemia, 7% had glucose intolerance
  - Smoking, drinking, use of recreational drug (cocaine, heroin, methamphetamine)
  - → atherosclerosis, hypertensive cardiovascular disease

Radiotherapy-induced cardiotoxicity

- Risk factors
  - Dose-dependent: esp >1500-3000 cGy
  - Area of heart exposed
  - Radiation technique: proton or photon
  - Age at radiation
- Mechanism
  - Acute injury and inflammation

  →long-term myocardial fibrosis

  →cardiomyopathy, early coronary disease, valvular and electrophysiological dysfunction

Novel agents

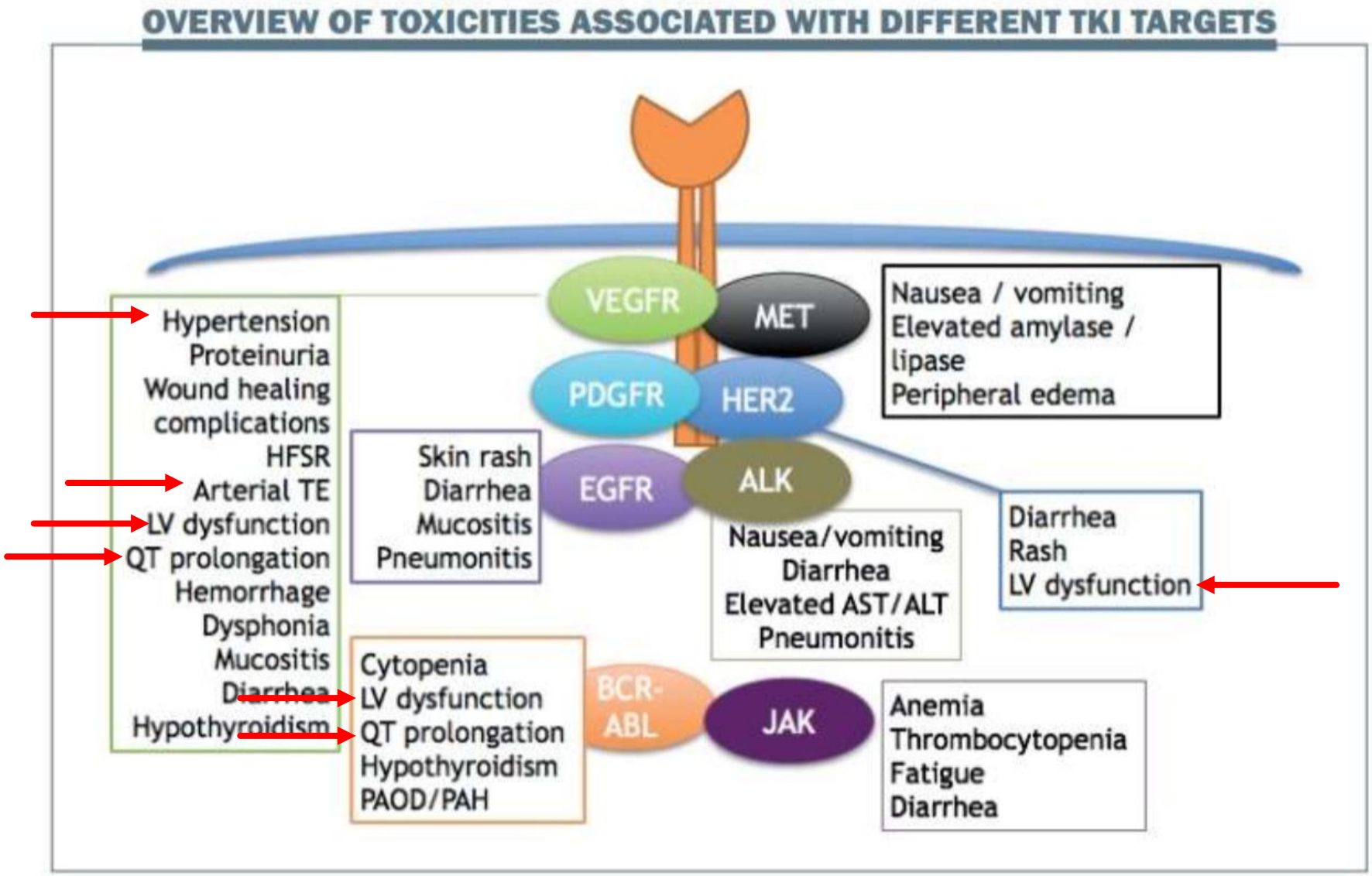
Target	Drug	Usage	Known toxicities
ALK	Crizotinib	High-risk neuroblastoma	Bradycardia QT prolongation
BCR-ABL 1, KIT PDGFR, SRC, EGFR, BRAF, DDR1, DDR2, Ephrin receptors	Dasatinib	ALL	Pulmonary hypertension Vascular events
BTK	Ibrutinib	GVHD prophylaxis and treatment Relapsed non-Hodgkin lymphoma	Atrial fibrillation
CTLA4, PD-1	Ipilimumab	High-grade glioma	Fatal myocarditis
HDAC	Vorinostat	ALL	QT prolongation
P13K-AKT-mTOR	Everolimus	Astrocytoma and subependymal giant cell	Hypercholesterolaemia Hyperglycaemia Hypertriglyceridaemia
	Sirolimus	GVHD prophylaxis	
	Temsirolimus	Hepatoblastoma Rhabdomyosarcoma	

