Evidence of Dexrazoxane (DXZ) & Other Interventions to Decrease Cardiotoxicity

MASCC 2018
Parallel Session: How to Prevent Cardiotoxicity – A Real Challenge
Andrea D. Orsey, MD, MSCE
Chair, Pediatric Study Group
Connecticut Children's, Hartford, CT USA

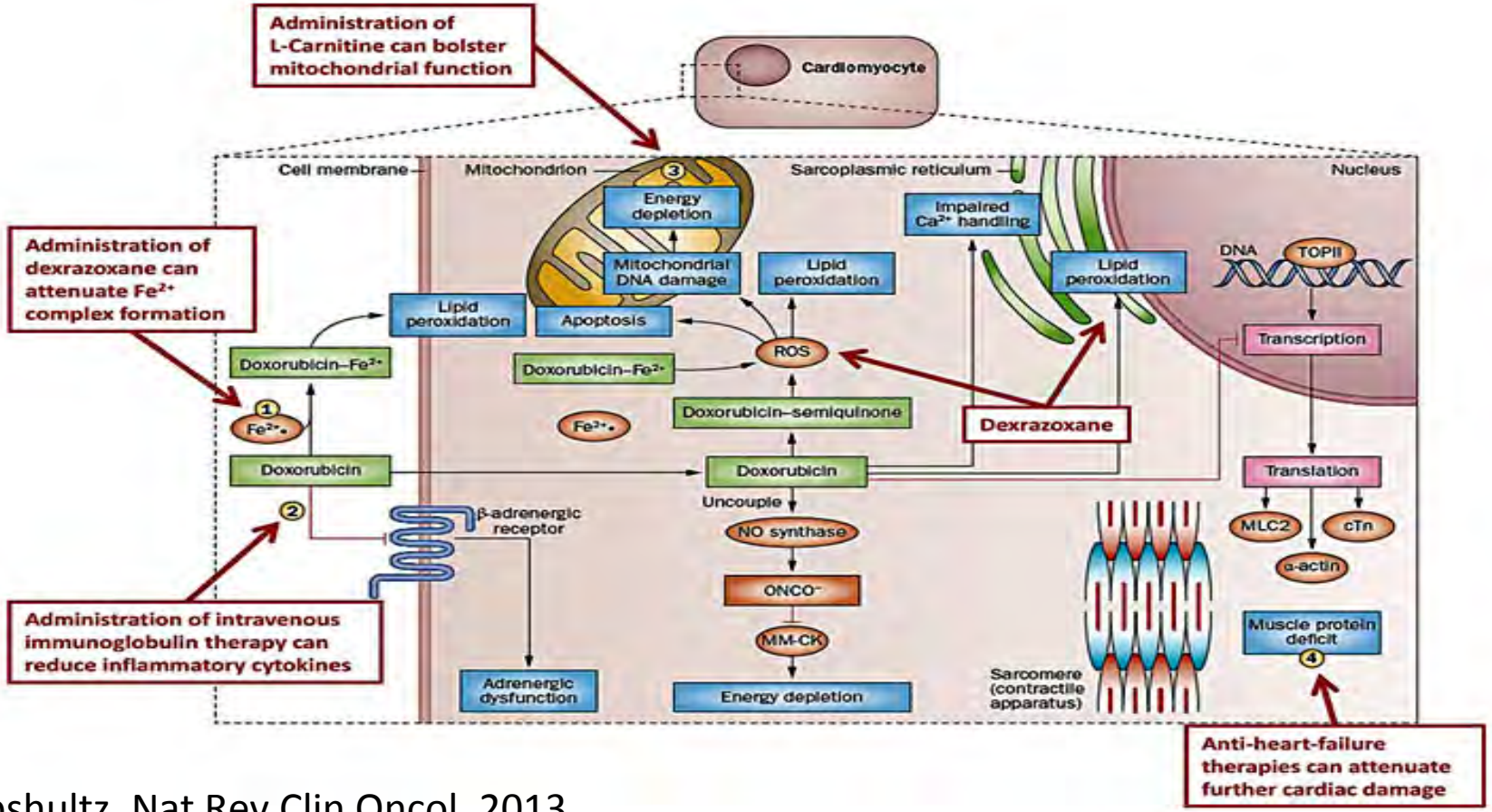
Disclosures

- No disclosures

Objectives

- To understand the indications for Dexrazoxane
- To review the benefits & risks of Dexrazoxane
- To review the evidence of other pharmaceutical interventions to decrease cardiotoxicity
- To discuss exercise as a non-pharmacological treatment to decrease cardiotoxicity

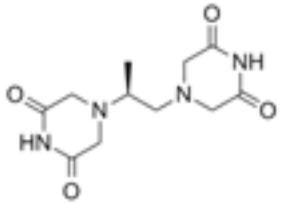
Potential Targets for Intervention

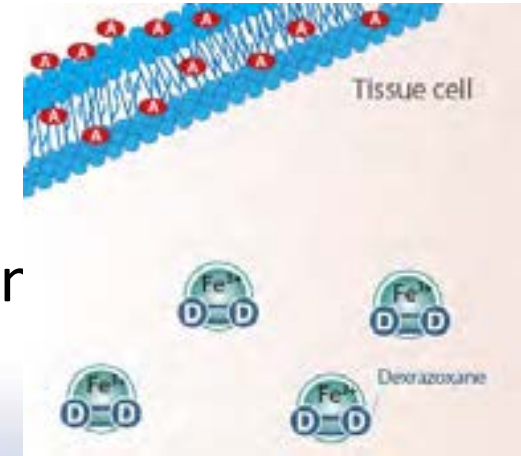


Lipshultz, Nat Rev Clin Oncol, 2013

Dexrazoxane (DXZ): Primary Prevention

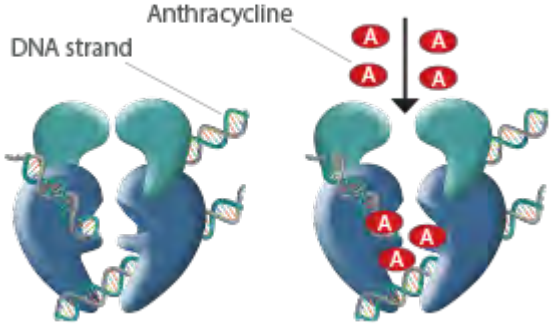
- Discovered: Kurt Hellman, Oxford 1972
- Potential Mechanisms
  - Cyclic derivative of EDTA
  - Intracellular iron chelation
    - Conversion to ring-opened chelating agent
    - Interferes with iron-mediated free radical generation
  - Reduces reactive oxygen species formation
    - ↓ Fe metal ion complexes → less superoxide free radicals

