Management of Cardiotoxicity in Childhood Cancer Patients

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No disclosure

Table 1
Distribution of cases of childhood and adolescent cancers in the United States with common, potentially cardiotoxic treatment exposures

	Proportion of Cancers, Children 0–14 y (%)	Proportion of Cancers, Adolescents 15–19 y (%)	Cumulative Anthracycline Dose[c]	Potential Thoracic Radiation Exposure Scenarios
Leukemia				
Acute lymphocytic leukemia	26	8	Low[d]	Craniospinal photon radiation
Acute myeloid leukemia	5	4	High	—
Lymphoma				
Hodgkin lymphoma	4	15	Low or high[d]	Site dependent
Non-Hodgkin lymphoma	6	8	Low or high[d]	Site dependent
Central nervous system[a]	21	10	—	Craniospinal photon radiation
Neuroblastoma	7	—	Low[d]	Site dependent
Retinoblastoma	3	—	—	—
Wilms tumor	5	—	Low[d]	Select metastatic patients or abdominal radiation
Bone tumors[b]	4	7	High	Select metastatic patients
Soft tissue sarcoma	7	7	High[e]	Select metastatic patients
Germ cell tumors	3	12	—	—
Carcinoma and melanoma	4	20	—	Site dependent

Treatment is highly variable based on diagnosis, patient age, disease stage, site of disease, and several other factors. Represented in this table are general trends only.

[a] Includes ependymoma, astrocytoma, and medulloblastoma.

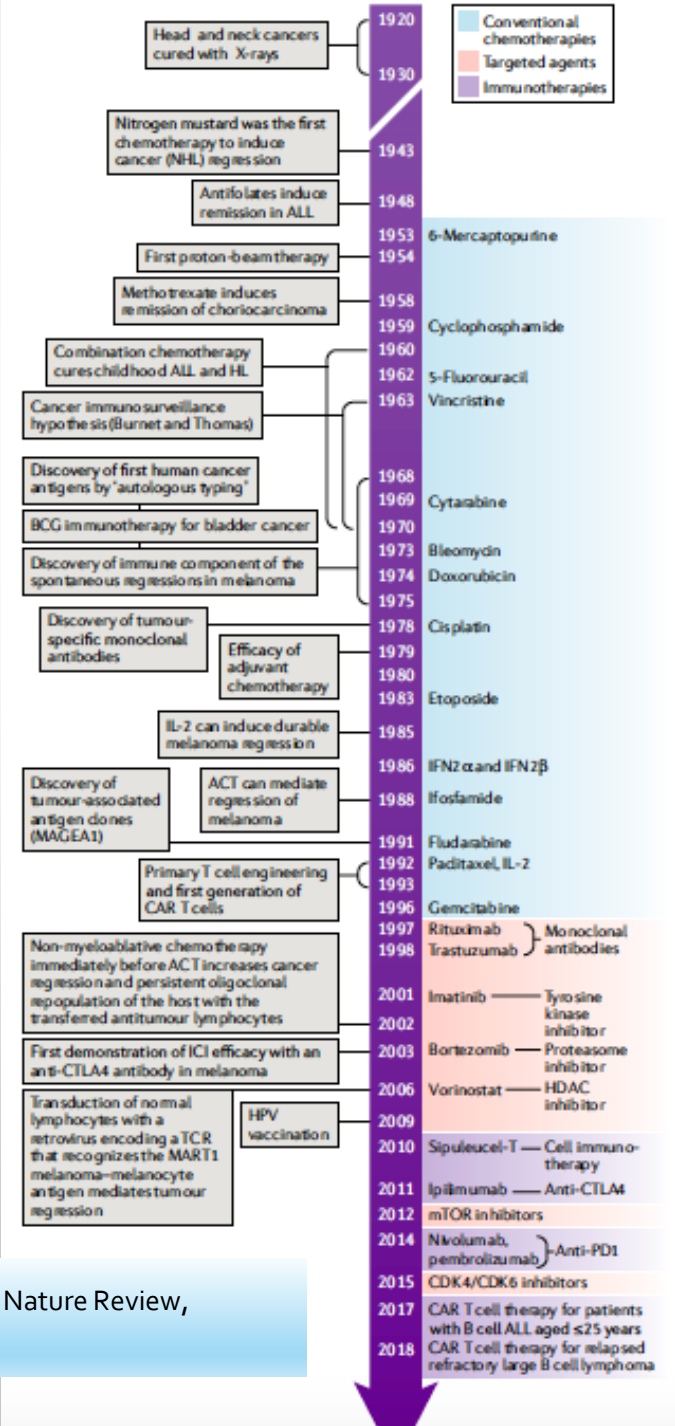
[b] Includes osteosarcoma and Ewing sarcoma.

[c] High (cumulative ≥250 mg/m^2) and low dose (<250 mg/m^2) applies to doxorubicin or doxorubicin equivalent of other anthracyclines.

[d] Anthracyclines included only in select high-risk and intermediate-risk regimens, not all treatment protocols.

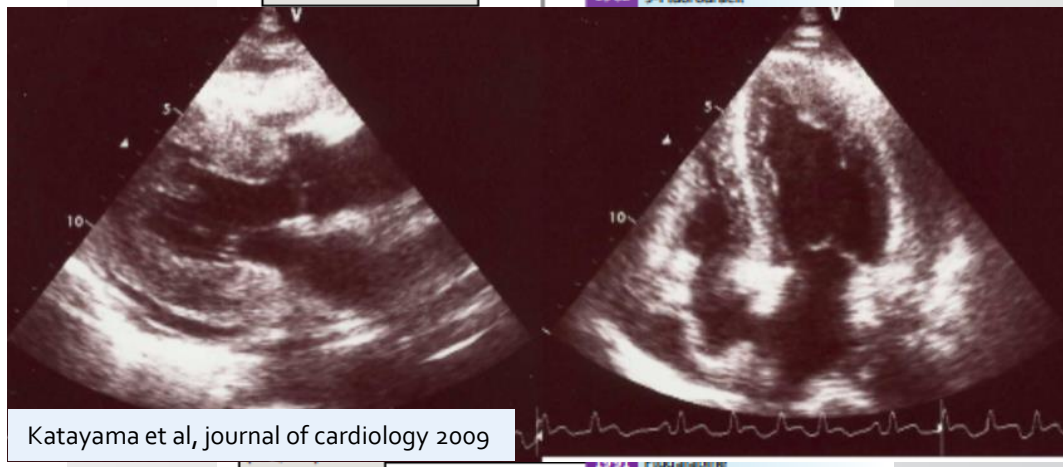
[e] Anthracycline inclusion dependent on the specific tumor type and therapy treatment selected included only in select high-risk regimens, not all treatment protocols.

Adapted from Ward E, DeSantis C, Robbins A, *et al.* Childhood and adolescent cancer statistics, 2014. *CA: a cancer journal for clinicians.* 2014;64(2):83-103 and *data from* Howlader N, Noone AM, Krapcho M, *et al.* SEER cancer statistics review, 1975-2009 (vintage 2009 populations), national cancer institute. Available at: https://seer.cancer.gov/csr/1975_2009_pops09.



Joerg Herrmann; Nature Review, cardiology 2019

	Arrhythmia	Cardio-myopathy	Arterial vascular disease	Venous thrombo-embolism	Pulmonary hypertension	Systemic hypertension	Pericardial disease	Valvular heart disease
Conventional chemotherapies								
Anthracyclines (doxorubicin, epirubicin)		✓						
Alkylating agents (cyclophosphamide, melphalan)	✓	✓	✓					
Antimetabolites (5-fluorouracil, capecitabine, cytarabine)		✓	✓				✓Cytarabine	
Microtubule-binding agents (paclitaxel)	✓ brady		✓					
Platinum-based therapy (cisplatin)			✓	✓		✓		
Antibiotic (bleomycin)			✓		✓			
Immunomodulatory drugs (thalidomide)	✓ brady			✓				
Targeted agents								
Proteasome inhibitors (bortezomib, carfilzomib)		✓	✓			✓		
HDAC inhibitors (vorinostat)	✓							
CDK4/CDK6 inhibitors (ribociclib)	✓							
mTOR inhibitors (everolimus)	✓	✓	✓	✓		✓		
HER2 inhibitors (pertuzumab, trastuzumab)		✓						
VEGF inhibitors (bevacizumab, sunitinib)		✓	✓	✓		✓		
BCR–ABL1 inhibitors (dasatinib, nilotinib, ponatinib)	✓ QT		✓	✓	✓Dasatinib			
BTK inhibitors (ibrutinib)	✓							
ALK inhibitors (alectinib, ceritinib, crizotinib)	✓				✓			
BRAF inhibitors (dabrafenib)	✓	✓						
MEK inhibitors (binimetinib, cobimetinib, trametinib)	✓	✓			✓			
Immunotherapies								
Immune checkpoint inhibitors	✓	✓	✓	✓	✓		✓	
CAR T cell therapy	✓	✓	✓	✓	✓		✓	
Other therapies								
Radiation therapy	✓	✓	✓		✓		✓	✓



Katayama et al, journal of cardiology 2009

Joerg Herrmann; Nature Review, cardiology 2019

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Modifiable Risk Factors and Major Cardiac Events Among Adult Survivors of Childhood Cancer

Gregory T. Armstrong, Kevin C. Oeffinger, Yan Chen, Toana Kawashima, Yutaka Yasui, Wendy Leisenring, Marilyn Stovall, Eric J. Chow, Charles A. Sklar, Daniel A. Mulrooney, Ann C. Mertens, William Border, Jean-Bernard Durand, Leslie L. Robison, and Lillian R. Meacham

ABSTRACT

Purpose

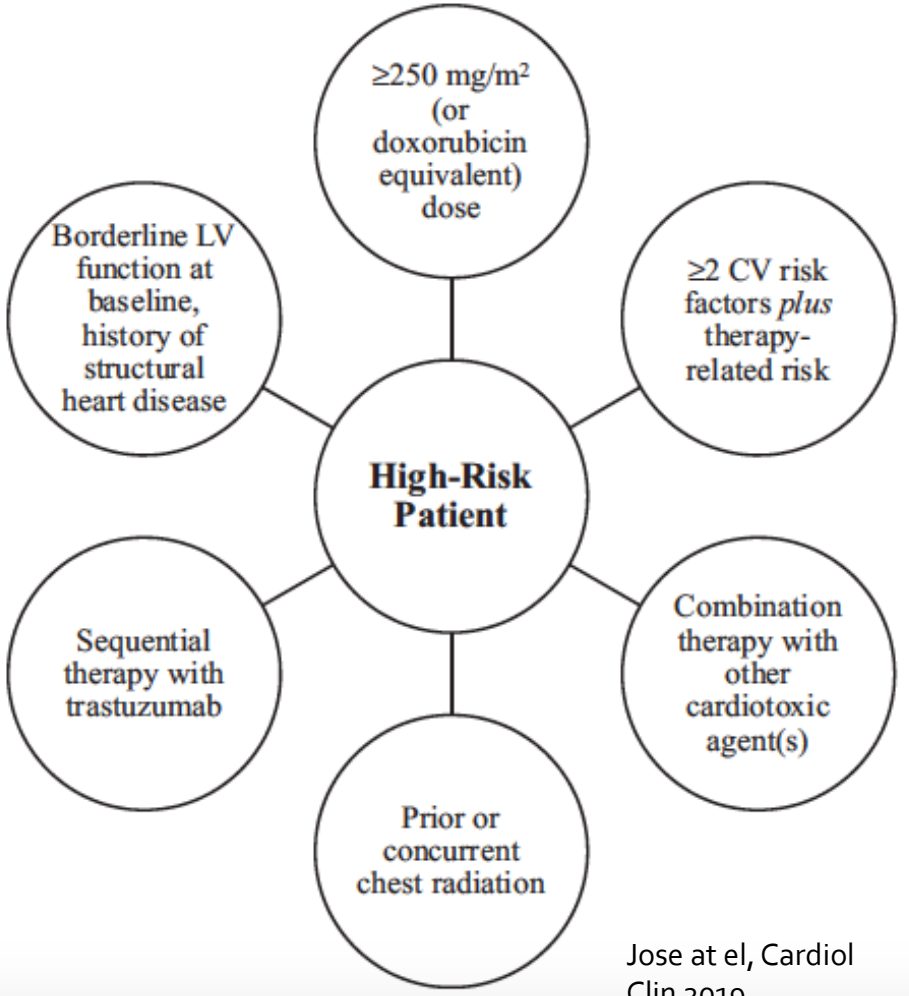
To evaluate the relative contribution of modifiable cardiovascular risk factors on the development of major cardiac events in aging adult survivors of childhood cancer.