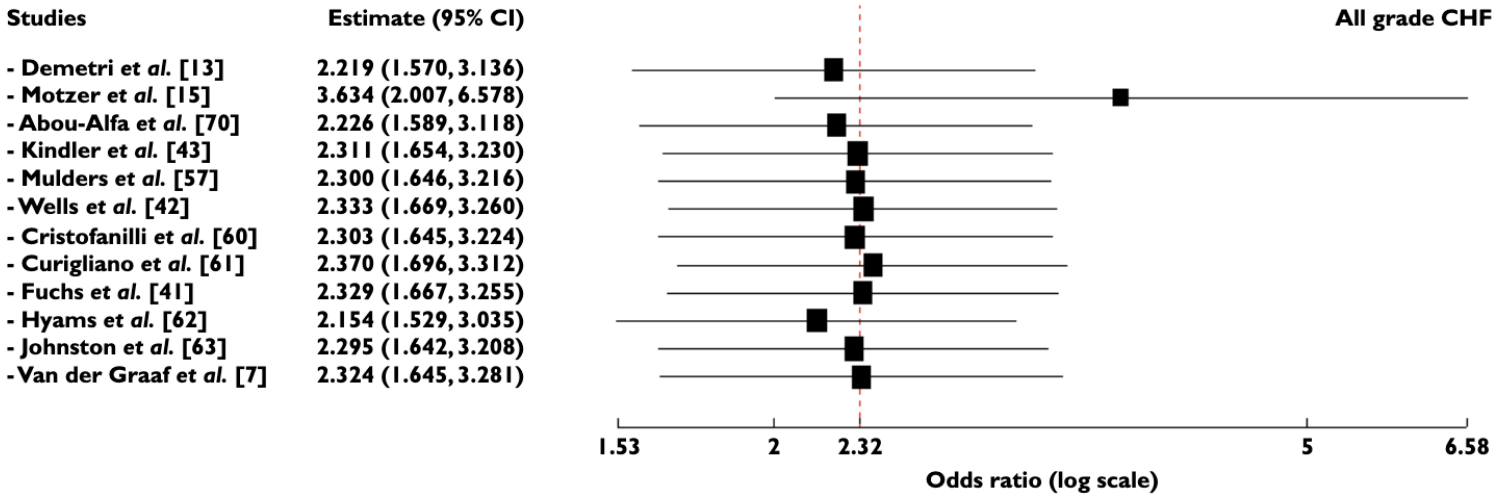
Novel agents

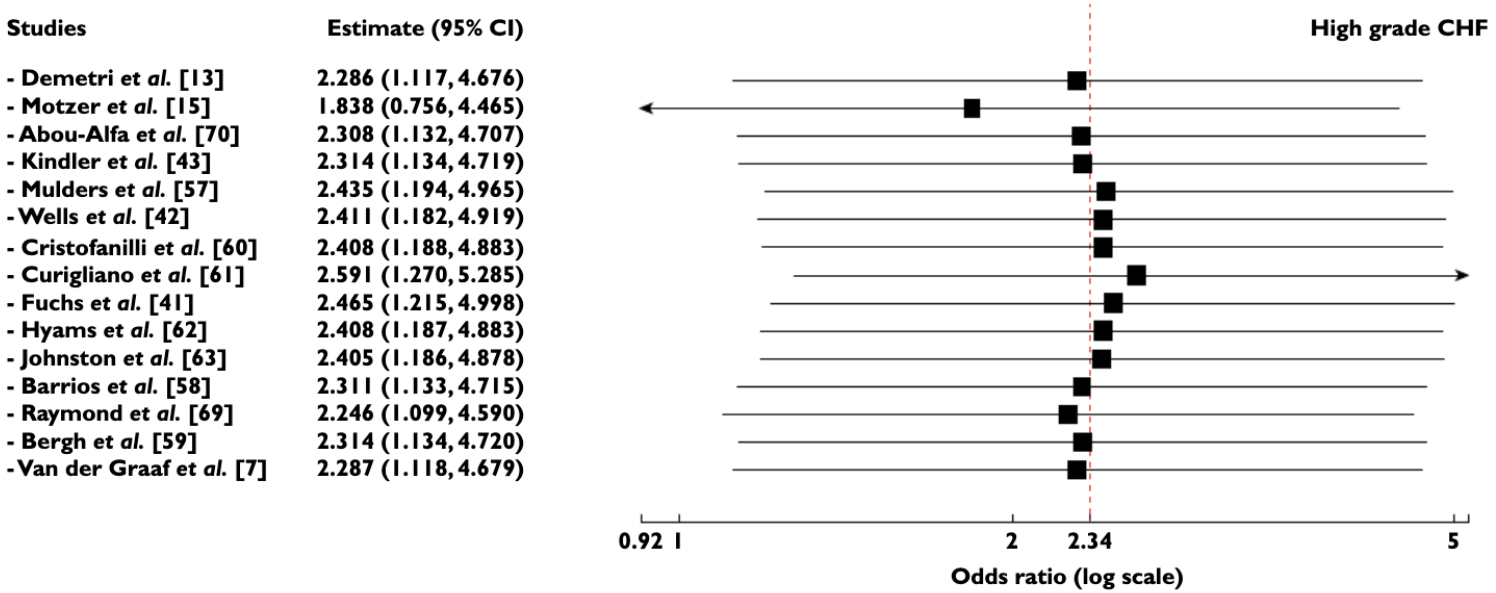
Target	Drug	Usage	Known toxicities
Ubiquitin-proteasome system	Bortezomib	ALL AML	Arrhythmia, cardiomyopathy, heart failure, HT, thromboembolic events
VEGF, VEGFR, PDGFR	Bevacizumab	High-grade glioma High risk neuroendocrine tumor	Cardiomyopathy, heart failure, HT, proteinuria, thromboembolic events
	Pazopanib	Advanced stage angiosarcoma Soft tissue sarcoma	
	Sorafenib	AML Hepatoblastoma Renal cell carcinoma	

Apatinib

- Tyrosine kinase inhibitor
- Selectively inhibits vascular endothelial growth factor receptor-2 (VEGFR2)
- Inhibits angiogenesis


OVERVIEW OF TOXICITIES ASSOCIATED WITH DIFFERENT TKI TARGETS
VEGFR
MET
PDGFR
HER2
EGFR
ALK
BCR-ABL
JAK
Hypertension
Proteinuria
Wound healing complications
HFSR
Arterial TE
LV dysfunction
QT prolongation
Hemorrhage
Dysphonia
Mucositis
Diarrhea
Hypothyroidism
Nausea / vomiting
Elevated amylase / lipase
Peripheral edema
Skin rash
Diarrhea
Mucositis
Pneumonitis
Nausea/vomiting
Diarrhea
Elevated AST/ALT
Pneumonitis
Diarrhea
Rash
LV dysfunction
Cytopenia
LV dysfunction
QT prolongation
Hypothyroidism
PAOD/PAH
Anemia
Thrombocytopenia
Fatigue
Diarrhea

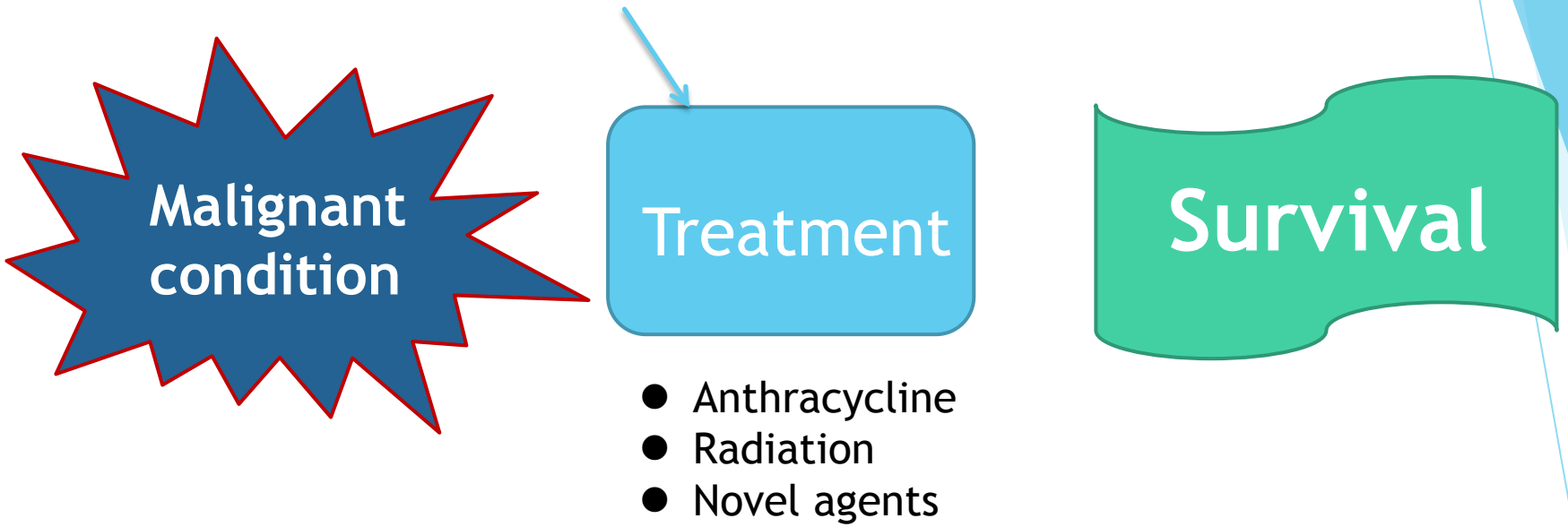




- Meta-analysis in 2014
- 36 clinical trials, 10553 patients
- Overall incidence
  - all CHF 3.2% (95%CI 1.8, 5.8%)
  - High-grade CHF 1.4% (95% CI 0.9, 2.3%)
- Odd ratios
  - All grade CHF 2.37
  - High grade CHF 3.51