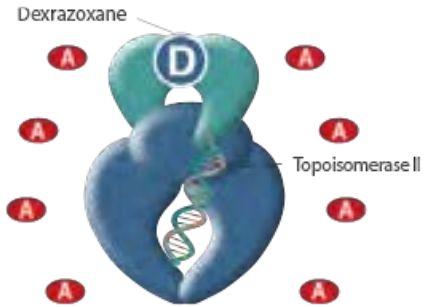




DXZ: Primary Prevention

- Weak topoisomerase inhibitor
- Depletes Topoisomerase 2 Beta (Topo2β)
- Reduces anthracycline-associated myocyte death in vitro





www.totect.com

DXZ: Pharmacokinetics

SUMMARY OF MEAN (%CV[a]) DEXRAZOXANE PHARMACOKINETIC PARAMETERS AT A DOSAGE RATIO OF 10:1 OF ZINECARD: DOXORUBICIN

Dose Doxorubicin (mg/m^2)	Dose ZINECARD (mg/m^2)	Number of Subjects	Elimination Half-Life (h)	Plasma Clearance ($L/h/m^2$)	Renal Clearance ($L/h/m^2$)	[b]Volume of Distribution (L/m^2)
50	500	10	2.5 (16)	7.88 (18)	3.35 (36)	22.4 (22)
60	600	5	2.1 (29)	6.25 (31)	—	22.0 (55)

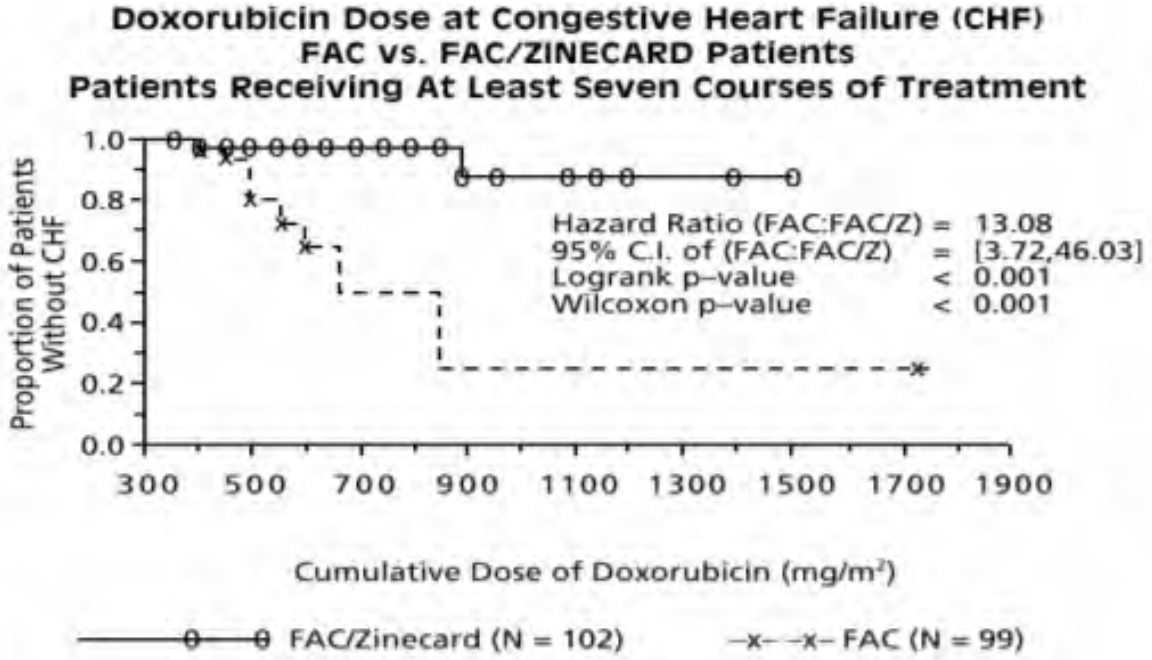
[a] Coefficient of variation
[b] Steady-state volume of distribution
gsatfda_docs/label/2012/020212s013lbl

Dosage ratio of dexrazoxane:doxorubicin is 10:1

DXZ: Indications

- **FDA**: doxorubicin ≥300 mg/m^2
  - Women with metastatic breast cancer
- **ASCO**: all adults doxorubicin ≥250 mg/m^2 (Armenian, JCO, 2017)
- **ESMO**: Appropriate cardioprotectant regimen to be considered & planned for all pts at high risk of cardiotoxicity (Curigliano, Ann Oncol, 2012)
- **EMA**: restricted in 2011 to adults with prior doxorubicin ≥300 mg/m^2 & advanced/metastatic breast cancer
  - Efficacy in peds not established but efficacy demonstrated in adults
  - Use in children contraindicated 2011 until 19 July 2017
    - Only contraindicated if 0-18 yrs old & expected to receive < 300 mg/m^2