Patients and Methods

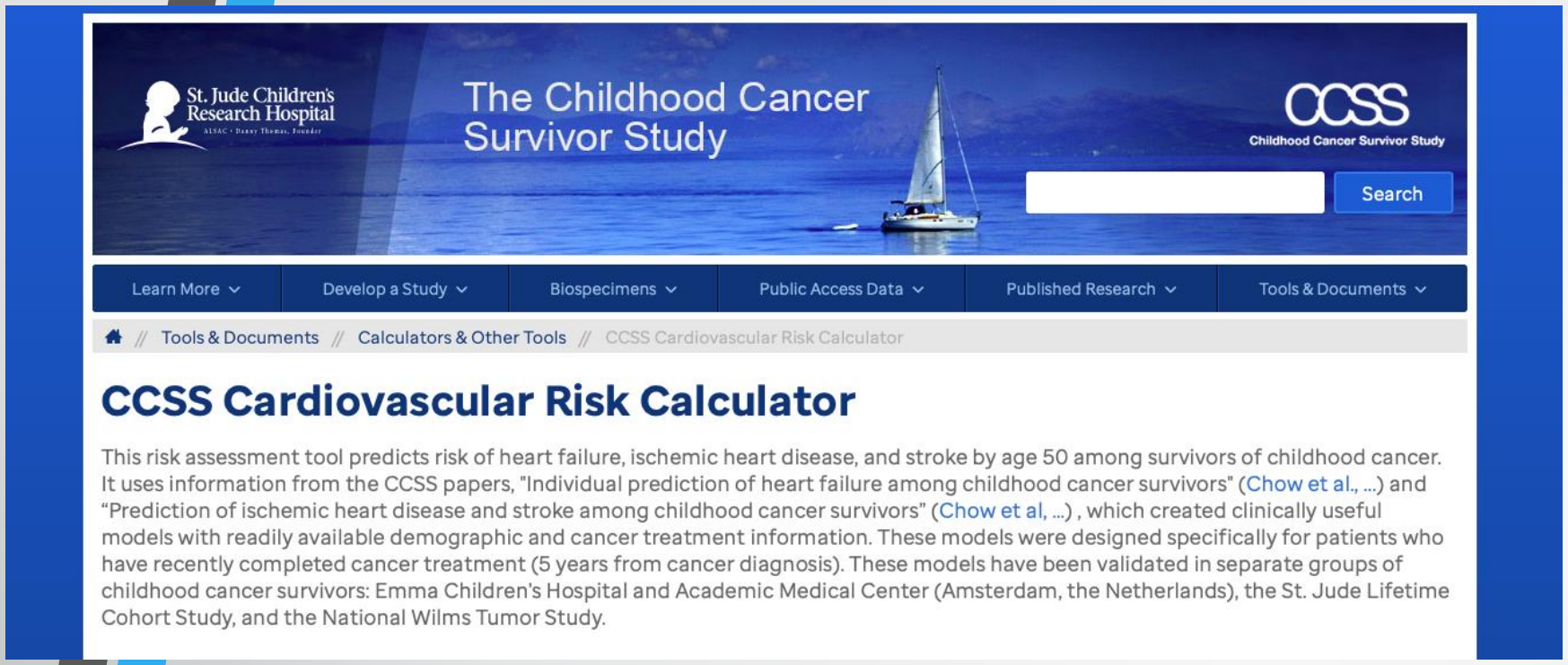
Among 10,724 5-year survivors (median age, 33.7 years) and 3,159 siblings in the Childhood Cancer Survivor Study, the prevalence of hypertension, diabetes mellitus, dyslipidemia, and obesity was determined, along with the incidence and severity of major cardiac events such as coronary artery disease, heart failure, valvular disease, and arrhythmia. On longitudinal follow-up, rate ratios (RRs) of subsequent cardiac events associated with cardiovascular risk factors and cardiotoxic therapy were assessed in multivariable Poisson regression models.

Results

Among survivors, the cumulative incidence of coronary artery disease, heart failure, valvular disease, and arrhythmia by 45 years of age was 5.3%, 4.8%, 1.5%, and 1.3%, respectively. Two or more cardiovascular risk factors were reported by 10.3% of survivors and 7.9% of siblings. The risk for each cardiac event increased with increasing number of cardiovascular risk factors (all $P_{trend} < .001$). Hypertension significantly increased risk for coronary artery disease (RR, 6.1), heart



Jose at el, Cardiol Clin 2019



https://ccss.stjude.org/tools-and-documents/calculators-and-other-tools/ccss-cardiovascular-risk-calculator.html

Calculation Results

Heart Failure

Using the **Standard+Heart Model** for survivors who are 5-years from cancer diagnosis::

- **Risk Group is Moderate**
- The overall risk score is **4**
- The estimated probability of developing Heart Failure by 50 years of age is **8.8%** (95% confidence interval = **6.6-10.9%**)
- The relative risk of developing Heart Failure compared to a non-cancer sibling comparison is **11.3** (95% confidence interval = **6.2-20.8**)
- Data Used For Calculation
  - Patient's current age? This calculator is primarily designed for people currently aged <40 years, and only provides predictions up to age 50. To see risks associated with 5-year survivors in general without the influence of subsequent aging, select <20 **< 20**
  - Gender? **Male**
  - Patient's age at diagnosis? **5 - 9**
  - Were any anthracyclines used? **Yes, cumulative dose known**
  - What was the anthracycline dose? **100 - 249 mg/m^2**
  - Was there radiation to the chest? **No**

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Volume 128, Issue 17, 22 October 2013, Pages 1927-1995
https://doi.org/10.1161/CIR.0b013e3182a88099

American Heart Association.

CHILDREN'S ONCOLOGY GROUP

AHA SCIENTIFIC STATEMENT

Long-term Cardiovascular Toxicity in Children, Adolescents, and Young Adults Who Receive Cancer Therapy: Pathophysiology, Course, Monitoring, Management, Prevention, and Research Directions

A Scientific Statement From the American Heart Association

Healthcare Improvement Scotland

SIGN 1993-2013

Help us to improve SIGN guidelines - click here to complete our survey

SIGN 132 • Long term follow up of survivors of child

Stichting Kinderoncologie Nederland

SKION

International Guideline Harmonization Group
for Late Effects of Childhood Cancer

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Cardiomyopathy

Home / Guidelines / Topics / Cardiomyopathy / Recommendations

At what frequency should surveillance be performed for high risk survivors?

Cardiomyopathy surveillance *is recommended* for *High Risk* survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis and continued every 5 years thereafter.

More frequent cardiomyopathy surveillance *is reasonable* for *High Risk* survivors.

ommendations

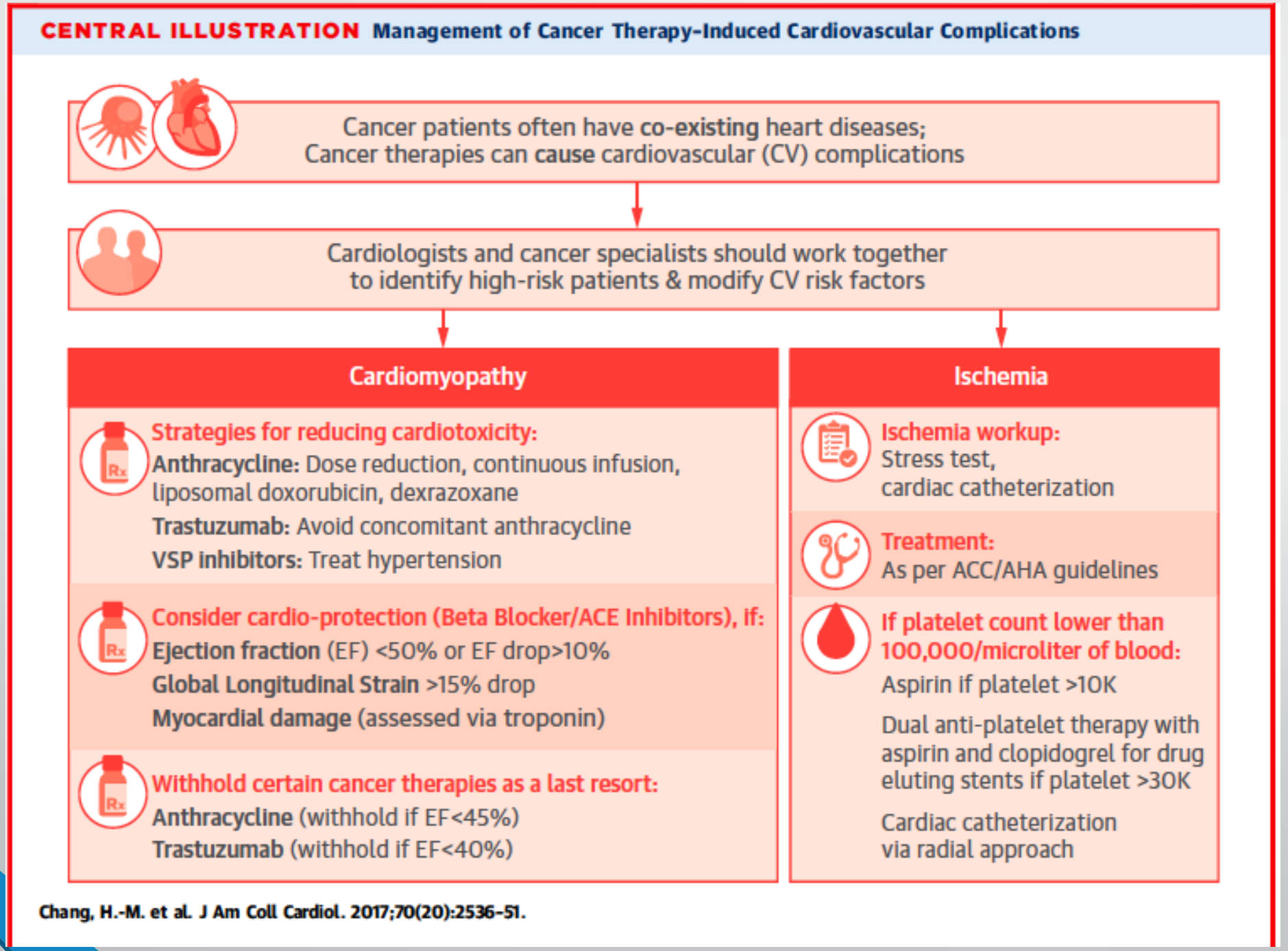
we present the recommendations for cardiomyopathy surveillance for childhood, adolescent
oung adult cancer survivors treated with anthracycline chemotherapy and/or radiation to
that include the heart (i.e. chest radiation).

Routine evaluation

- History: background, CVS risk factor, heart failure symptoms, palpitation, syncope
- Examination: BP / HR / gallop rhythm
- ECG – QT interval
- CXR
- Echocardiogram: systolic/ diastolic function, valve, PHT .....

On request:

- MUGA (Multigated radionuclide angiography)
- cMRI
- Troponins, BNP, NT-proBNP
- Holter
- Cardiopulmonary exercise testing



Chang, H.-M. et al. J Am Coll Cardiol. 2017;70(20):2536–51.

Cardiomyopathy/ heart failure

Anthracycline-induced cardiotoxicity

Characteristic	Acute Cardiotoxicity	Early-Onset Progressive Cardiotoxicity	Late-Onset Progressive Cardiotoxicity
Onset	Within the first week of anthracycline treatment	<1 y after completion of anthracycline treatment	≥1 y after completion of anthracycline treatment
Risk factor dependence	Unknown	Yes*	Yes*
Clinical features in adults	Transient depression of myocardial contractility	Dilated cardiomyopathy	Dilated cardiomyopathy
Clinical features in children	Transient depression of myocardial contractility	Restrictive cardiomyopathy and/or dilated cardiomyopathy	Restrictive cardiomyopathy and/or dilated cardiomyopathy
Course	Usually reversible on discontinuation of anthracycline	Can be progressive	Can be progressive

Simbre, Paeditr drugs 2005

TABLE 1. Proposed HF Classification for Infants and Children

STAGE	DEFINITION	EXAMPLES
A	Patients with increased risk of developing HF but who have normal cardiac function and no evidence of cardiac chamber volume overload.	Previous exposure to cardiotoxic agents, family history of heritable cardiomyopathy, univentricular heart, congenitally corrected transposition of the great arteries.
B	Patients with abnormal cardiac morphology or cardiac function, with no symptoms of HF, past or present.	Aortic insufficiency with LV enlargement, history of anthracycline with decreased LV systolic function.
C	Patients with underlying structural or functional heart disease, and past or current symptoms of HF.	Dilated cardiomyopathy with chronic HF due to decreased LV systolic function.
D	Patients with end-stage HF requiring continuous infusion of inotropic agents, mechanical circulatory support, cardiac transplant, or hospice care.	Acute decompensated HF due to viral myocarditis.

HF=heart failure, LV=left ventricular.