Risk factors

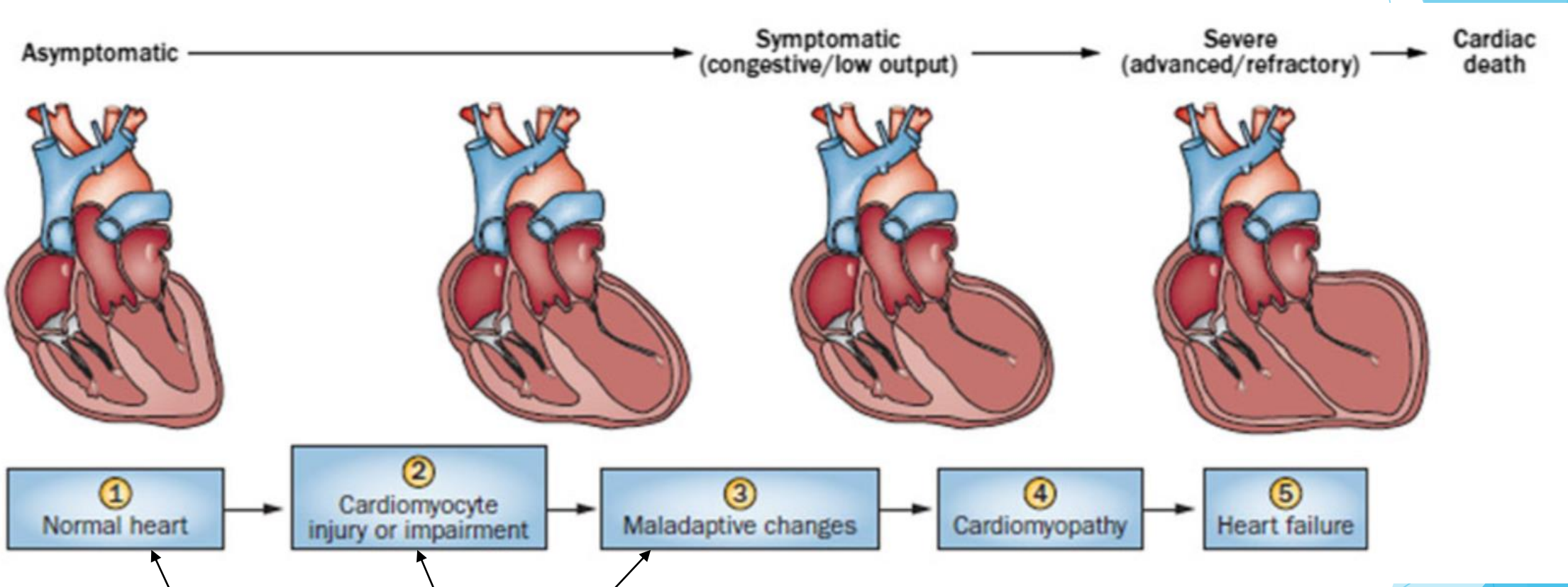
- Treatment-related
- Modifiable
- Non-modifiable



- Anthracycline
- Radiation
- Novel agents

Prevention of cardiotoxicity

- Primary prevention
  - To prevent onset
- Secondary prevention
  - Screening and early detection of cardiotoxicity
  - Prompt and effective treatment
- Tertiary prevention
  - Rehabilitation of patients with an established disease
  - Minimize residual disabilities and complications, improving quality of life


Asymptomatic
Symptomatic (congestive/low output)
Severe (advanced/refractory)
Cardiac death
1 Normal heart
2 Cardiomyocyte injury or impairment
3 Maladaptive changes
4 Cardiomyopathy
5 Heart failure
Primary prevention
Secondary prevention

Primary prevention – Predisposition to cardiotoxicity

- Genetic factor
  - E.g. RARG S427L variant, UGT1A6*4 haplotype
  - Pre-treatment genetic screening → tailor-made protocol?
- CVS comorbidities
  - HT, dyslipidaemia, glucose intolerance
  - identify and control

Primary prevention - Treatment protocol

- Reduce unnecessary anthracyclines
- Switch to alternative agents
- Reduce unnecessary radiation

TABLE 2. Use of Anthracyclines in Contemporary Childhood Cancer Therapeutic Protocols

Primary Cancer	Anthracycline Dose (mg/m^2)*	Plans for Reduction in Anthracycline Dose for All Patients	Alternative Therapeutic Options if Patient Is at High Risk for CD
ALL	75–225	No plans for reduction in dose across the board	May consider alternative therapies on a case-by-case if a patient is at very high risk for CD
AML	450	No plans for reduction in dose across the board	May consider alternative therapies on a case-by-case basis if a patient is at very high risk for CD
HL	250	No plans for reduction in dose across the board	May consider lowering anthracycline dose for patients at very high risk for CD; would need to add agents that could cause other toxicities
ES	375	No plans for reduction in dose across the board	No alternative treatment; focus on aggressive screening/pharmacologic interventions for those at very high risk for CD
OS	450	No plans for reduction in dose across the board	May consider noncardiotoxic drugs if at high risk for CD (slightly inferior survival)
NBL	300	No plans for reduction in dose across the board	For patients at very high risk for CD, would reserve anthracyclines only if the patients do not respond to other treatments on a case-by-case basis