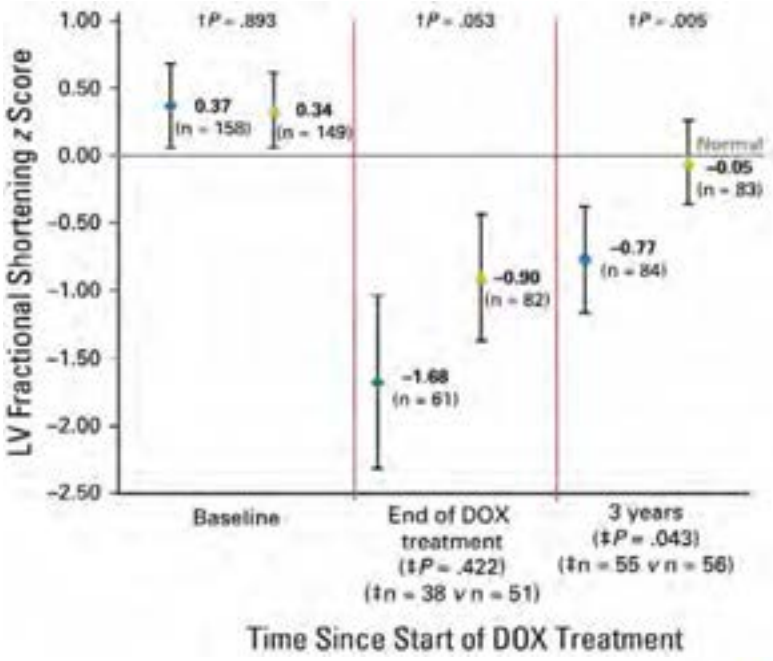
DXZ: Data for FDA indication



www.accessdata.fda.gov

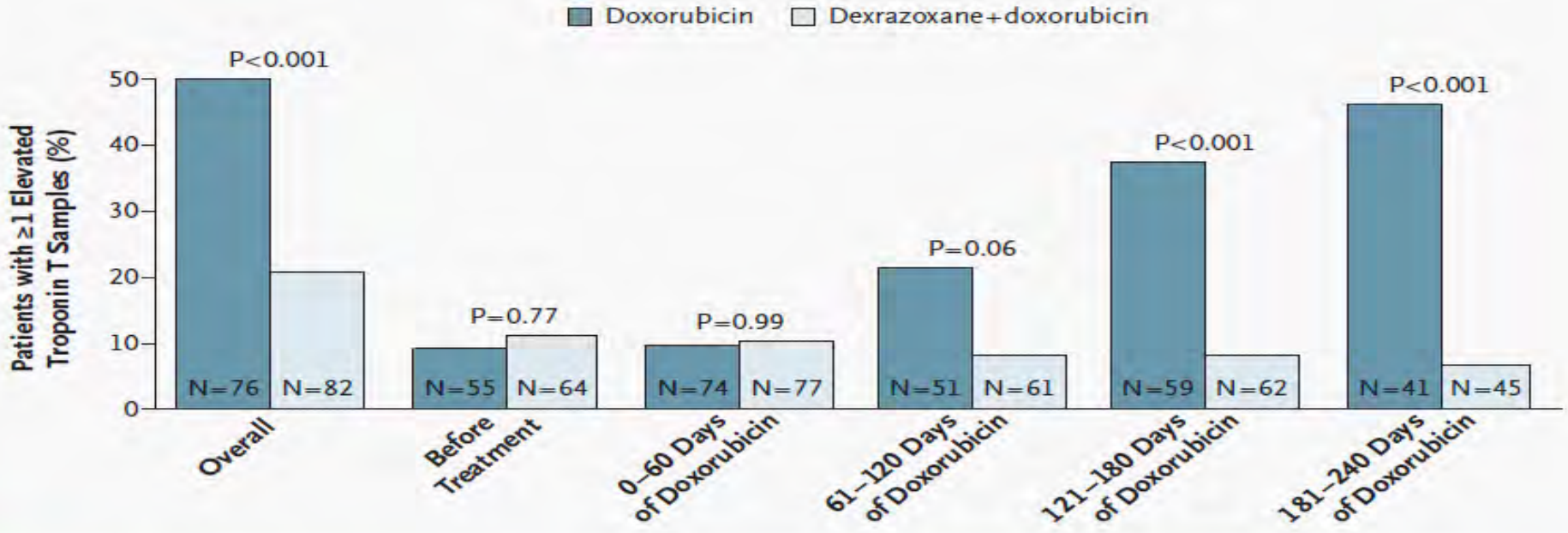
DXZ: COG Trial P9404

- RCT of 537 children/ adolescents
  - Dx: T-cell ALL, lymphoblastic non-Hodgkin lymphoma
  - Outcomes: oncologic efficacy, cardioprotective effectiveness, safety
  - Results: Eechocardiographic measures better at 3 years in DXZ group
  - No difference in survival ± DXZ



Asselin, JCO, 2015

Effect of DXZ on Myocardial Injury Among Children with ALL Treated with Doxorubicin

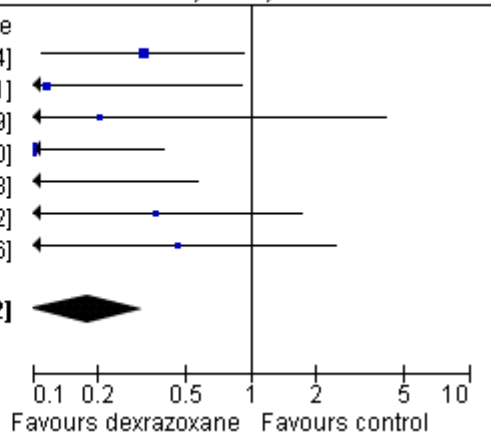


Lipshultz, et al: *N Engl J Med, 2004.*

DXZ: Cardioprotectant

Study or Subgroup	Dexrazoxane Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lipshultz 2004	0	105	0	101		Not estimable
Lopez 1998	4	63	13	66	18.4%	0.32 [0.11, 0.94]
Marty 2006	1	85	8	79	12.0%	0.12 [0.01, 0.91]
Schwartz 2009	0	107	2	109	3.6%	0.20 [0.01, 4.19]
Speyer 1992	2	76	20	74	29.4%	0.10 [0.02, 0.40]
Swain 1997a(088001)	0	168	15	181	21.7%	0.03 [0.00, 0.58]
Swain 1997a(088006)	2	81	7	104	8.9%	0.37 [0.08, 1.72]
Venturini 1996	2	84	4	78	6.0%	0.46 [0.09, 2.46]
Total (95% CI)		**769**		**792**	**100.0%**	**0.18 [0.10, 0.32]**
Total events	11		69			

Heterogeneity: Chi² = 5.49, df = 6 (P = 0.48); I² = 0%
Test for overall effect: Z = 5.67 (P < 0.00001)



Cochrane Database of Systematic Reviews
15 JUN 2011 DOI: 10.1002/14651858.CD003917.pub4
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003917.pub4/full#CD003917-fig-0001

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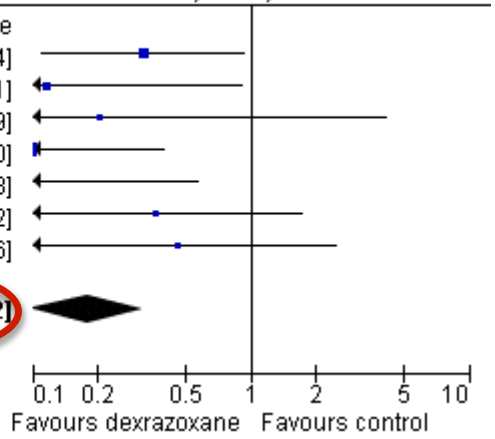