From Rosenthal D, Chrisant MR, Edens E, et al. International Society for Heart and Lung Transplantation: practice guidelines for management of heart failure in children. J Heart Lung Transplant. *2004;23(12):1313.*

Congestive Heart failure in Children; Jack F. Price; Pediatrics in Review 2019

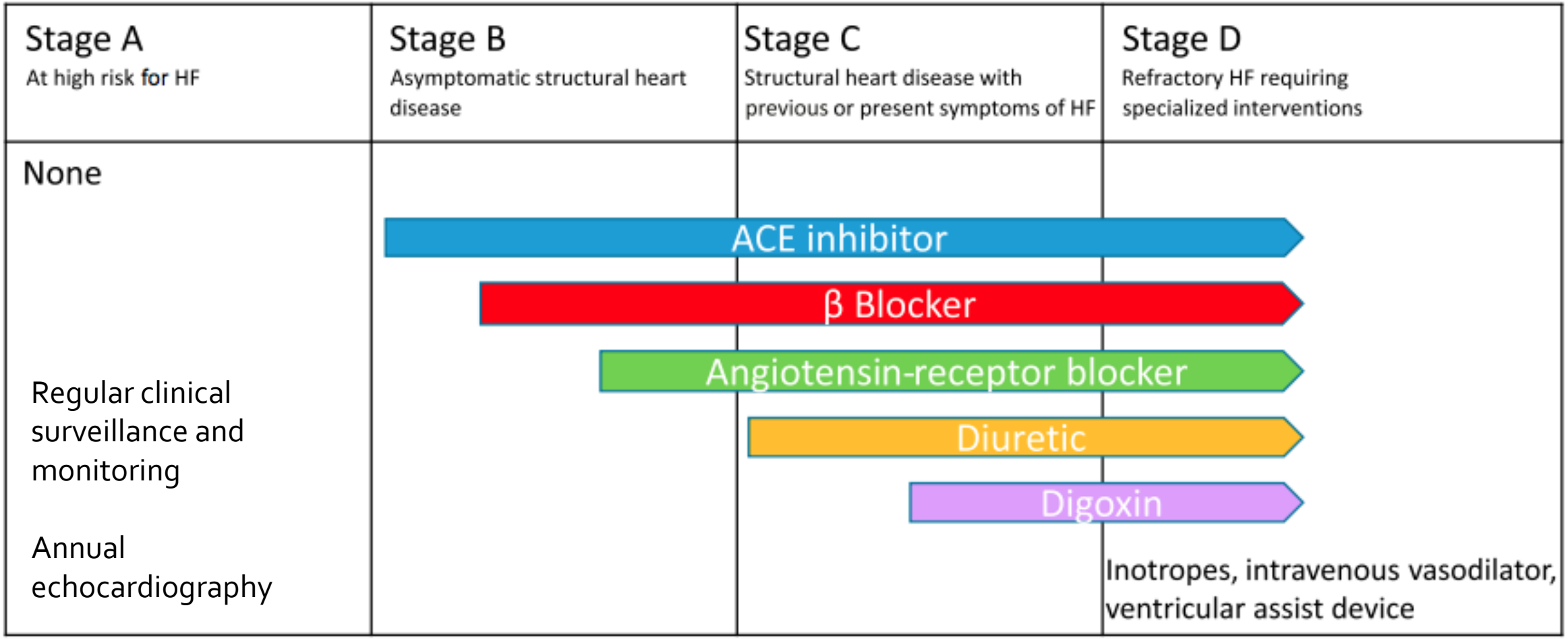
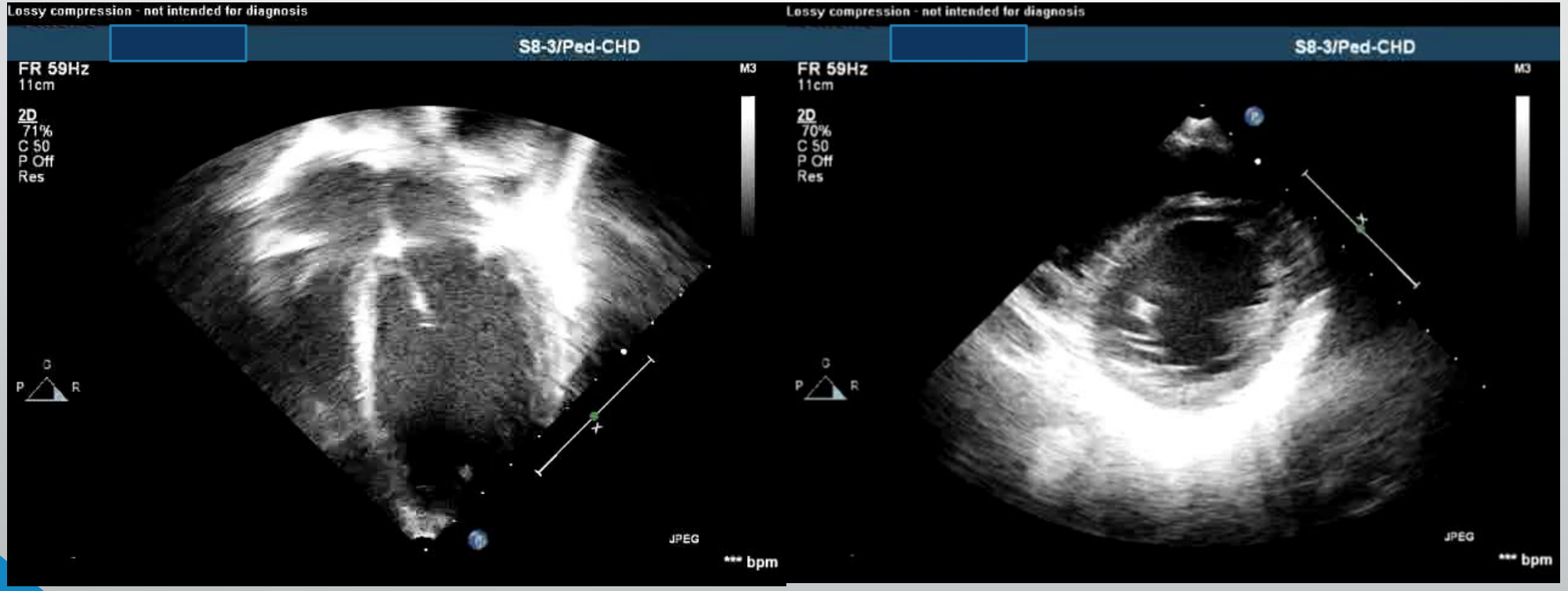


Figure 3. Medical therapy for heart failure (HF) by stage. Angiotensin-converting enzyme (ACE) inhibitors and β-blockers may by initiated in asymptomatic individuals with ventricular dysfunction at a low dose and uptitrated to the target dosage based on tolerance of the medication. (Modified with permission from Kantor PF, Lougheed J, Dancea A, et al; Children's Heart Failure Study Group. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. *Can J Cardiol*. 2013;29(12):1535–1552.)

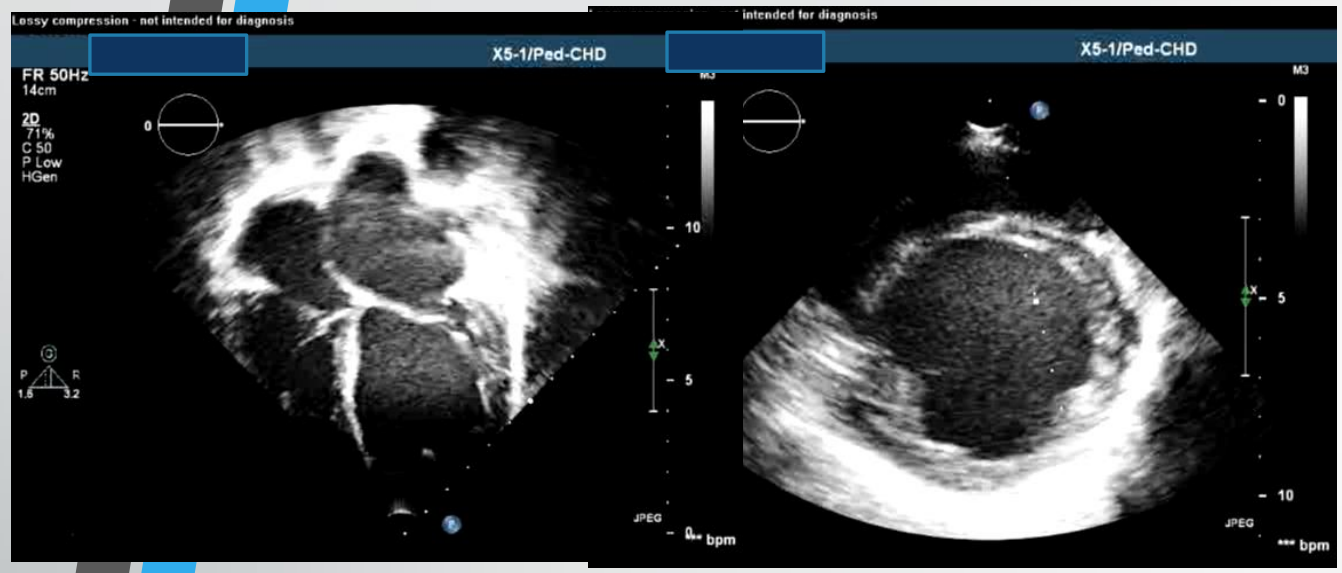
Congestive Heart failure in Children; Jack F. Price; Pediatrics in Review 2019

- F/ 8 year - AML (M1 subtype)
- Treated with HKPHOSG-DBH-AML protocol 2012 – diagnose 6/2018
- Completed chemotherapy- 12/2018
- Cumulative dose of anthracycline – 180 mg/m^2



LVIDD 4.42 cm, LVEF 40.6%; LV E/e' 17.6

Enalapril was started → 3 months later

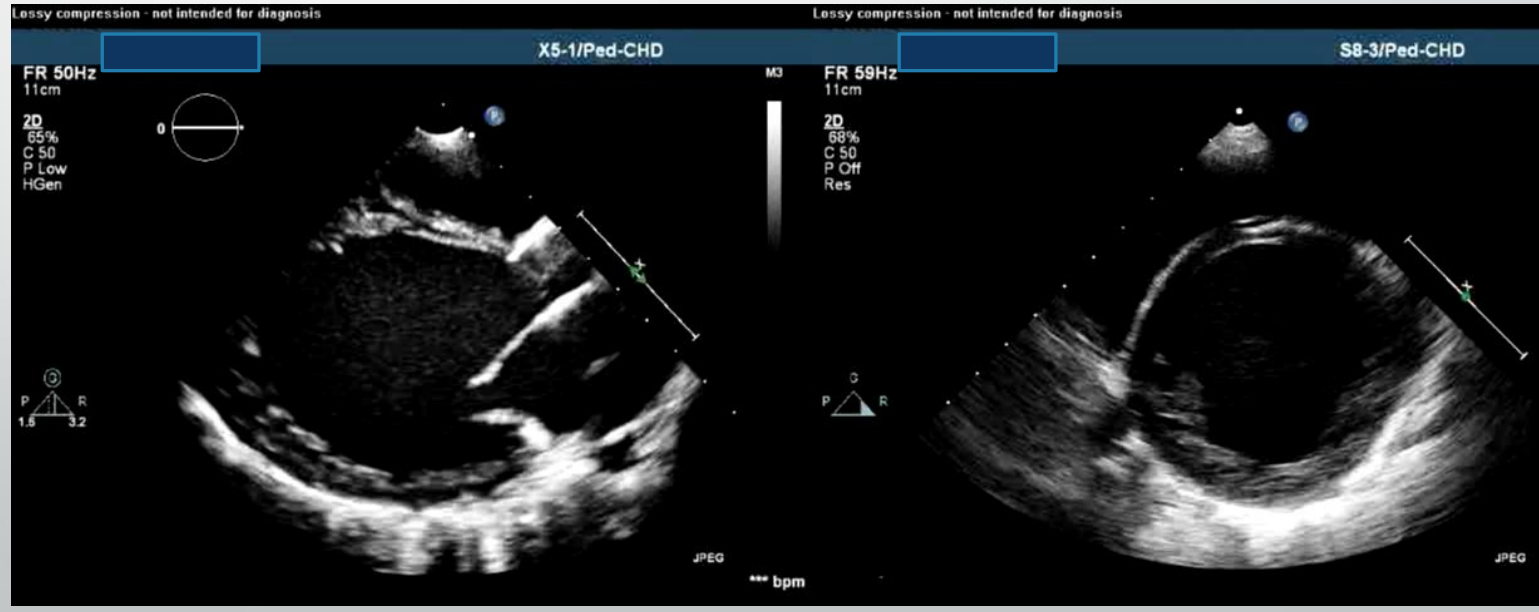


LVIDD 4.84 cm, LVEF 31% (Simpson biplane)

Carvedilol was added → 6 month later start to have exertional symptoms

6MWT = 375 m
NT-proBNP 4850 pg/ml

LVIDD 5.28 cm, LVEF 20% (simpson biplane)
LV E/e' = 14.3
Cannot walk more than 15 minutes on level ground



Cardiomyopathy

Strategies for reducing cardiotoxicity:

Anthracycline: Dose reduction, continuous infusion, liposomal doxorubicin, dexrazoxane

Trastuzumab: Avoid concomitant anthracycline

VSP inhibitors: Treat hypertension

Consider cardio-protection (Beta Blocker/ACE Inhibitors), if:

Ejection fraction (EF) <50% or EF drop>10%

Global Longitudinal Strain >15% drop

Myocardial damage (assessed via troponin)

Withhold certain cancer therapies as a last resort:

Anthracycline (withhold if EF<45%)

Trastuzumab (withhold if EF<40%)

Chang, H.-M. et al. J Am Coll Cardiol. 2017;70(20):2536-51.

ACC/AHA/HFSA FOCUSED UPDATE

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

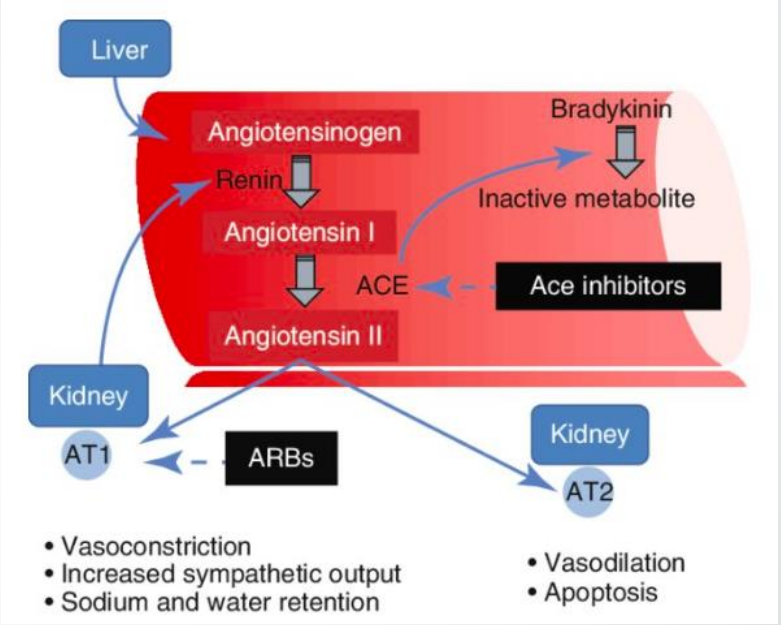
A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI

COR	LOE	Recommendations	Comment/Rationale
I	ACE-I: A ARB: A ARNI: B-R	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)*,[128–133] OR ARBs *(Level of Evidence: A)*,[134–137] OR ARNI *(Level of Evidence: B-R)*[138] in conjunction with evidence-based beta blockers,[9,139,140] and aldosterone antagonists in selected patients,[141,142] is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.	**NEW:** New clinical trial data prompted clarification and important updates.