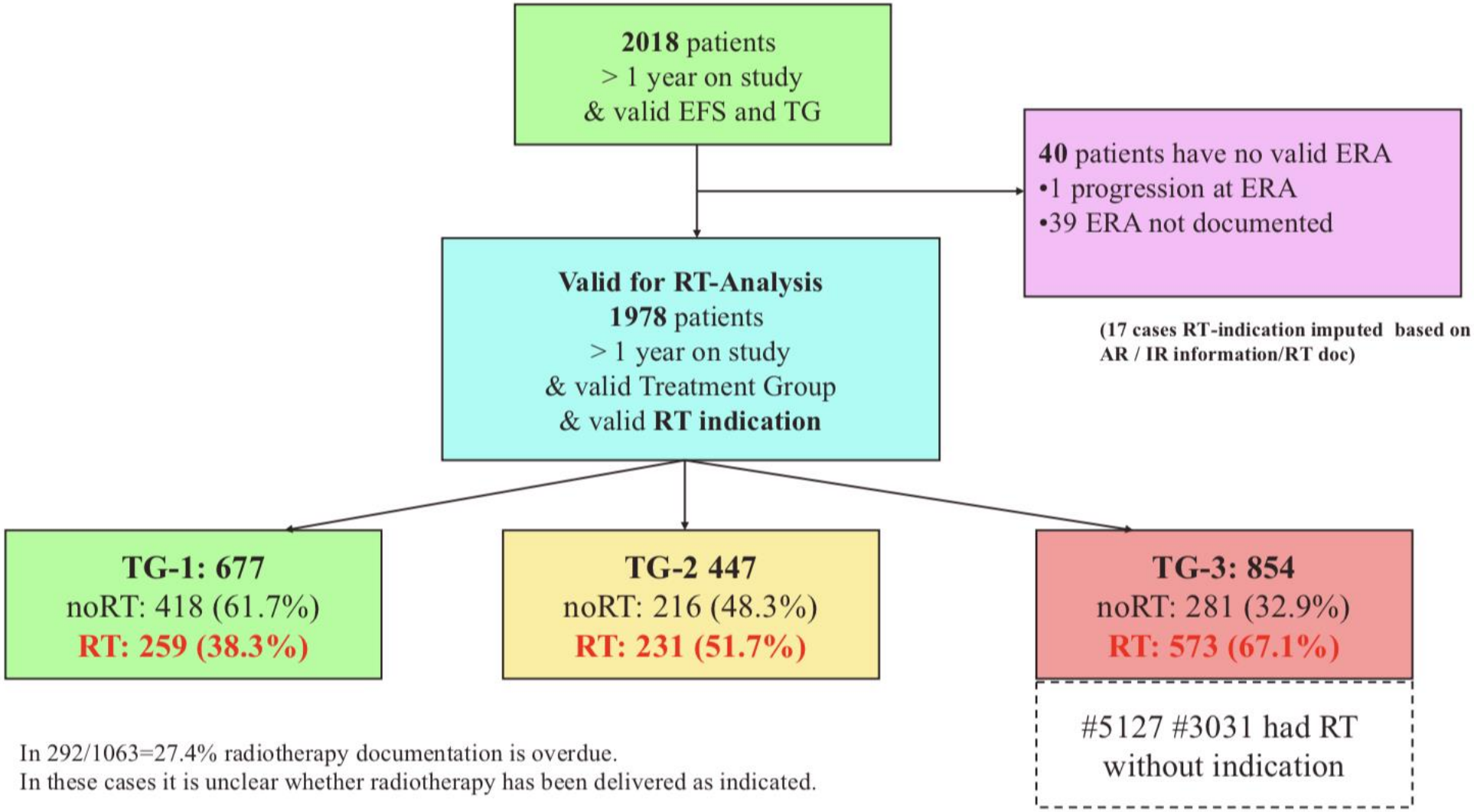
Risk factors	Comment	References
Cumulative anthracycline dose	Cumulative doses >300 mg m^{-2} are associated with significantly elevated long-term risk	[9, 13, 35, 36, 82]
Time after therapy	The incidence of clinically important cardiotoxicity increases progressively over decades	[9, 13, 35, 83]
Rate of anthracycline administration	Continuous infusion not cardioprotective in children	[25, 83]
Individual anthracycline dose	Higher individual doses are associated with increased late cardiotoxicity, even when cumulative doses are limited; no dose is risk-free	[13, 35, 64]
Type of anthracycline	Liposomal encapsulated preparations may reduce cardiotoxicity. Data on anthracycline analogues and differences in cardiotoxicity are conflicting	[79, 84, 85]
Radiation therapy	Cumulative cardiac radiation dose >30 Gy before or concomitant with anthracycline treatment; as little as 5 Gy increased the risk	[28, 82, 83, 86]
Concomitant therapy	Trastuzumab, cyclophosphamide, bleomycin, vincristine, amsacrine and mitoxantrone, among others, may increase susceptibility or toxicity	[28, 85]
Preexisting cardiac risk factors	Hypertension; ischemic, myocardial and valvular heart disease; prior cardiotoxic treatment	[85]
Personal health habits	Smoking; consumption of alcohol, energy drinks, stimulants, prescription and illicit drugs	[83, 49]
Comorbidities	Diabetes, obesity, renal dysfunction, pulmonary disease, endocrinopathies, electrolyte and metabolic abnormalities, sepsis, infection, pregnancy, viruses, elite athletic participation, low vitamin D concentrations	[25–27, 40, 83, 85, 87]
Age	Young (<1 year) and advanced age at treatment are associated with elevated risk	[9, 35, 82, 83]
Sex	Females are at greater risk than males	[35, 64]
Complementary therapies	More information needs to be collected to assess risk	[83]
Additional factors	Trisomy 21; African–American ancestry	[36]

Lipshultz SE, Franco VI, Miller TL, Colan SD, Sallan SE. (2015) Cardiovascular disease in adult survivors of childhood cancer. *Annu Rev Med* 66: 161–176. [11]

Reducing unnecessary radiation - Hodgkin lymphoma

- Very radiosensitive
- Good survival after combining chemotherapy and radiotherapy
- EuroNet-PHL group
  - C1
  - C2

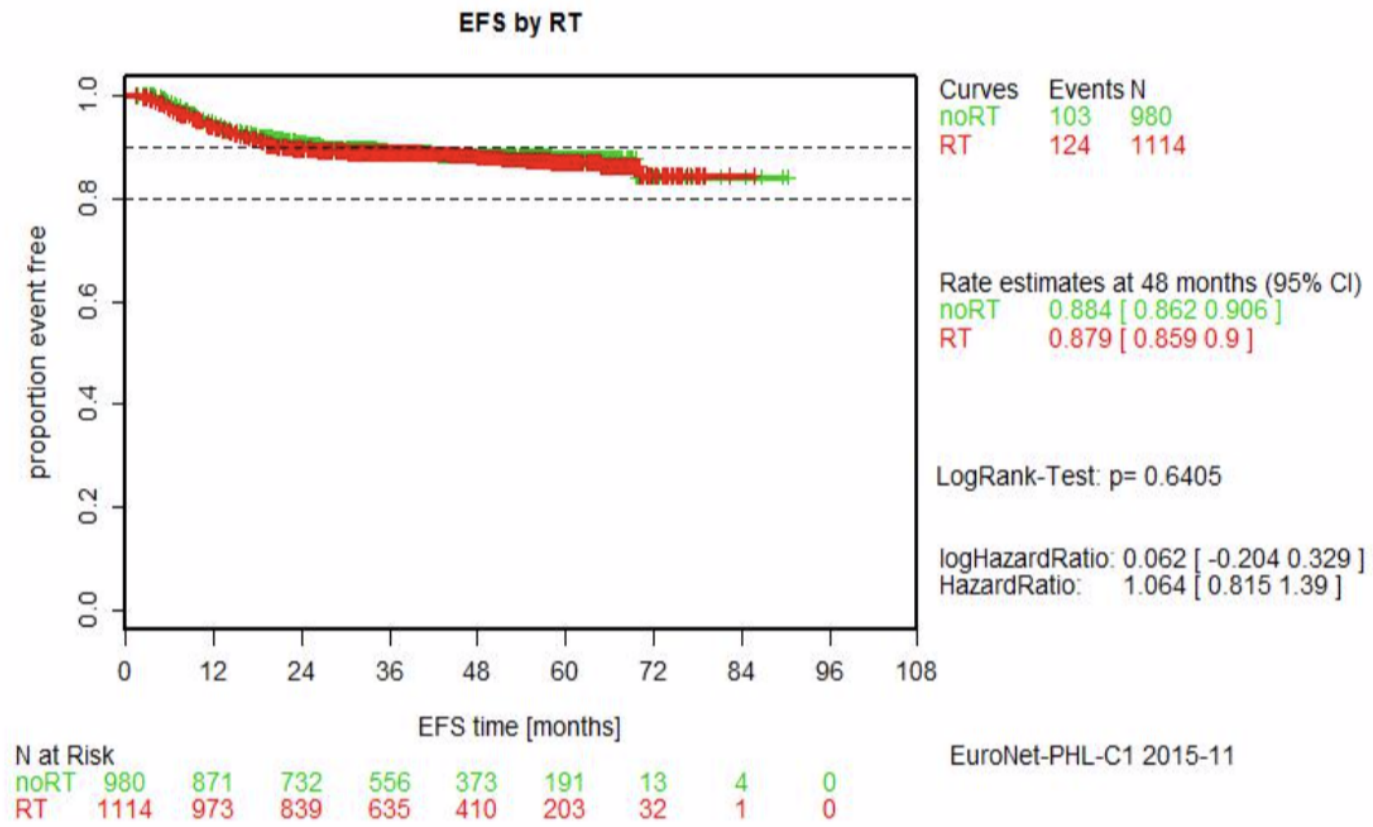
Analyse set for outcome by radiotherapy assignment