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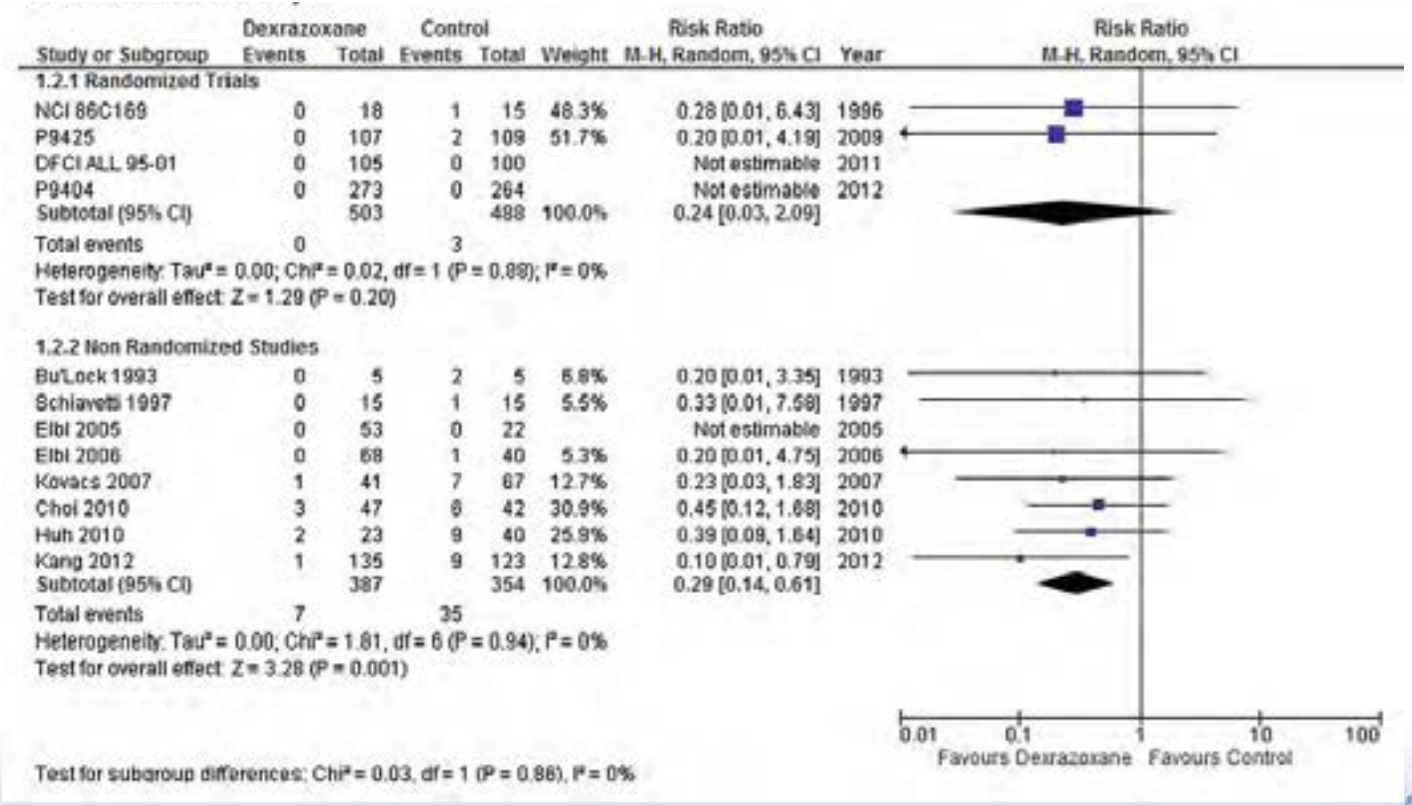
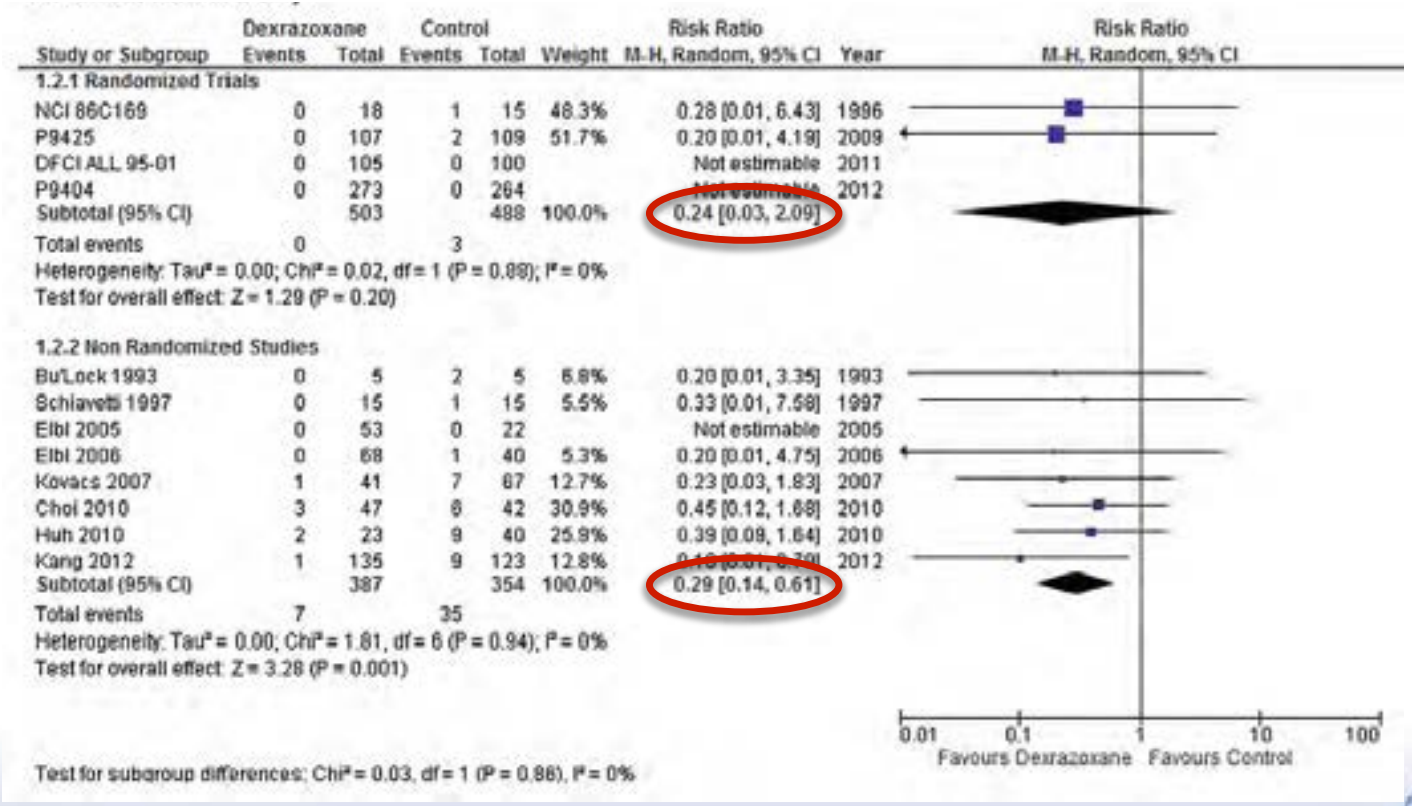
DXZ: Pediatric Clinical Cardiotoxicity