Diuretics, Fluid restriction and Nutrition

- Loop diuretics – s/s of congestion; symptomatic relief
- Adolesterone antagonists – weak diuretics but have other features, e.g. antifibrotic; evidence in adults non-oncology patients to reduce mortality / alleviate HF symptoms
- Metabolic demand increases /high conc of neurohormones such TNF-alpha → cardiac cachexia



Banik et al 2014

Angiotensin-converting enzyme inhibitors/ Angiotensin 2 receptor blockers

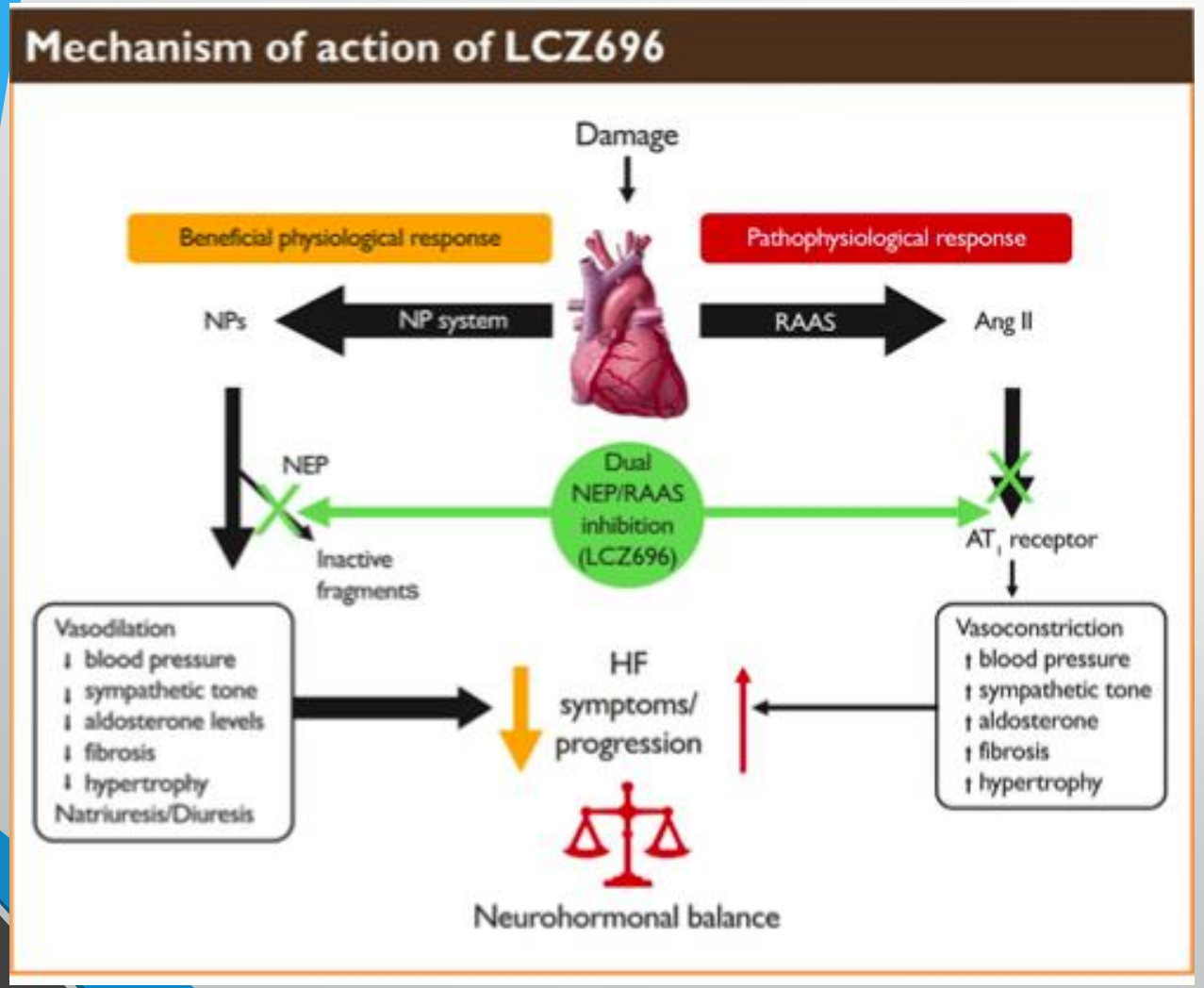
Use of ACEI/ARB in the treatment of heart failure/ cardiac dysfunction in Paediatric Cancer survivors

Authors	Design	Drug	n	Median age of diagnosis	Imaging	Remarks	Results
Harrington et al 2018	Retrospective	ACEI/ARB	22	14.8 (6.4-21.6)	Echo strain	Retrospective improvement "on own" possible ? reason to start ACEI	Improvement maintained for >= 1 year (p=0.02)
Silber at al 2004	RCT, double blinded (SF <=29% or 10% drop; EF< = 55%, MCI <= 7.4)	Enalapril 0.05 → 0.15 mg/kg/day	135	7.2-8.2 (0.3-21.8)	Echo – wall stress	High rate of dizziness/ Hypotension	No change in exercise performance, LVESWS maintained beyond 1 year of treatment
Lipshultz et al 2002	Retrospective (long term data)	Enalapril 18 mg /d	18	8 (1-18.1)	Echo	Mean time from completion of doxorubuiin to start of enalapril – 6.95 (0.42-14.2) Median FU since enalapril – 10.0 (6.5 – 13.1) No control	First 6 year – Progressive improvement toward normal values (LV dimension, FS, mass) but deteriorated 6-10 years LV wall thickness , LV contractility ↓ , SBP/DBP worsen

Carvedilol

- Alpha-1 blockade – afterload reduction
- Beta-1 and beta-2 blockade – blockade of adrenergic activation
- potent antioxidant (~ 10 times more potent than a-tocopherol) and antiapoptotic properties
- Have shown carvedilol significantly reduced LVESV but enalapril only arrested further dilatation
- Established treatment for heart failure

ARNI



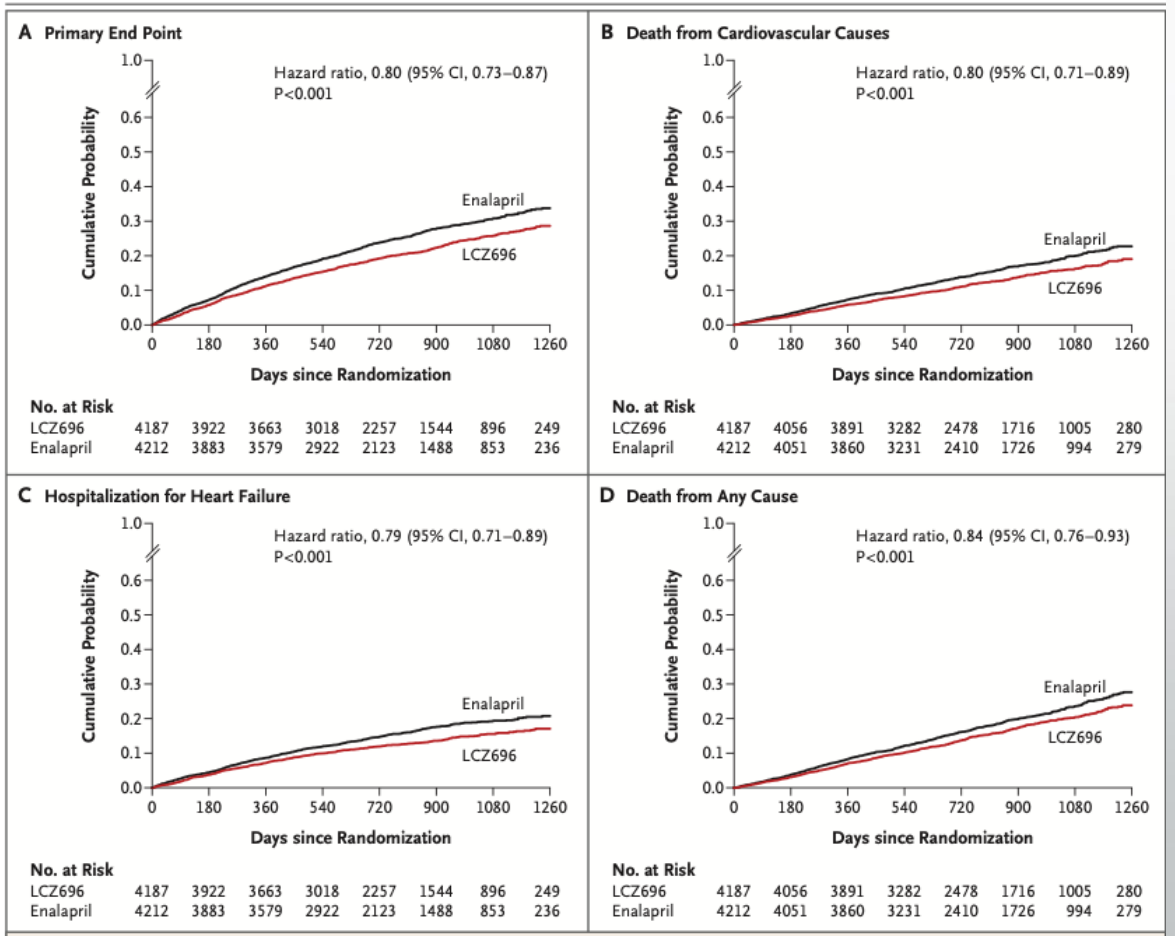
- Valsartan/ sacubitril
- Side effects: angioedema, hypotension, renal insufficiency

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D.,



N= 8442

Class II-IV heart failure
LVEF <= 40%

LCZ696 200 mg BD
Enalapril 10 mg BD

FU 27 month
(premature termination because of overwhelming benefit)

Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

ACC/AHA/HFSA FOCUSED UPDATE

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

COR	LOE	Recommendations
I	ARNI: B-R	In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.[138]
III: Harm	B-R	ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.[148,149]
III: Harm	C-EO	ARNI should not be administered to patients with a history of angioedema.

ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 763–767
Published online 5 February 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12627

SHORT COMMUNICATION

Effectiveness of sacubitril–valsartan in cancer patients with heart failure

Ana Martín-Garcia[1,2*‡†], Teresa López-Fernández[2,3‡†], Cristina Mitroi[4], Marinela Chaparro-Muñoz[5], Pedro Moliner[6], Agustin C. Martin-Garcia[1,2], Amparo Martinez-Monzonis[2,7], Antonio Castro[2,5], Jose L. Lopez-Sendon[2,3] and Pedro L. Sanchez[1,2]

Sacubitril-vasartan - Entresto

- Retrospective multicenter – 6 Spanish hospitals
- FU 4.6 month
- N= 67 ; median age 63+/- 14
- Median time from anti-CA therapy to cardiac dysfunction = 41 month
- Baseline median LVEF = 33 [27;37]%; 90% symptomatic NYHA class II-IV
- Sacubitril-valsartan 50 mg BD – 200 mg BD

  Discontinued in 4 (symptomatic Hypotension, renal impairment, sever pruritis)