In 292/1063=27.4% radiotherapy documentation is overdue.
In these cases it is unclear whether radiotherapy has been delivered as indicated.

EuroNet-PHL-C1

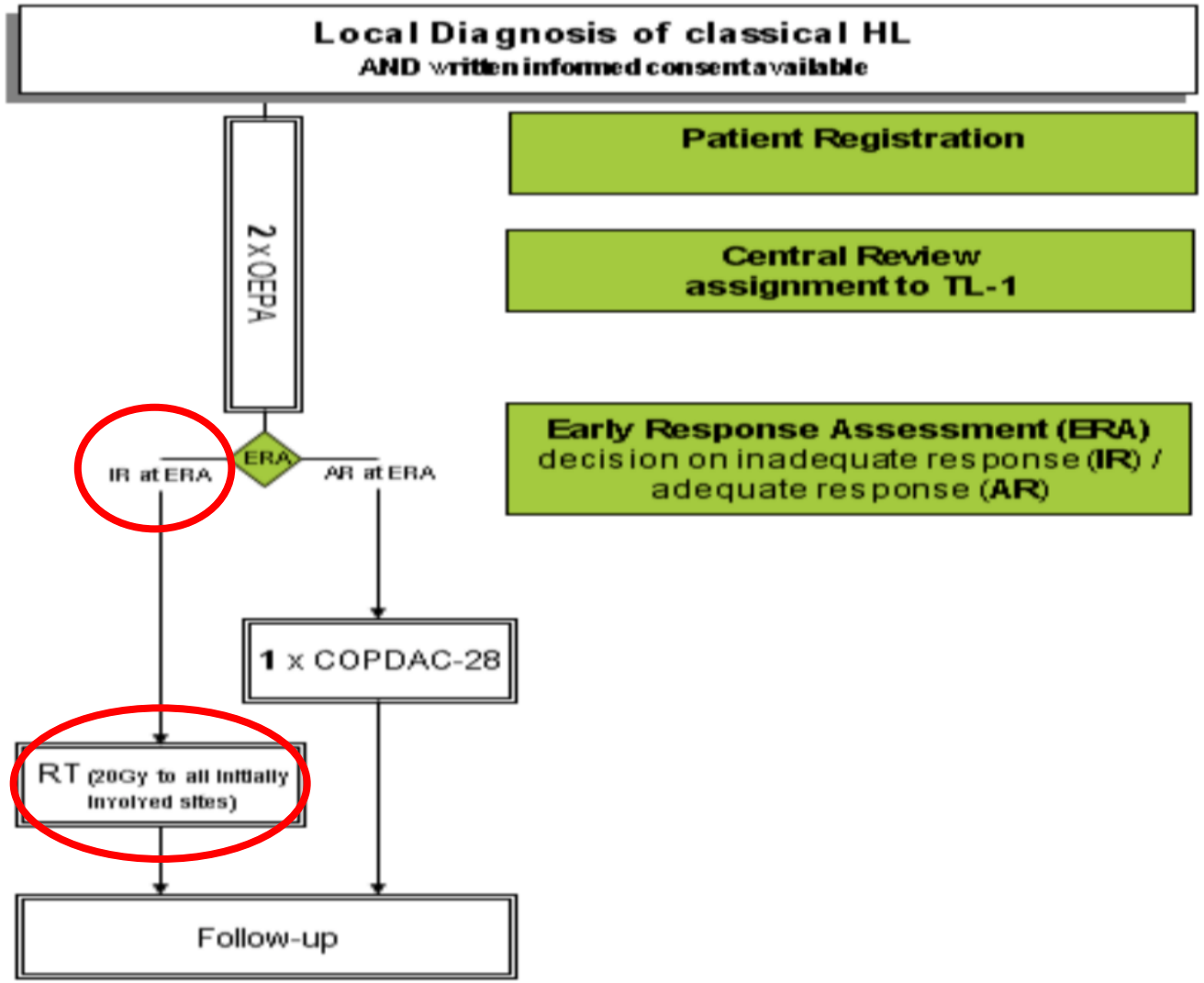
Radiotherapy assigned by ERA



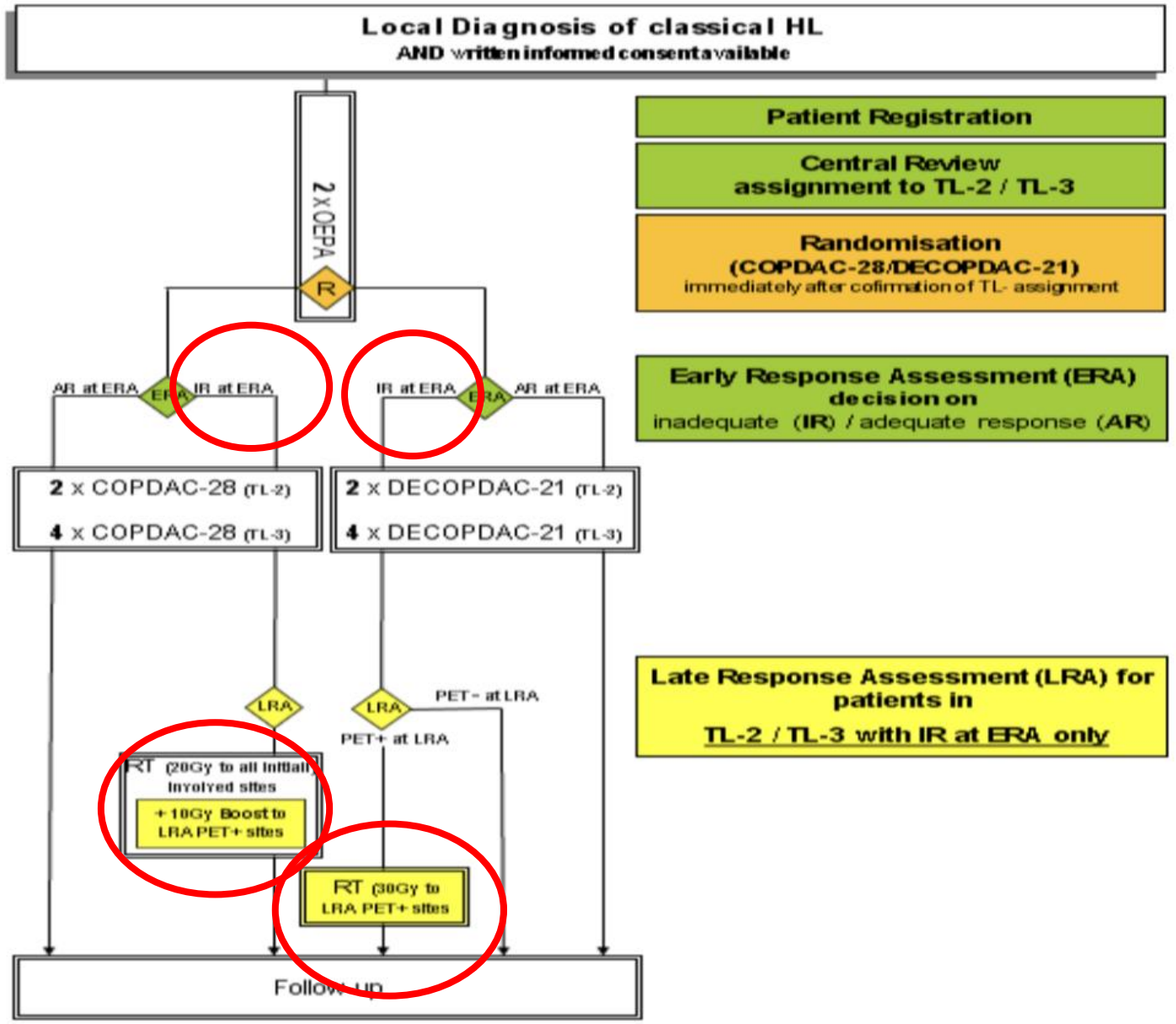
EuroNet-PHL-C1

- Avoided RT in 56% of patients with intermediate or high-risk HL treated with OEPA-COPDAC
- Only irradiated sites of disease with inadequate response to OEPA x2