Shaikh F et.al, *JNCI J Natl Cancer Inst* (2016) 108(4): djv357

DXZ: Pediatric Clinical Cardiotoxicity



Study or Subgroup	Dexrazoxane Events	Dexrazoxane Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 Randomized Trials							
NCI 86C169	0	18	1	15	48.3%	0.28 [0.01, 6.43]	1996
P9425	0	107	2	109	51.7%	0.20 [0.01, 4.19]	2009
DFCI ALL 95-01	0	105	0	100		Not estimable	2011
P9404	0	273	0	284		[illegible]	2012
Subtotal (95% CI)		503		488	100.0%	0.24 [0.03, 2.09]	
Total events	0		3				
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%							
Test for overall effect: Z = 1.29 (P = 0.20)							
1.2.2 Non Randomized Studies							
Bu'Lock 1993	0	5	2	5	6.8%	0.20 [0.01, 3.35]	1993
Schiavetti 1997	0	15	1	15	5.5%	0.33 [0.01, 7.58]	1997
Elbl 2005	0	53	0	22		Not estimable	2005
Elbl 2006	0	68	1	40	5.3%	0.20 [0.01, 4.75]	2006
Kovacs 2007	1	41	7	87	12.7%	0.23 [0.03, 1.83]	2007
Choi 2010	3	47	6	42	30.9%	0.45 [0.12, 1.68]	2010
Huh 2010	2	23	9	40	25.9%	0.39 [0.09, 1.64]	2010
Kang 2012	1	135	9	123	12.8%	[illegible]	2012
Subtotal (95% CI)		387		354	100.0%	0.29 [0.14, 0.61]	
Total events	7		35				
Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 6 (P = 0.94); I² = 0%							
Test for overall effect: Z = 3.28 (P = 0.001)							
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%							

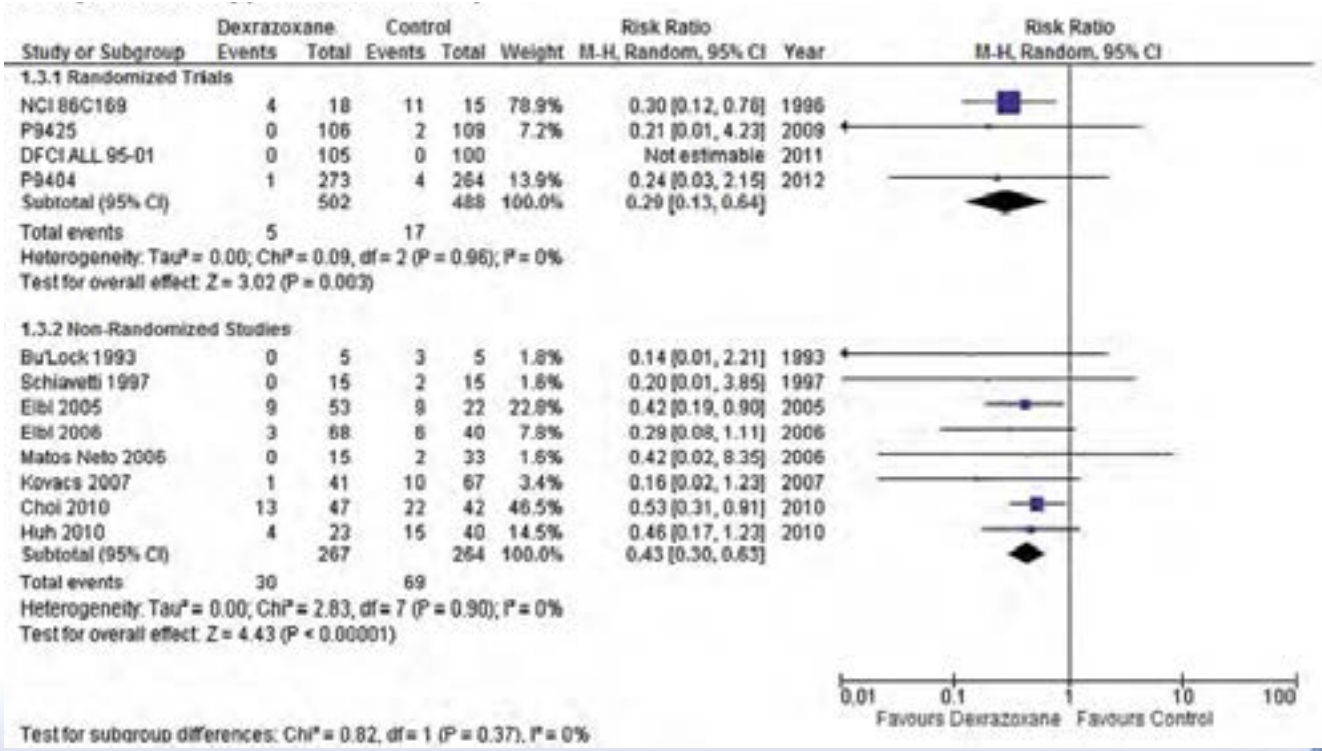
Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours Dexrazoxane Favours Control