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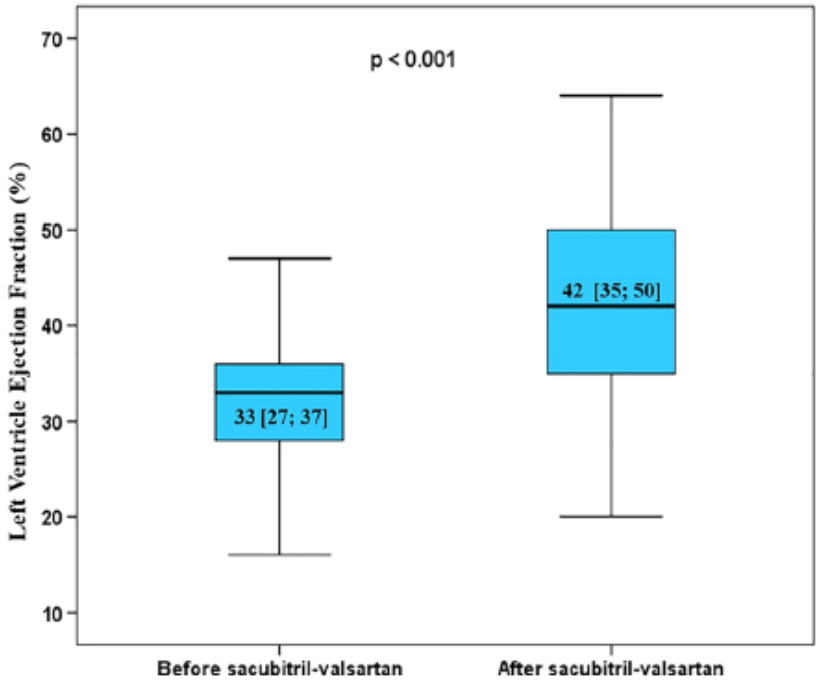
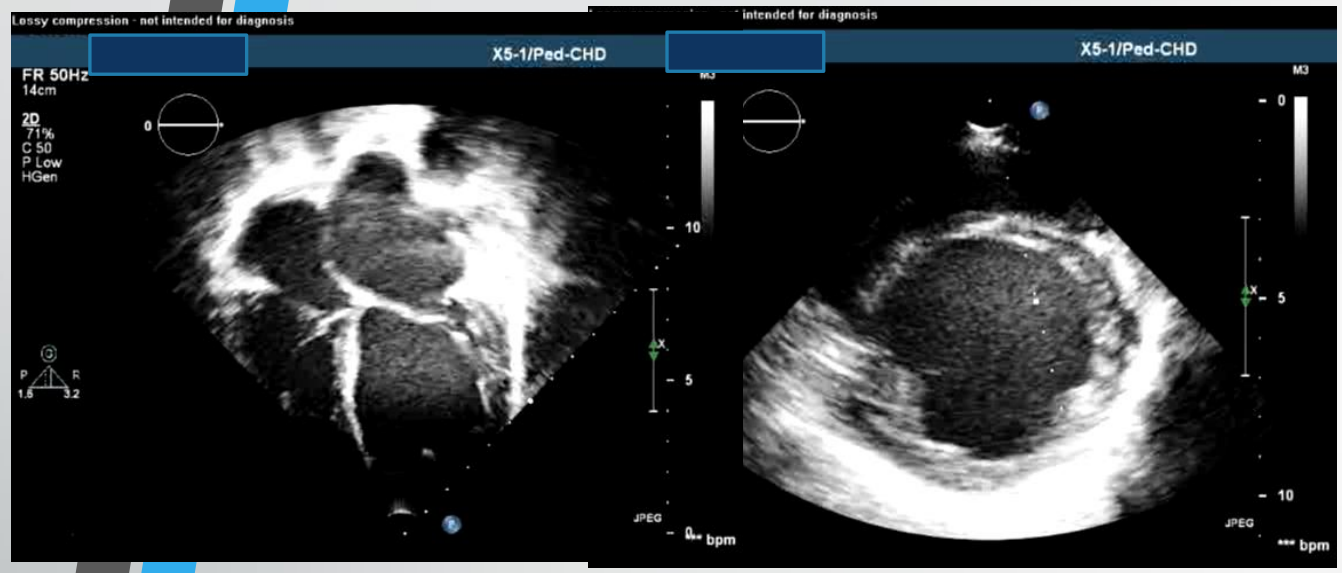
Figure 1 Left ventricular ejection fraction before and after sacubitril-valsartan treatment



	Before sacubitril–valsartan	After sacubitril–valsartan	*P* value
Left ventricle end-diastolic volume (mL)	144 [119; 184]	129 [107; 168]	0.006
Left ventricle end-systolic volume (mL)	93 [72; 128]	73 [54; 104]	<0.001
e/e´	13 [9; 18]	11 [8; 15]	0.053
Global longitudinal strain (%)	−10.5 [−13; −7.3]	−12 [−15; −8]	0.49
Systolic blood pressure (mmHg)	116 [106; 119]	112 [100; 126]	0.006
Diastolic blood pressure (mmHg)	70 [61; 76]	68 [60; 72]	0.30
Heart rate (b.p.m.)	74 [65; 81]	68 [60; 75]	0.01
Creatinine (mg/dL)	0.9 [0.7; 1.1]	0.9 [0.7; 1.1]	0.055
Estimated glomerular filtration rate (mL/min/1.73 m^2)	76 [64; 90]	70 [53; 88]	0.02
Potassium serum levels (mg/dL)	4.5 [4.1; 4.8]	4.5 [4.2; 4.8]	0.50
NT-proBNP (pg/mL)	1552 [692; 3624]	776 [339; 1458]	0.001
NYHA functional class	2.2 ± 0.6	1.6 ± 0.6	<0.001

NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Enalapril was started → 3 months later

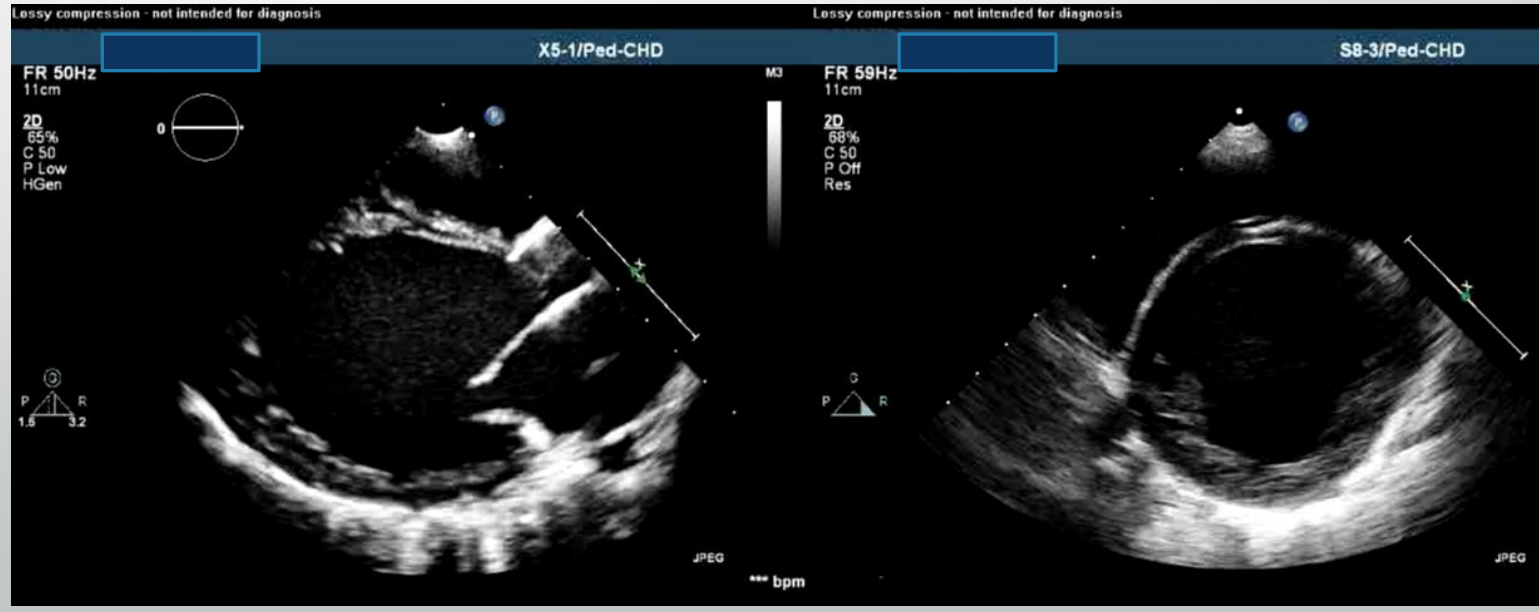


LVIDD 4.84 cm, LVEF 31% (Simpson biplane)

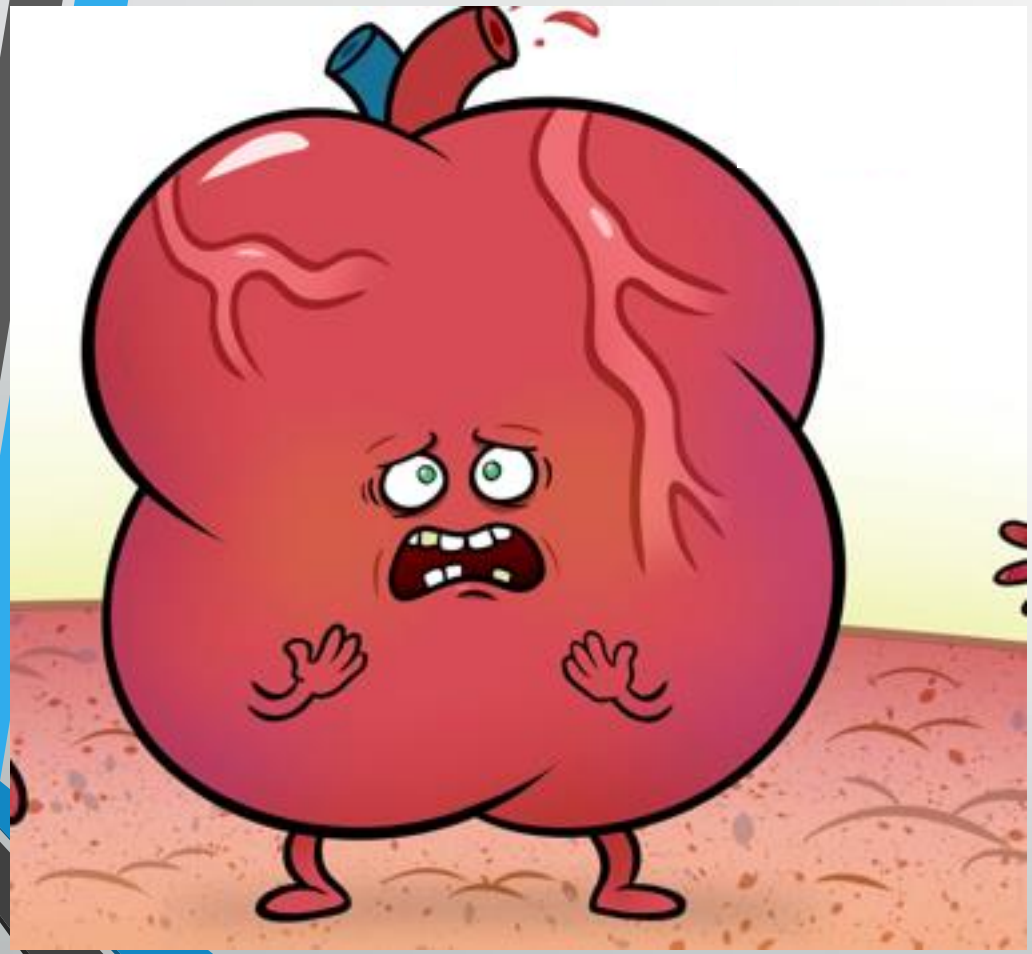
Carvedilol was added → 6 month later start to have exertional symptoms

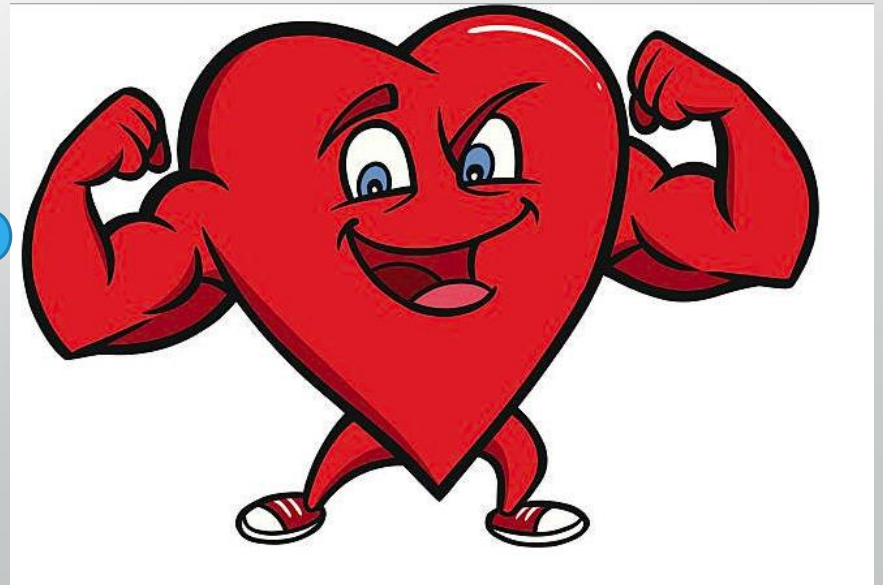
6MWT = 375 m
NT-proBNP 4850 pg/ml

LVIDD 5.28 cm, LVEF 20% (simpson biplane)
LV E/e' = 14.3
Cannot walk more than 15 minutes on level ground



Could you do something earlier ?





Primary prevention – general measures

- Comorbidities: HT, systolic dysfunction, metabolic disorders
- HT has been proved the most important modifiable CVS risk factors for cancer survivors (Armstrong et al. J Clin Oncol 2013)
- Unfavorable lifestyle choices: smoking, overweight, reduced physical activities

Recommendations for patients treated for cancer

Recommendations	Class[a]	Level[b]	Ref[c]
Cardio-protection in high-risk patients[d] receiving type I chemotherapy should be considered for LV dysfunction prevention	IIa	B	160, 161
Optimization of the CV risk profile should be considered in cancer treated patients.	IIa	C	

2016 European guidelines on cardiovascular disease prevention in clinical practice

International Guideline Harmonization Group
for Late Effects of Childhood Cancer

Vul uw zoekterm in

Home | About IGHG | Guidelines | Patient education | News | Meetings | Contact

Cardiomyopathy

Home / Guidelines / Topics / Cardiomyopathy / Recommendations

Topics
- Breast cancer
- Cardiomyopathy

Recommendations

Here we present the recommendations for cardiomyopathy surveillance for childhood, adolescent and young adult cancer survivors treated with anthracycline chemotherapy and/or radiation to fields that include the heart (i.e. chest radiation).

What advice should be given regarding physical activity?

Regular exercise, as recommended by the AHA and ESC, offers potential benefits to survivors treated with anthracyclines and/or chest radiation.