- Other ways to reduce radiotherapy toxicity
  - Deep inspiration breath hold
  - Intensity modulated radiation therapy
  - Proton beam
- Trial of C2: to give radiotherapy only when patient showed inadequate response?

Flow Diagram for patients in TL-1

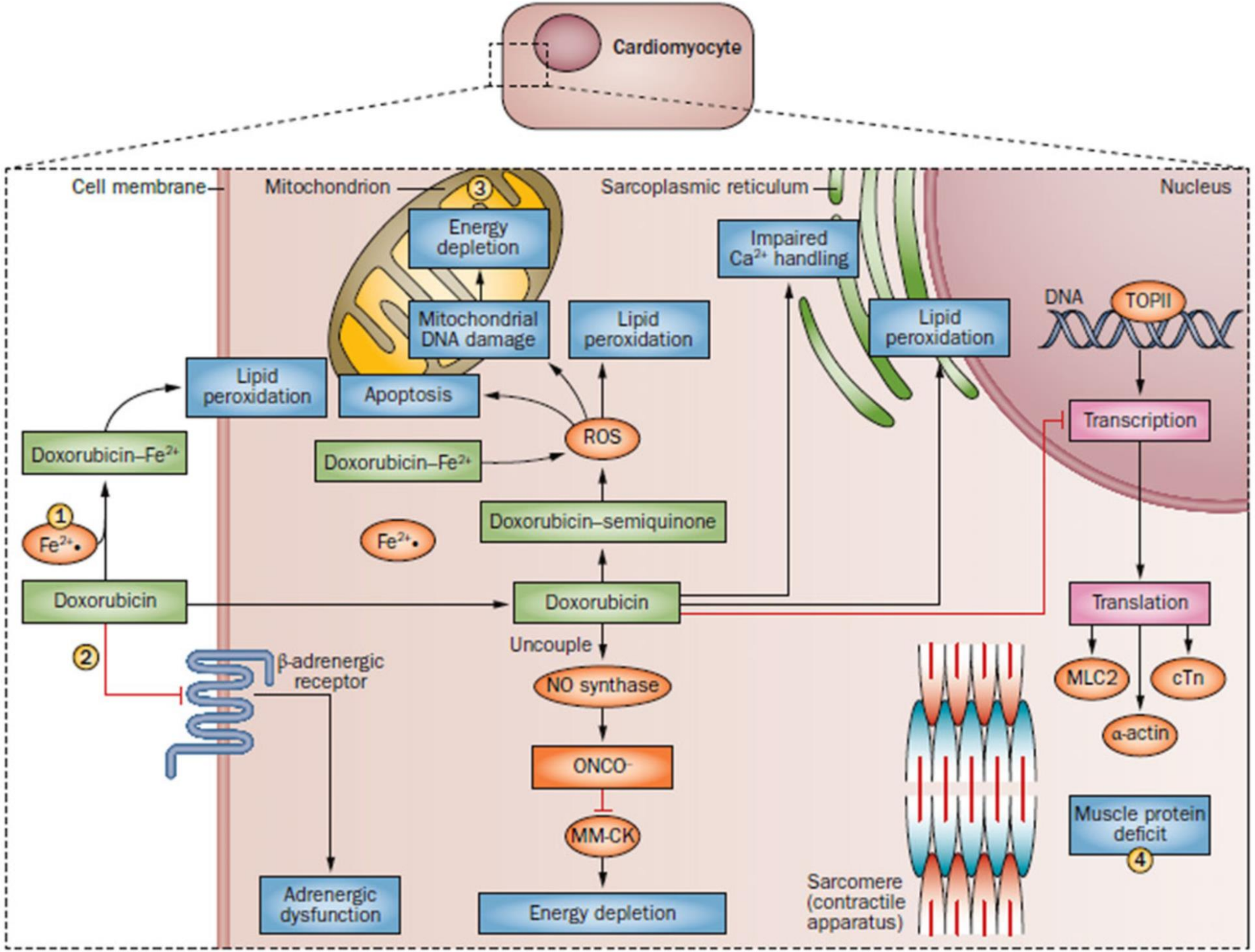


Flow Diagram for patients in TL-2 / TL-3



Primary prevention - Cardioprotectant

- Dexrazoxane
- Carvedilol
- Supplements (coenzyme Q10, L-carnitine, glutathione)