Shaikh F et.al, *JNCI J Natl Cancer Inst* (2016) 108(4): djv357

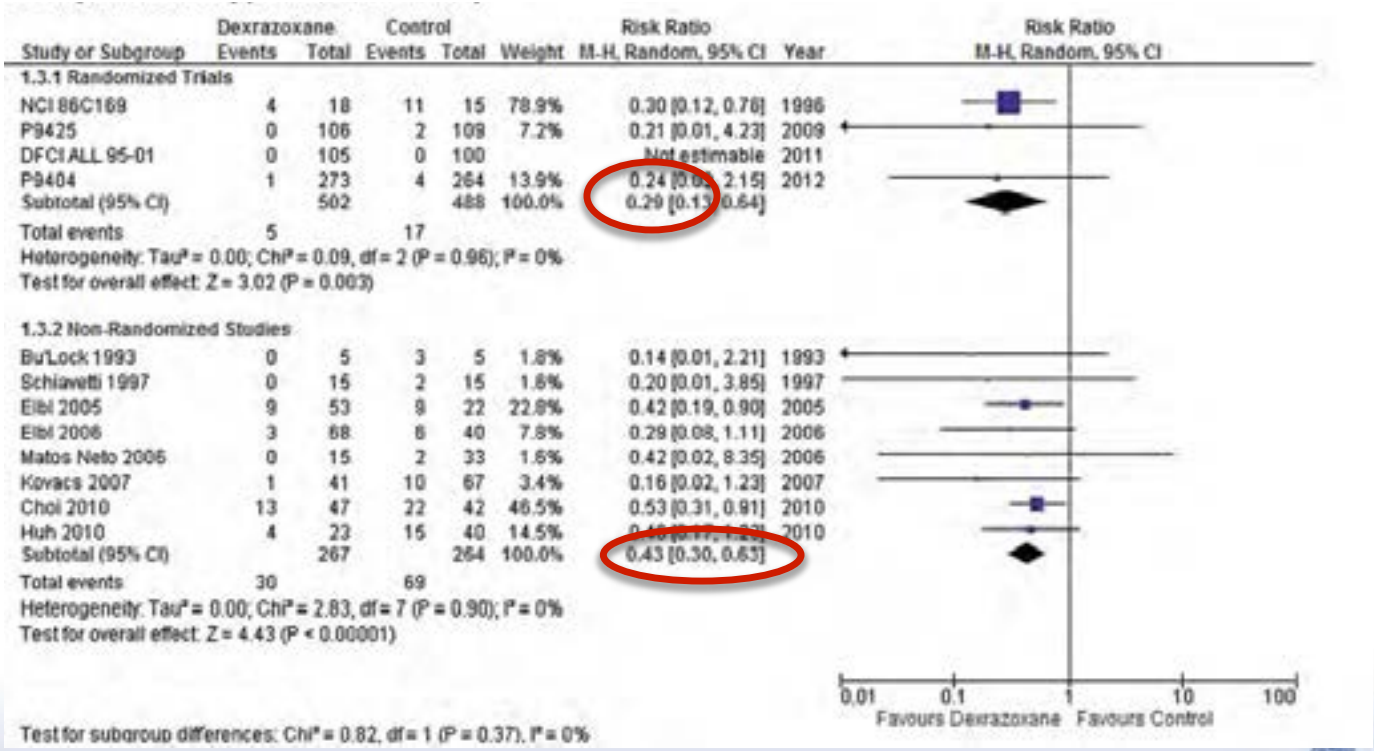
DXZ: Pediatric Cardiotoxicity (Clinical or Subclinical)



Study or Subgroup	Dexrazoxane Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.3.1 Randomized Trials							
NCI 86C169	4	18	11	15	78.9%	0.30 [0.12, 0.76]	1996
P9425	0	106	2	109	7.2%	0.21 [0.01, 4.23]	2009
DFCI ALL 95-01	0	105	0	100		Not estimable	2011
P9404	1	273	4	264	13.9%	0.24 [0.03, 2.15]	2012
Subtotal (95% CI)		502		488	100.0%	0.29 [0.13, 0.64]	
Total events	5		17				
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 2 (P = 0.96); I² = 0%							
Test for overall effect: Z = 3.02 (P = 0.003)							
1.3.2 Non-Randomized Studies							
Bu'Lock 1993	0	5	3	5	1.8%	0.14 [0.01, 2.21]	1993
Schiavetti 1997	0	15	2	15	1.8%	0.20 [0.01, 3.85]	1997
Elbl 2005	9	53	9	22	22.8%	0.42 [0.19, 0.90]	2005
Elbl 2006	3	68	6	40	7.8%	0.29 [0.08, 1.11]	2006
Matos Neto 2006	0	15	2	33	1.6%	0.42 [0.02, 8.35]	2006
Kovacs 2007	1	41	10	67	3.4%	0.16 [0.02, 1.23]	2007
Choi 2010	13	47	22	42	46.5%	0.53 [0.31, 0.91]	2010
Huh 2010	4	23	15	40	14.5%	0.46 [0.17, 1.23]	2010
Subtotal (95% CI)		267		264	100.0%	0.43 [0.30, 0.63]	
Total events	30		69				
Heterogeneity: Tau² = 0.00; Chi² = 2.83, df = 7 (P = 0.90); I² = 0%							
Test for overall effect: Z = 4.43 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.37), I² = 0%							

Shaikh F et.al, *JNCI J Natl Cancer Inst* (2016) 108(4): djv357

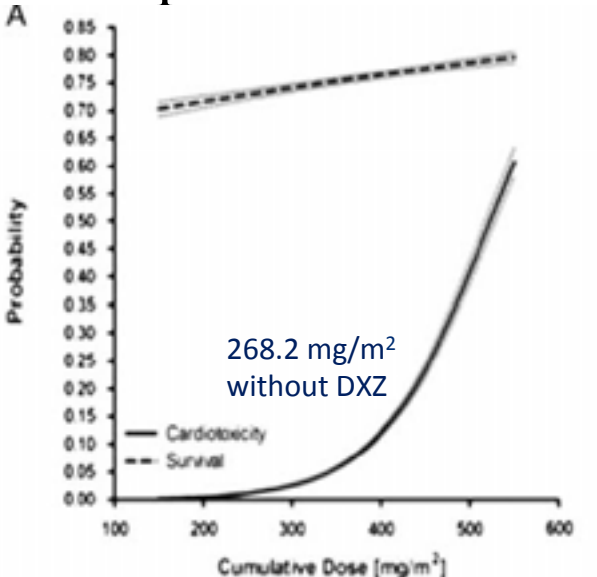
DXZ: Pediatric Cardiotoxicity (Clinical or Subclinical)