Regular exercise *is recommended* for survivors treated with anthracyclines and/or chest radiation who have normal LV systolic function.

Cardiology consultation *is recommended* for survivors with asymptomatic cardiomyopathy to define limits and precautions for exercise.

Cardiology consultation *may be reasonable* for *High Risk* survivors who plan to participate in high intensity exercise to define limits and precautions for physical activity.

Screening for modifiable cardiovascular risk factors (hypertension, diabetes, dyslipidemia, obesity) *is recommended* for all survivors treated with anthracyclines and/or chest radiation so that necessary interventions can be initiated to help avert the risk of symptomatic cardiomyopathy.

Circulation
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https://doi.org/10.1161/CIR.0000000000000679

American Heart Association.

AHA SCIENTIFIC STATEMENT

Cardio-Oncology Rehabilitation to Manage Cardiovascular Outcomes in Cancer Patients and Survivors: A Scientific Statement From the American Heart Association

Cardiac rehabilitation:
"the provision of comprehensive long-term services involving medical evaluation, prescriptive exercise, cardiac risk factor modification, and education, counseling, and behavioral interventions."

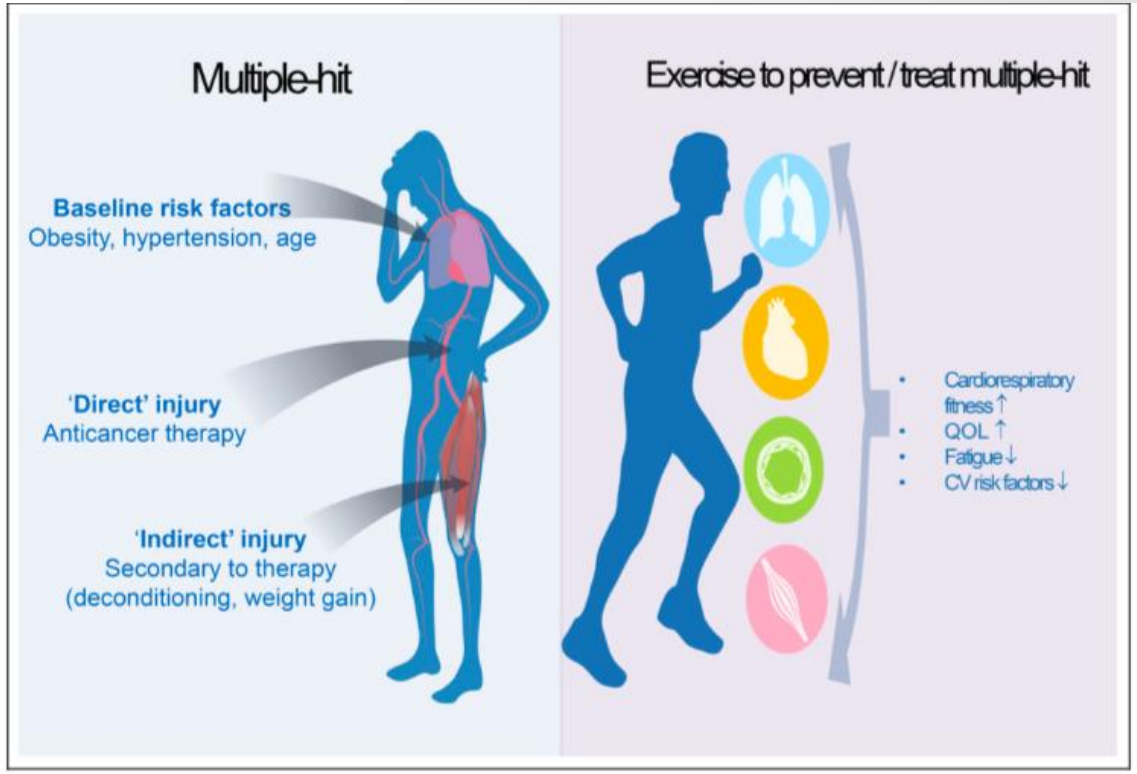


Figure 2. Potential benefits that exercise training may confer to patients with cancer at heightened risk for cardiovascular (CV) disease. QOL indicates quality of life.

Prophylactic ACEI/ARB

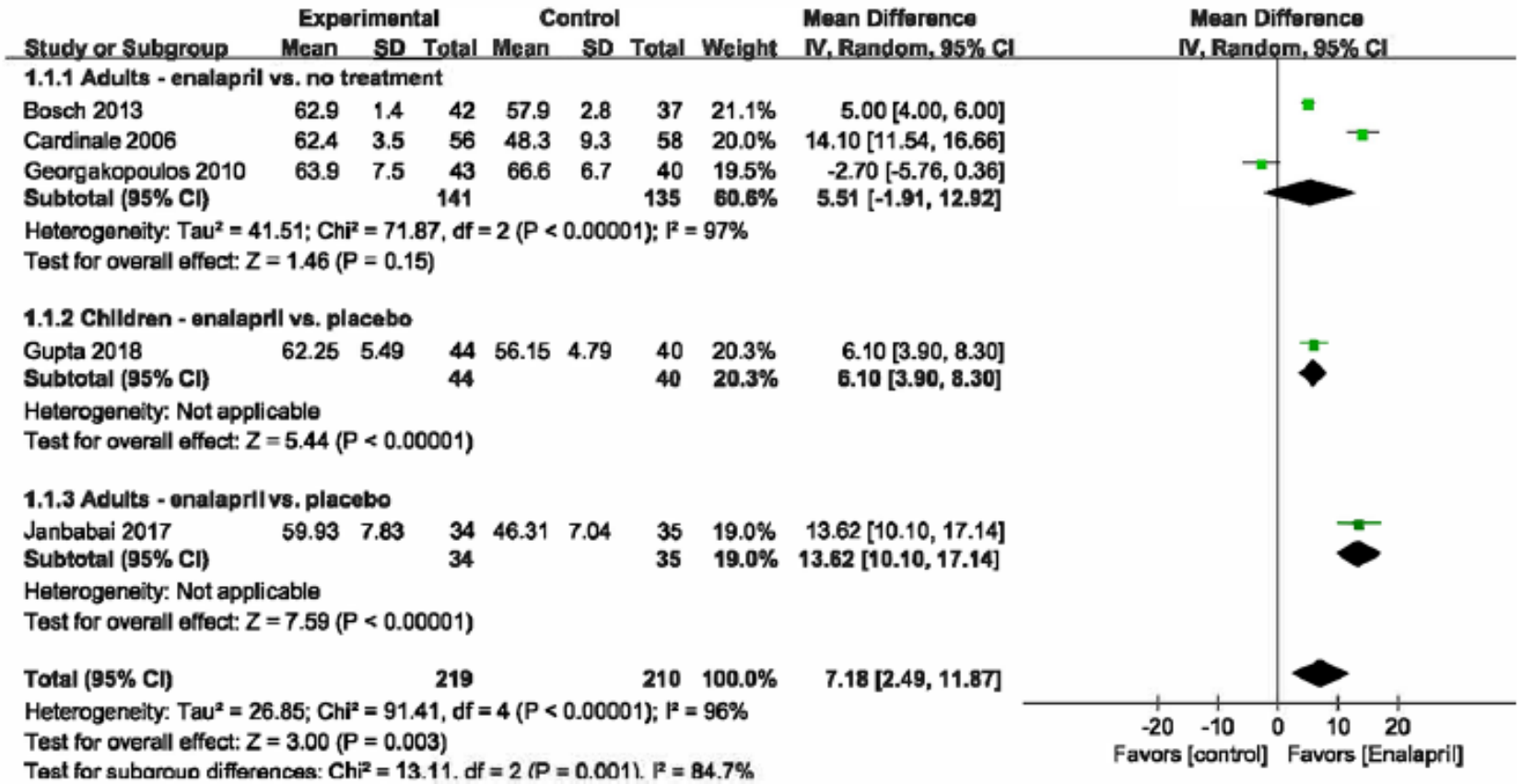
Authors	Design	Drug	n	Cancer	Imaging	Biochem	Limitation	Results
Cardinale et al 2006	RCT	Enalapril (2.5 → 20 mg daily) [1 month after chemo; high TnI as treatment group – till 1 year]	114	Leukemia, breast, sarcoma, lymphoma, myoloma	Echo	TnI	No placebo, open-label, lack of pre-specified and well-defined end-points	✓✓ less LVEF reduction, less LVESV/LVEDV increase ↓ 9.7% (echo) in control
Georgakopoulos et al 2010	RCT	Enalapril (11 +/- 0.68 mg daily) or metoprolol (88+/- 3.1 mg daily)	125	Lymphoma	Echo		Open-label no placebo	✘ 36-month – less HF but not satistically significant
Liu et al 2013	RCT	Carvedilol (5→ 10 mg daily) + candesartan (2.5 mg daily) [start at 1st cycle]	40	Breast	Echo, ECG	TnI	Small sample size Short FU	✓ not prevent LVEF decline, but prevent TnI and ECG changes
Bosch et al 2013 OVERCOME	RCT	Enalapril (2.5 → 20 mg daily) + carvedilol (12.5 → 50 mg daily) [start at 1st cycle]	90	ALL/AML, lymphoma, myeloma	Echo, cMRI	TnI, BNP	Small sample size, not blinded, no placebo	✓✓ lower mortality, heart failure, less LVEF changes ↓ 3.1% (echo); ↓ 3.4% (CMR)
Boekhout et al 2016	RCT, placebo	Candesartan (16 → 32 mg daily) [before → 26 week after trastuzumab]	206	Breast	Echo	hsTnT, BNP, ERBB2	Lack of universally used definition of trastuzumab-related cardiotoxic effects	✘
Gulati et al 2016 PRADA	RCT, placebo, double blind	Candesartan (8→ 32 mg daily); metoprolol (50 →100 mg daily) [Before]	130 (block of 4)	Breast	Echo, cMRI	TnI, BNP	Lack of FU info beyond adjuvant therapy	✓ not reduce TnI Affect remodeling, lower LVEF decline (0.8% vs 2.6%)
Cadeddu et al 2010; Dessi et al 2013	RCT, placebo	Telmisartan 40 mg daily [before]	49	Lymphoma, endometrium, breast, ..	Echo	IL-6, TNF-α, ROS, GPx	Small sample size, short FU	✓✓ 18-month FU
Pituskin et al 2017 MANTICORE	RCT, placebo, double blinded	Bisoprolol (2.5 → 10 mg daily); Perindopril (2 → 8 mg daily) [before]	94	breast	cMRI		Small sample size	✓ attenuated trastuzumab-mediated decline in LVEF, not prevent ventricular remodeling (3% vs 5%)
Guglin et al 2019 USF study	RCT, placebo, double-blined	Lisinopril 10mg daily Carvedilol CR 10 mg daily	468	Breast TZB with or without anthracycline	Echo MUGA	TnI, BNP	Intercentre variability in LVEF measurement	✓ Post anthracycline exposed group: Cardiac events: placebo 47%; lisinopril 37%; carvedolol 31% [2 year]

Korzeniowska et al, Therapeutic and clinical risk management 2019

Protective Role of Enalapril in Anthracycline-Induced Cardiotoxicity: A Systematic Review

Frontiers in Pharmacology May 2020

Yili Zhang[1†], Junjie Liu[2†], Yuan Li[2†], Nannan Tan[1†], Kangjia Du[1], Huihui Zhao[1,3], Juan Wang[1,3], Jian Zhang[4], Wei Wang[1,3*] and Yong Wang[1*]*



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Pediatr Blood Cancer. 2018;65:e27308.

DOI: 10.1002/pbc.27308

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

Role of ACE inhibitors in anthracycline-induced cardiotoxicity: A randomized, double-blind, placebo-controlled trial

Vineeta Gupta[1] | Sunil Kumar Singh[1] | Vikas Agrawal[2] | Tej Bali Singh[3]

RCT, placebo-controlled
N= 84 (41 leukemia; 43 lymphoma)
Primary outcome – LVEF decrease by <20%

2-16 years at diagnosis, cumulative anthracycline >= 200 mg/m^2
Enalapril 0.1mg/kg/day

TABLE 3 Comparison of LVEF and cardiac biomarkers at 0 and at 6 months between groups

Variables	Time period	Group A (enalapril) mean ± SD $n = 44$	Group B (placebo) mean ± SD $n = 40$	P value
LVEF	0 months	65.73 ± 5.41	64.85 ± 4.94	0.442
	6 months	62.25 ± 5.49	56.15 ± 4.79	<0.001
cTnI	0 months	0.01 ± 0.00	0.01 ± 0.00	1.00
	6 months	0.01 ± 0.00	0.011 ± 0.003	0.035
proBNP	0 months	5.00 ± 0.00	5.00 ± 0.00	-
	6 months	49.60 ± 35.97	98.60 ± 54.24	<0.001
CK-MB	0 months	1.00 ± 0.00	1.00 ± 0.00	-
	6 months	1.08 ± 0.18	1.21 ± 0.44	0.079

Prophylactic Beta-blocker

Meta-Analysis of Carvedilol for the Prevention of Anthracycline-Induced Cardiotoxicity

Table 1
Characteristics of the included randomized clinical trials.