Cardiomyocyte
Cell membrane
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Doxorubicin–Fe2+
ROS
Doxorubicin–Fe2+
Doxorubicin–semiquinone
1
Fe2+•
Fe2+•
Doxorubicin
Doxorubicin
2
β-adrenergic receptor
Uncouple
NO synthase
ONCO-
MM-CK
Adrenergic dysfunction
Energy depletion
Sarcoplasmic reticulum
Impaired Ca2+ handling
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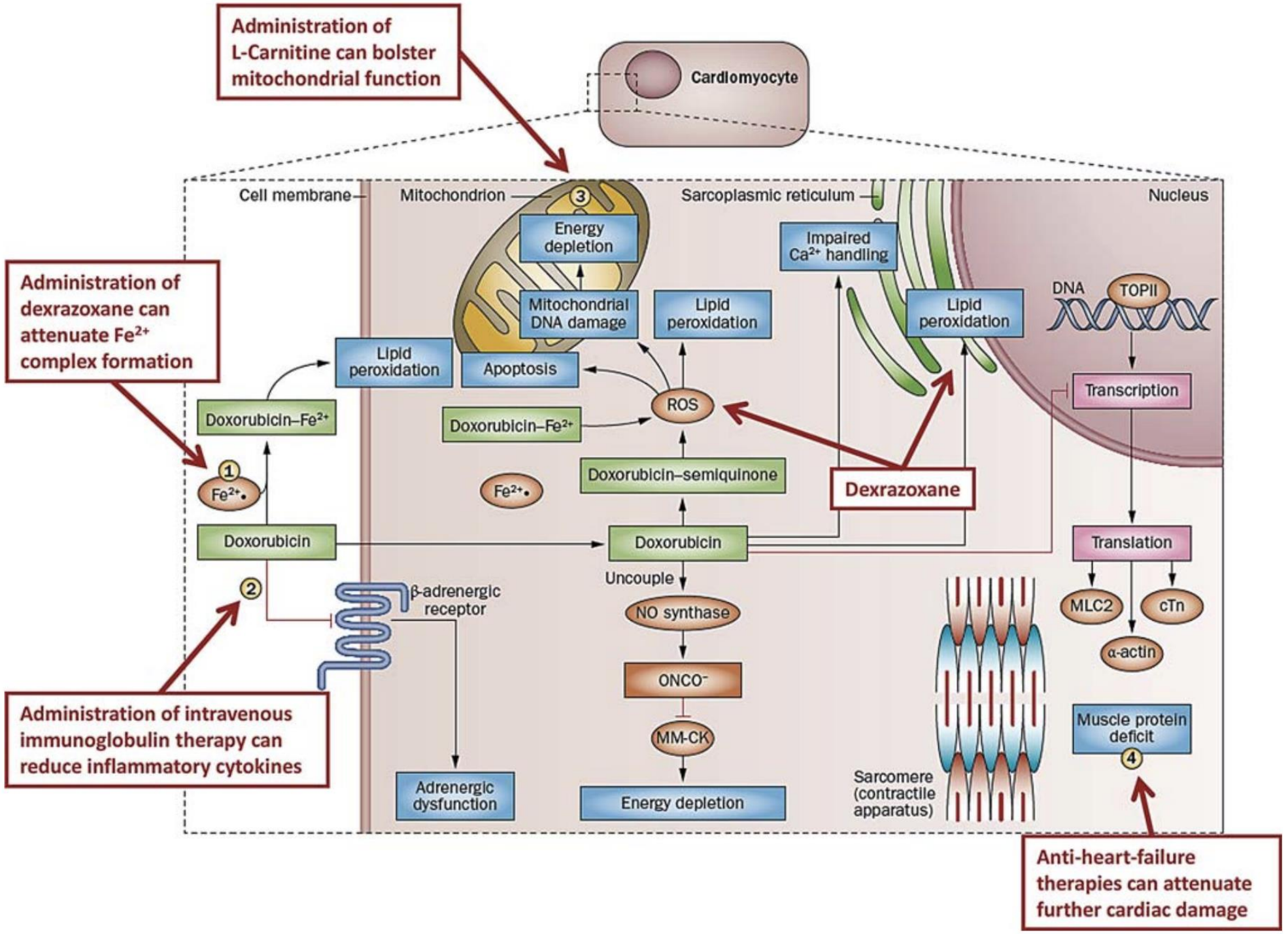

Administration of L-Carnitine can bolster mitochondrial function
Cardiomyocyte
Cell membrane
Mitochondrion
Sarcoplasmic reticulum
Nucleus
Energy depletion
Impaired Ca2+ handling
Administration of dexrazoxane can attenuate Fe2+ complex formation
Mitochondrial DNA damage
Lipid peroxidation
Lipid peroxidation
Lipid peroxidation
DNA
TOPII
Apoptosis
Transcription
ROS
Doxorubicin–Fe2+
Doxorubicin–Fe2+
Doxorubicin–semiquinone
Fe2+
Dexrazoxane
Doxorubicin
Doxorubicin
Translation
Uncouple
β-adrenergic receptor
NO synthase
MLC2
cTn
α-actin
ONCO−
MM-CK
Muscle protein deficit
Sarcomere (contractile apparatus)
Adrenergic dysfunction
Energy depletion
Administration of intravenous immunoglobulin therapy can reduce inflammatory cytokines
Anti-heart-failure therapies can attenuate further cardiac damage

Dexrazoxane (Cardioxane®)

- Discovered in 1972
- In the early 1980s: able to reduce chronic doxorubicin cardiotoxicity
- Proposed mechanism
  - Chelates iron
  - Interferes with iron-mediated free radical generation
  - Interferes with Top2β, reducing DNA damasge
- Doxorubicin combined with bortezomib/carfilzomib/proteasome inhibitors: also effective
- Damaging effects of anthracyclines
  - Attenuated by pre-treatment with dexrazoxane
- All its protective effects: demonstrated by clinical trials among adult women with breast cancer
  - Significant decrease in incidence of clinical heart failure
  - Cost-effective