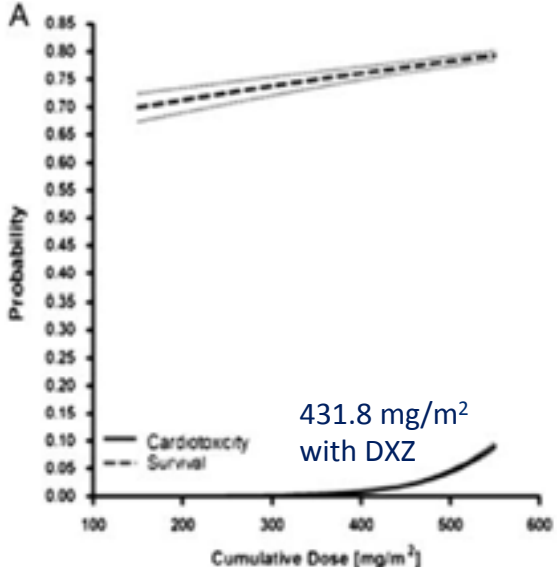


Shaikh F et.al, *JNCI J Natl Cancer Inst* (2016) 108(4): djv357

DXZ: Systemic Review of Solid Tumors

- 4782 patients in 22 studies after 2000
  - Osteosarcoma (n=14), Wilm's (n=3), Neuroblastoma (n=5)
- With ↑ cumulative anthracycline dose, linear survival ↑ & exponential cardiotoxicity ↑





Liesse, J Pediatr Hemato Onco, 2018.

DXZ: Systemic Review of Solid Tumors

TABLE 4. Cardiotoxicity Rates as a Function of Follow-up Time

	Dose (mg/m^2)	% at 5 y (95% CI)	% at 20 y (95% CI)
Without dexrazoxane	200	0.485 (0.456-0.517)	0.992 (0.831-1.18)
	300	2.47 (2.35-2.59)	4.94 (4.25-5.73)
	400	11.6 (11.0-12.2)	21.2 (19.0-23.7)
With dexrazoxane	300	0.164 (0.143-0.188)	0.337 (0.261-0.434)
	400	0.846 (0.758-0.943)	1.72 (1.37-2.16)
	500	4.24 (3.87-4.64)	8.33 (6.86-10.1)

- Cardiotoxicity rates double from 5 to 20 years
- DXZ ↓ rate cardiotoxicity but does not protect from late cardiotoxic effects
- Are current regimens overvaluing anthracycline doses?

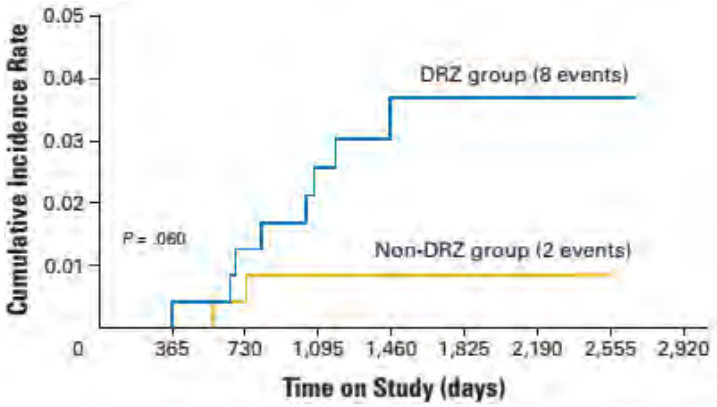
Liesse, J Pediatr Hemato Onco, 2018.

DXZ: Possible Risks

- Second Malignant Neoplasms (SMNs)
- Increased mortality
- Impair Chemotherapy Efficacy
- Infection
- Cytopenias

DXZ: SMNs

- Report of ↑incidence AML/MDS in children with Hodgkin's lymphoma who received dexrazoxane
- Possible synergistic effect with etoposide on DNA repair
  - Both bind topoisomerase II at different sites
- Contributed to EMA ban use of dexrazoxane

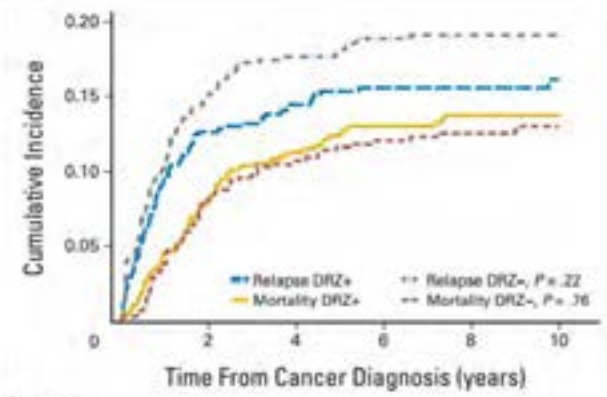


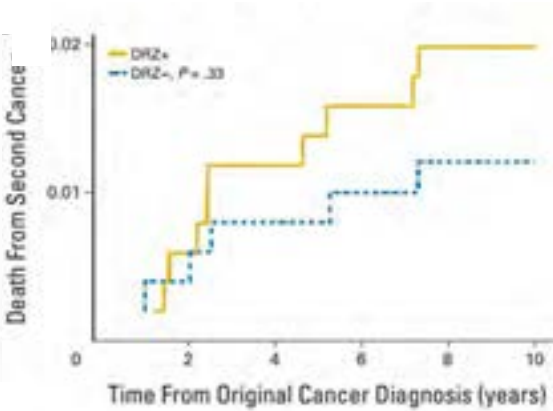
Tebbi CK et al. JCO, 2007.