First author	Location	Follow-up (months)	Study period	Total no.	Malignancy	Anthracycline type	Average cumulative dose	End points			
								Primary outcome	C	P	p value
Avila 2018 CECCY	Brazil	6	2013–2017	192	Breast cancer	Doxorubicin	240 mg/m^2	Prevention of a ≥ 10% reduction in LVEF	14.5%	13.5%	1.0
Nabati 2017	Iran	6	2014–2016	91	Breast cancer	Doxorubicin	354 mg/m^2	Changes in LVEF	−0.55 ± 5.60	−9.46 ± 5.93	<0.001
Beheshti 2016	Iran	0.25	–	70	Breast cancer	Doxorubicin	240 mg/m^2	Mean differences in strain rates	0.39 ± 4.5	2.77 ± 2.09	0.005
Jhorawat 2016	India	6	2008–2009	54	Lymphoreticular malignancy	Adriamycin	260 mg/m^2	Mortality	22.2%	18.5%	–
Elitok 2014	Turkey	6	2012–2013	80	Breast cancer	Doxorubicin	530 mg/m^2	Mortality	0%	0%	–
Liu 2013*	–	4.2	–	40	Breast cancer	Not specified	–	LVEF at sixth cycle	57.50 ± 2.57	45.95 ± 3.68	<0.05
Salehi 2011	Iran	4	–	66	Breast cancer and lymphoma	Doxorubicin and epirubicin	530 mg/m^2	Incidence of cardiomyopathy	13.6%	22.7%	0.284
Kalay 2006	Turkey	6	2003–2004	50	Various malignancies	Adriamycin and epirubicin	520 mg/m^2	EF < 50%	4%	20%	–

Abbreviations: C = carvedilol; CECCY = carvedilol effect in preventing chemotherapy induced cardiotoxicity; EF = ejection fraction; LVEF = left ventricular ejection fraction; P = placebo.
* Intervention group received both carvedilol and candesartan.

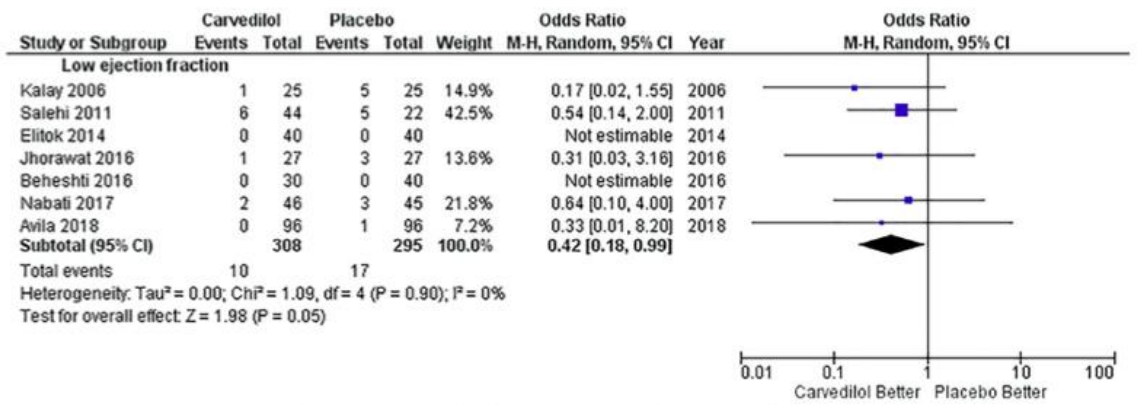


Figure 2. Forest plot of the occurrence of low ejection fraction.

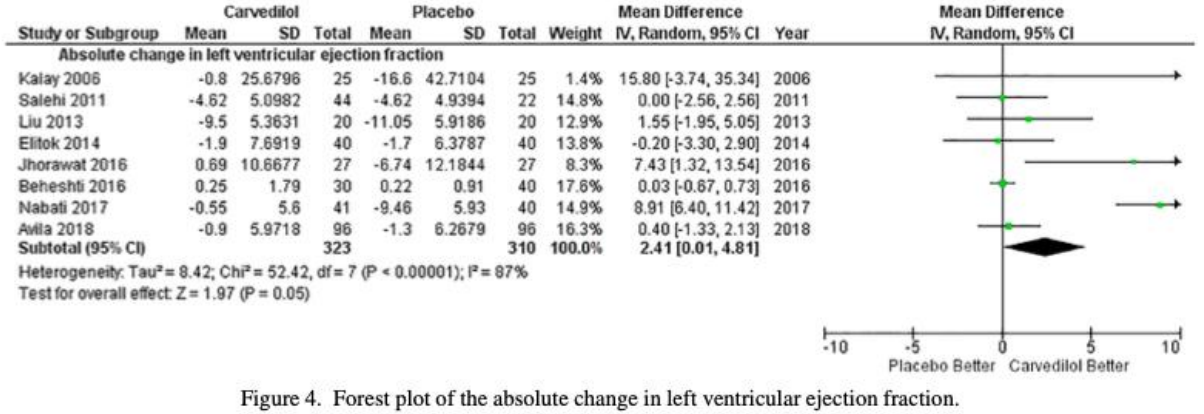


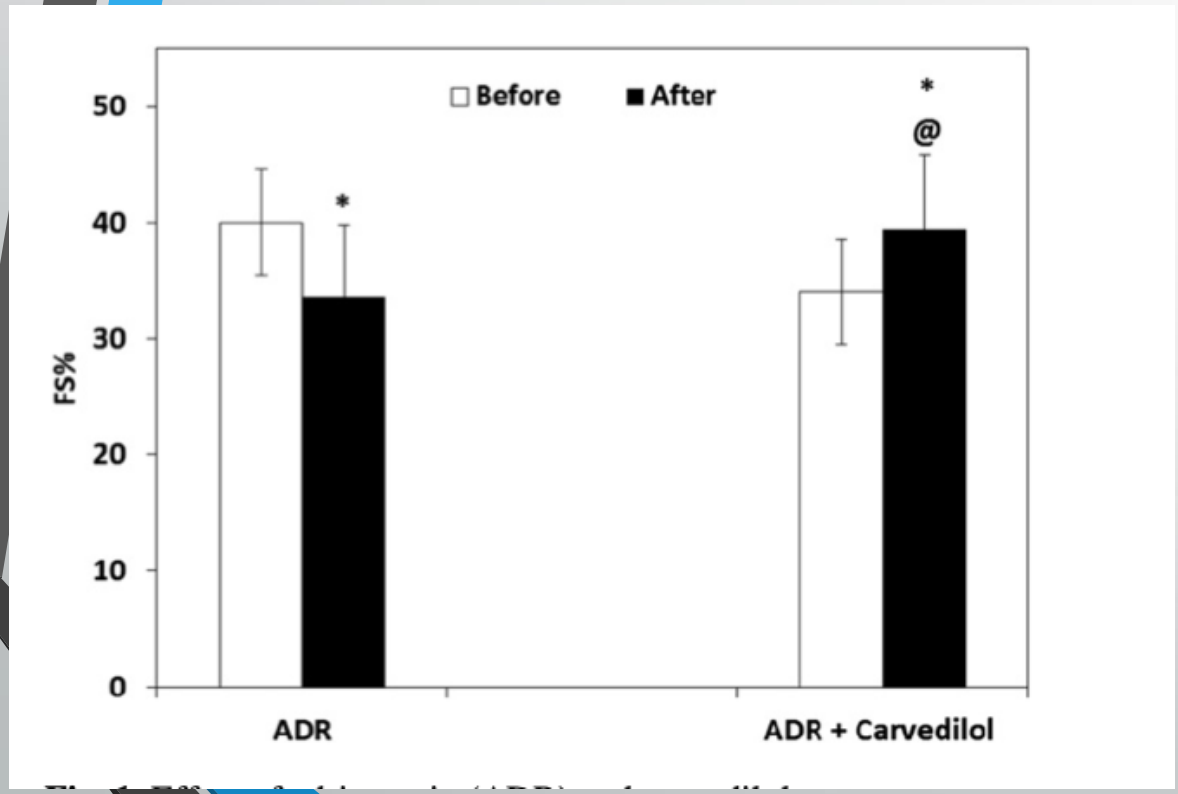
Figure 4. Forest plot of the absolute change in left ventricular ejection fraction.

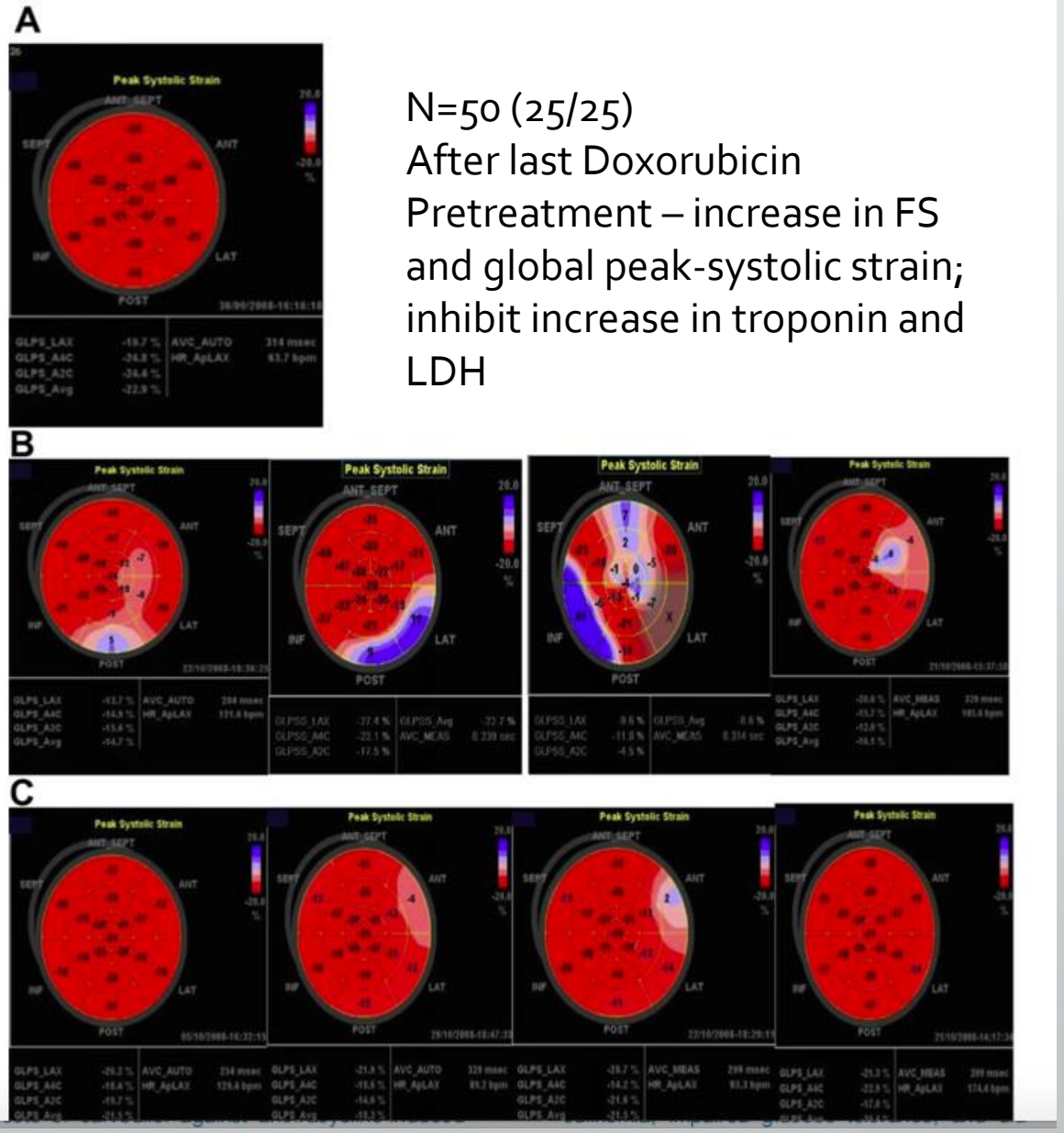
Journal of Cardiac Failure Vol. 18 No. 8 2012

Protective Effect of Carvedilol on Adriamycin-Induced Left Ventricular Dysfunction in Children With Acute Lymphoblastic Leukemia

NAGLA A. EL-SHITANY, PhD,[1,2] OSAMA A. TOLBA, MD, PhD,[3] MOHAMED R. EL-SHANSHORY, MD, PhD,[4] AND ESLAM E. EL-HAWARY, MS[4]

Tanta, Egypt; and Jeddah, Saudi Arabia





N=50 (25/25)
After last Doxorubicin
Pretreatment – increase in FS and global peak-systolic strain; inhibit increase in troponin and LDH

Conclusion

- No robust data in paediatric
- Results – LVEF; not real symptoms of heart failure
- Long-latency between asymptomatic (stage A/B) and clinical evident (stage C/D) disease
- ? ACEI cannot halt the progression of disease
- Expose to complication and side effects

Armenian *et al. BMC Cardiovascular Disorders* (2016) 16:187
DOI 10.1186/s12872-016-0364-6

BMC Cardiovascular Disorders

STUDY PROTOCOL Open Access

Rationale and design of the Children's Oncology Group (COG) study ALTE1621: a randomized, placebo-controlled trial to determine if low-dose carvedilol can prevent anthracycline-related left ventricular remodeling in childhood cancer survivors at high risk for developing heart failure

Echo markers of cardiac remodelling and HF risk: LV wall thickness/dimension ratio; LVEF, volume