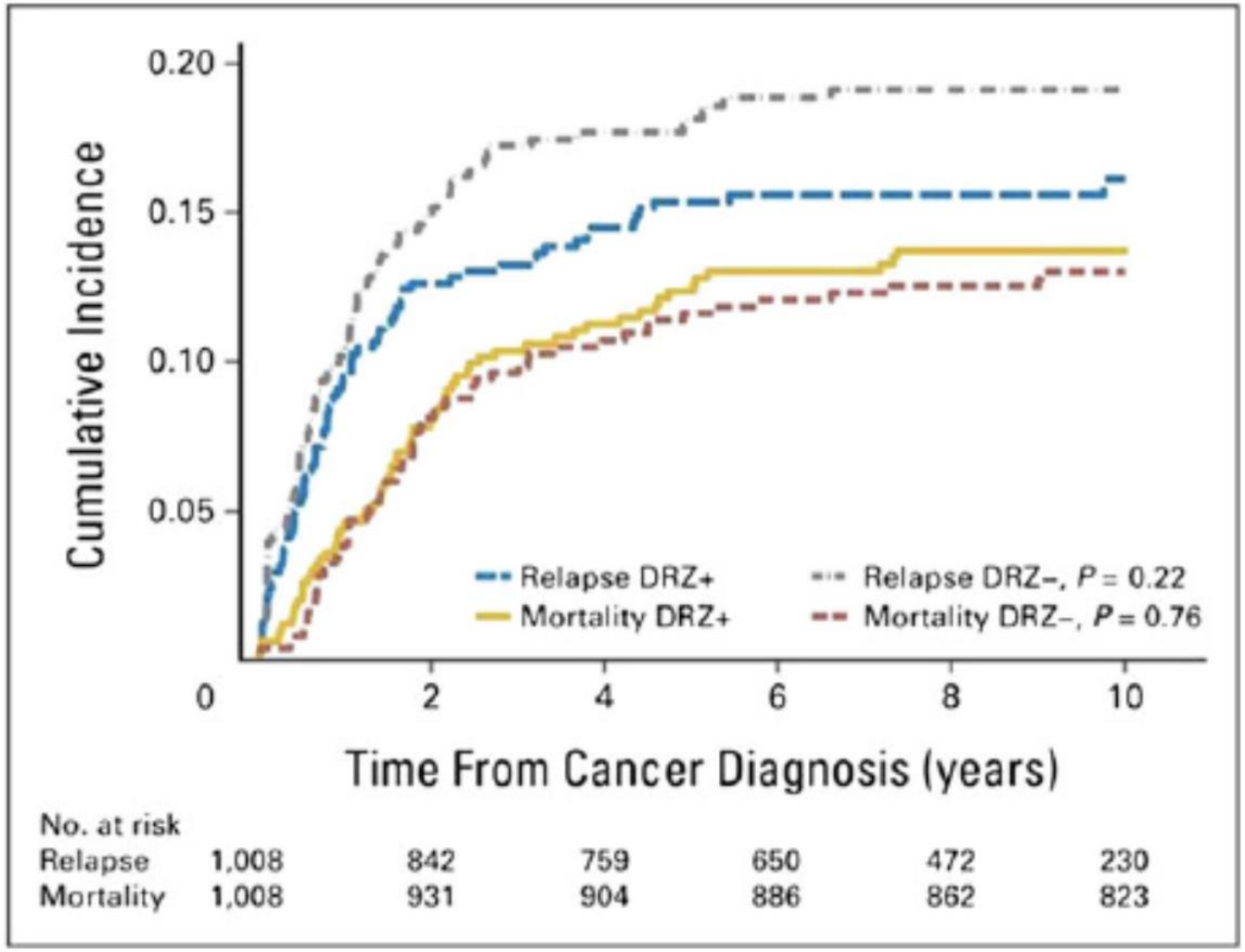
Dexrazoxane's effect

- Effective in paediatric cardioprotection
- Does not decrease effectivness of anthracyclines
- Does not compromise event-free survival
- Multi-centered RCT
  - ALL treated with doxorubicin: higher cardiac troponin T in patients without dexrazoxane treatment
  - Long-term cardioprotection: echo 5 years after completion
  - No significant difference in EFS at 8.7 years

Dexrazoxane‘s safety - leukemia/lymphoma

- Use as a cardioprotectant: endorsed by AHA and AAP
- COG report (2015), with median FU of 12.6 years
  - dexrazoxane has no adverse effect on overall survival in T-ALL, T-cell acute lymphoblastic lymphoma, Hodgkin lymphoma of all risk-group
- Paediatric oncology group (2016)
  - in patients with newly-diagnosed T-ALL or lymphoblastic non-Hodgkin lymphoma, it is not associated with increased incidence of secondary malignant neoplasms or toxicities

COG report 2015



Dexrazoxane's safety - solid tumor

- Osteosarcoma
  - HER2-positive metastatic osteosarcoma
    - Combination of trastuzumab/doxorubicin/ dexrazoxane did not increase the risk of acute myocardial injury
  - Localised disease
    - Dexrazoxane allowed doxorubicin to be intensified without impairing tumor response or increasing risk of secondary malignancies

European view

- European Medicine Agency (EMA)
  - Restricting use to adult patients with advanced or metastatic breast cancer
- EMA Committee for Medicinal Products for Human Use
  - Recommended contraindicating the use of dex in children
- Main concern
  - Linked to an increased risk of acute myeloid leukemia and myelodysplastic syndromes (case reports)
  - ? The benefits only outweighs risks in adults with advanced or metastatic breast cancer
  - Ratio of administration
    - Dex: doxo 10:1
    - Dex : epirubicin 10:1

Dexrazoxane in Hong Kong

- Unregistered
- Unit cost $4359 per 500 mg vial
- No standby stock
- Named-patient request, SFI

Dexrazoxane in Hong Kong Children Hospital

- 2 patients treated with dexrazoxane so far
  - An osteosacroma patient who developed impaired cardiac function after repeated courses of doxorubicin
  - A relapsed AML patient who had doxorubicin cumulative dose >300 mg/m^2
- NOT a routine
- Proposed prescribing guideline
  - For paediatric patients who have received a **prior cumulative dose of 300 mg/m^2 of doxorubicin**

Potential budget impact

Protocol	Cumulative doxo equiv dose	Patients per annum
• AML 2012	370	10 – 15
• Osteosacroma 2009	360 (good responders) 420 (poor responders)	10 – 15
• RMS high risk	375	5 – 10
• Ewing 2012	375	5 – 10
• PHITT 2019	360 (Group C C5VD arm)	2

Estimated yearly drug expenditure

= 40 patients x 2 vials/course x 130% (for relapse cases)

= $460K

Carvedilol

- In vitro studies
  - Inhibits reactive oxygen species
  - Scavenges free radicals
  - Prevents lipid peroxidation
  - Increases vitamin E concentration

Supplements

- Coenzyme Q10
  - anti-oxidant
  - pre-clinical and clinical studies
- L-carnitine
  - Anti-oxidant
  - Insufficient evidence
- Glutathione
  - Anti-oxidant
  - Effects demonstrated in in vitro and animal studies

When to perform cardiac assessment

- As baseline before 1st cycle of anthracycline
- For normal baseline cardiac function, repeat when
  - Before a cycle of anthracycline when cumulative dose of daunorubicin and doxorubicin reaches
    - 120mg/m^2 for <5 years old
    - 200mg/m^2 for >= 5 years old
  - When cumulative dose of anthracycline is increased by 50mg/m^2
- Idarubicine 12mg equivalent to 50mg daunorubicin or doxorubicin for calculation
- Indications of deteriorating cardiac function
  - FS <29%, with Hb >10g/dL and not on hyperhydration therapy
  - Significant decrease in FS by >10 percentile points from baseline or previous echo

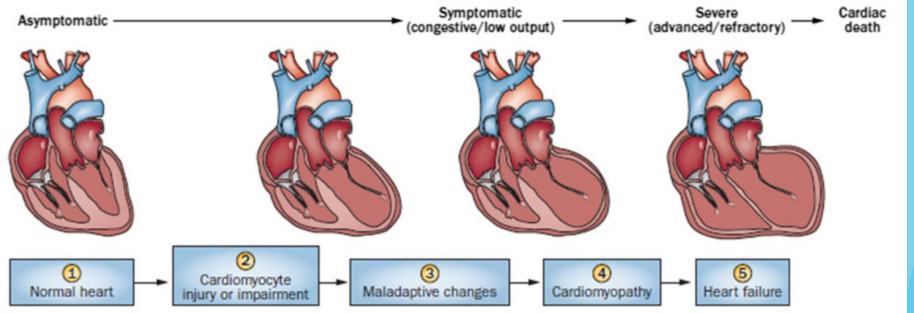
→ If either of the above occurs, assess LVEF by MUGA or MRI heart

When to perform cardiac screening

- Pay attention to situations with extra CVS stress
  - Infection, bacterial sepsis
  - Generalized anaesthesia
- Long-term survivor clinics
  - Regular screening even for asymptomatic patients

Control CV risk factors

Risk factors
- Treatment-related
- Modifiable
- Non-modifiable



Malignant condition

Treatment

- Anthracycline
- Radiation
- Novel agents

Survival

Streamline protocol

Lowest doses possible

Cardioprotectant

Regular screening

Early detection, diagnosis, and treatment

Primary prevention

Secondary prevention

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  - Apatinib drug information
  - Dexrazoxane Use in Hong Kong Children Hospital

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Thank you!