Biomakers: BNP, galectin-3

250 childhood + HD anthracyclines

randomized, double blind, placebo-controlled trial

target dose 12.5 mg/day

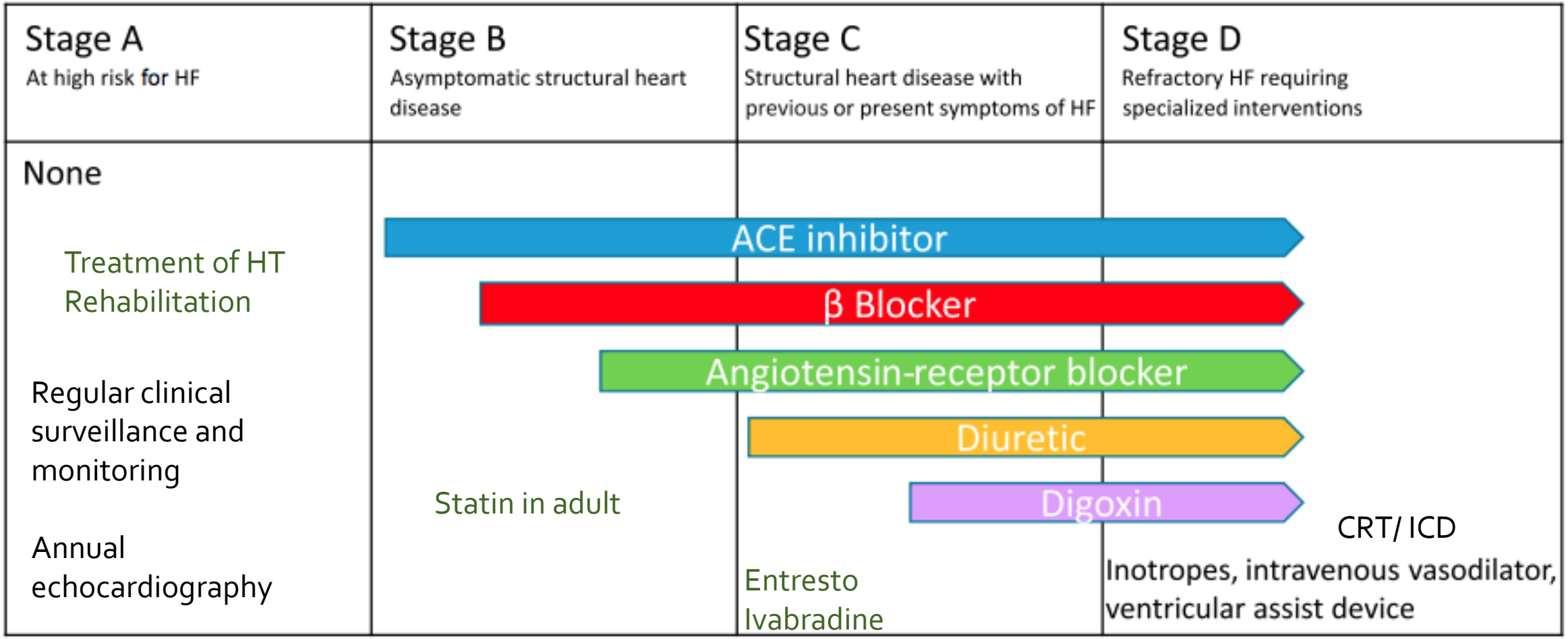


Figure 3. Medical therapy for heart failure (HF) by stage. Angiotensin-converting enzyme (ACE) inhibitors and β-blockers may by initiated in asymptomatic individuals with ventricular dysfunction at a low dose and uptitrated to the target dosage based on tolerance of the medication. (Modified with permission from Kantor PF, Lougheed J, Dancea A, et al; Children's Heart Failure Study Group. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. *Can J Cardiol*. 2013;29(12):1535–1552.)

Congestive Heart failure in Children; Jack F. Price; Pediatrics in Review 2019

Hypertension

- Main issues in adult cancer patients/ survivor
- Major risk factor for development of anthracycline toxicity
- ACEI

PHT

- CML – dasatinib (0.45%)
- Partial or complete reversal of PHT after discontinuation

QT prolongation

TABLE 3 Anticancer Agents Associated With QT Prolongation

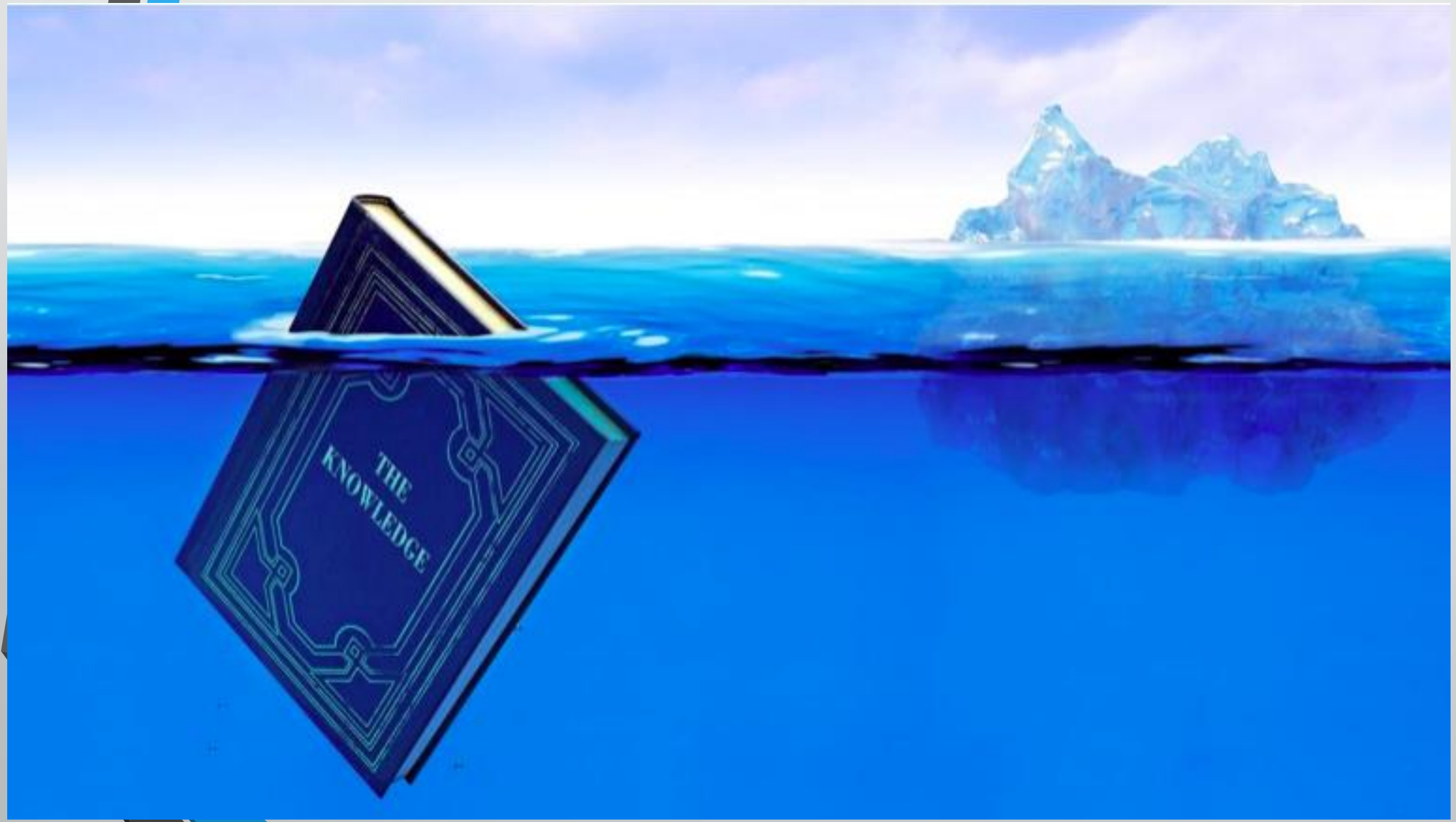
Chemotherapy Agents	Frequency of Use	Incidence (%)	Comments
Histone deacetylase inhibitors			Tangent method of QT measurement
Belinostat	+	4-11	
Vorinostat	++++	3.5-6.0	
Chemicals			Fridericia correction formula
Arsenic trioxide	++	26-93	
Small molecule tyrosine kinase inhibitors			
Dabrafenib	++++	2-13	Correct low K or Mg
Dasatinib	++++	<1-3	
Lapatinib	++++	10-16	Remove QTc prolonging medications
Nilotinib	++++	<1-10	
Vandetanib	++++	8-14	QTc >500 ms or >60 ms above baseline associated with TdP
BRAF inhibitor			
Vemurafenib	++++	3	TdP reported for arsenic trioxide, sunitinib, pazopanib, vandetanib, vemurafenib

See Table 1 for frequency of use description (55,72).

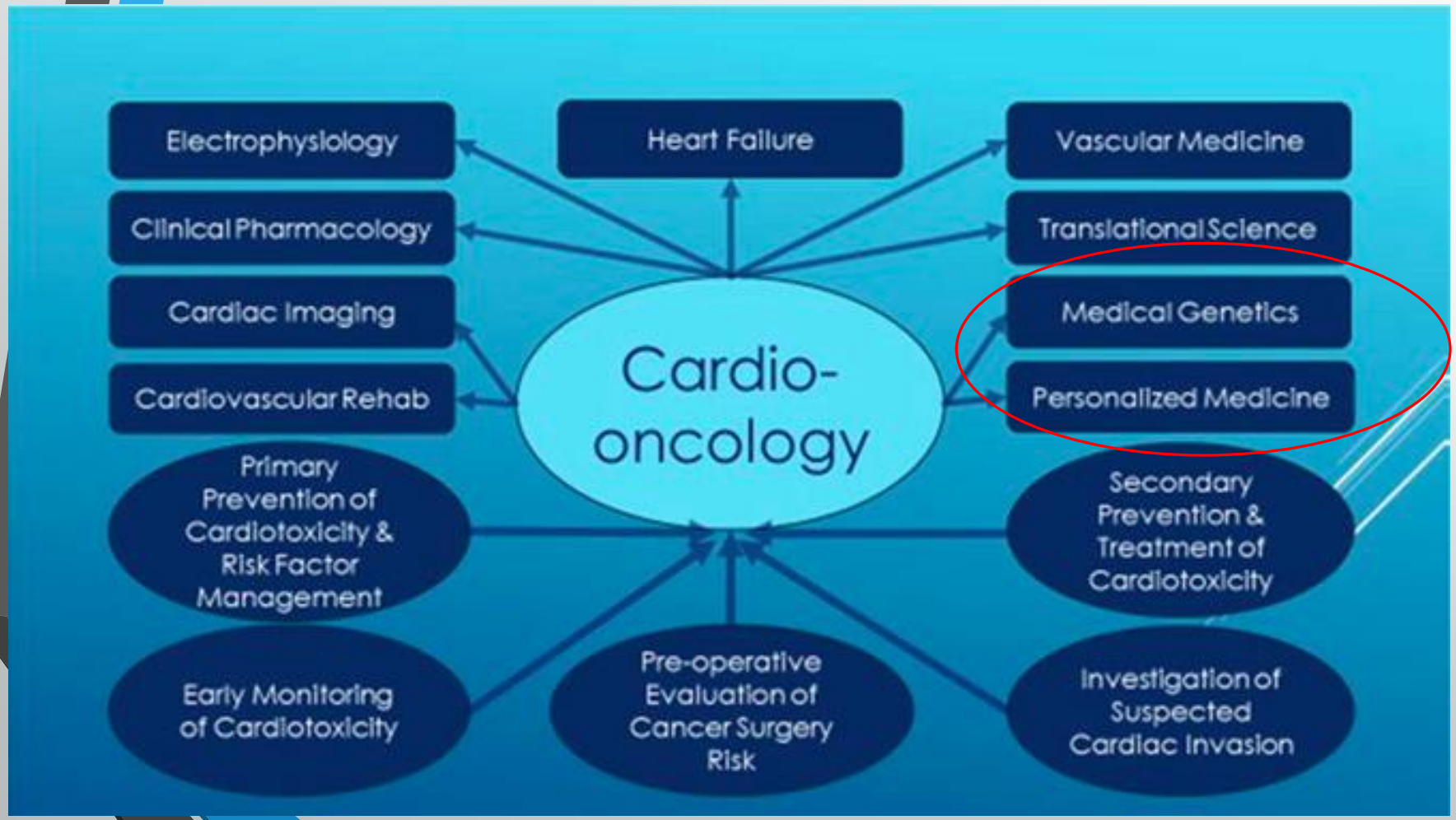
K = potassium; Mg = magnesium; QTc = corrected QT interval; TdP = torsades de pointes.

JACC VOL. 70, NO. 20, 2017
NOVEMBER 14/21, 2017:2552-65

- Antiemetics, H2-blocker, PPI, antimicrobial agents, antipsychotics
- Vomiting -> electrolytes
- Treatment stopped when QTc > 500 ms
- QT prolongation medication avoidance www.qtdrugs.org


THE
KNOWLEDGE

Genetic predispose in developing cardiomyopathy
Increase risk:
RARG rs2229774 (retinoic acid receptor gamma)
SLC28A3 rs7853758 (solute carrier family 28 member 3)
UGT1A6*4 re17863783 (UDP glucuronosyltransferase family 1 member a6)



Han at al, Precision Oncology 2017

AMERICAN COLLEGE of CARDIOLOGY

Monitoring and Treatment of CV Toxicities in Pediatric Cancer: What's Known and What's Needed

Nov 12, 2019 | Thomas D. Ryan, MD, FACC

Fewer than 10% of programs had cardio-oncology-specific training opportunities
No formalized training for paediatric cardio-oncology

Oncologist's good understanding is equally importance - to ensure proper surveillance is followed, as well as integration of cardiology into care pathways when indicated

Involvement of adult cardiologists !

More than anthracycline to come !!

Thank you!