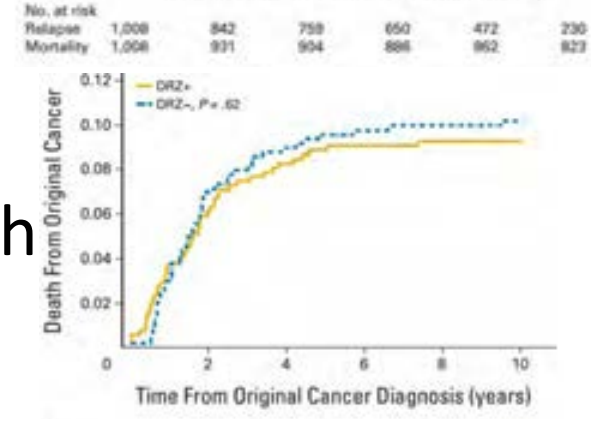
DXZ: SMNs

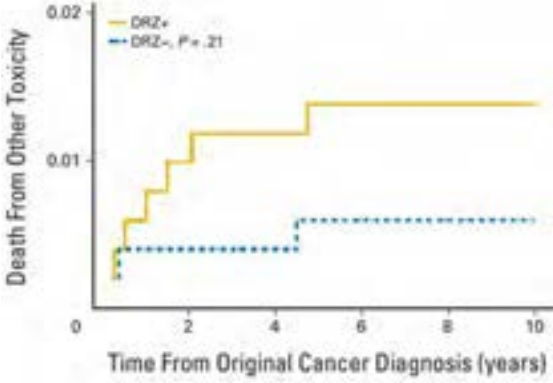
- Initial borderline risk not seen on longer follow-up
- No difference is OS, EFS, death from second cancer, death from other toxicity

(Chow, JCO, 2015)



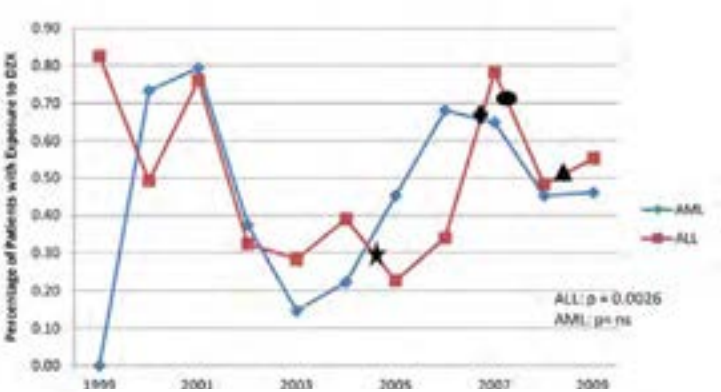


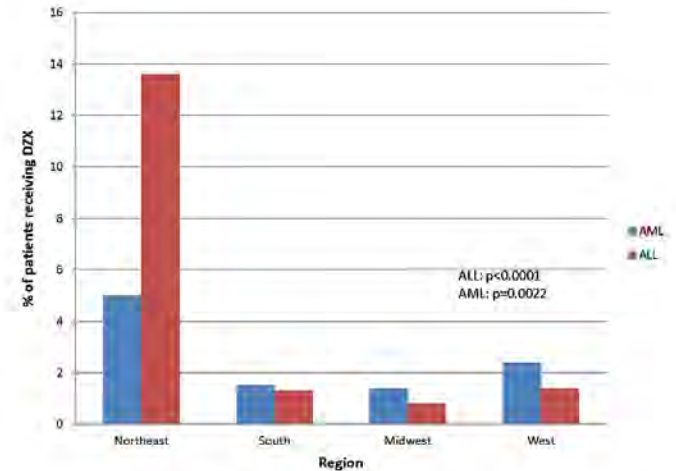




PHIS Data: Variation & SMNs

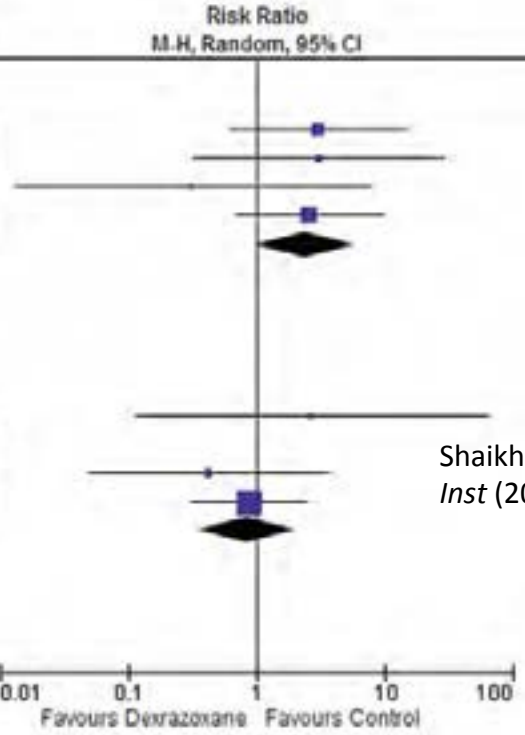
- From 1999-2009, 2.4% (207/8,733) ALL and 2.0% (52/2,556) AML given DXZ (Walker, PBC, 2013)
  - Older children, black patients, males with ALL
  - Varied by time/region for ALL but not AML
  - Timing of first dose varied
- From 1999-2011, Secondary AML 0.21% (3/1406) in DXZ group & 0.55% (77/14,126) unexposed group (Seif, PBC, 2015)
  - OR = 0.38 (CI 0.11-1.26)





DXZ: Pediatric SMNs

Study or Subgroup	Dexrazoxane Events	Dexrazoxane Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 Randomized Trials							
NCI 86C169	0	23	0	18		Not estimable	1996
P9426	6	127	2	128	31.4%	3.02 [0.62, 14.70]	2007
P9425	3	107	1	109	15.5%	3.06 [0.32, 28.92]	2009
DFCI ALL 95-01	0	105	1	100	7.7%	0.32 [0.01, 7.71]	2011
P9404	8	273	3	264	45.3%	2.58 [0.69, 9.62]	2012
Subtotal (95% CI)		635		619	100.0%	2.37 [0.98, 5.74]	
Total events	17		7				
Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 3 (P = 0.64); I² = 0%							
Test for overall effect: Z = 1.91 (P = 0.06)							
1.1.2 Non Randomized Trials							
Choi 2010	1	47	0	42	7.8%	2.69 [0.11, 64.24]	2010
Huh 2010	0	23	0	40		Not estimable	2010
Vrooman 2011	1	452	5	966	17.1%	0.43 [0.05, 3.65]	2011
Kopp 2012 [abstract]	5	338	13	777	75.1%	0.88 [0.32, 2.46]	2012
Subtotal (95% CI)		860		1825	100.0%	0.85 [0.35, 2.07]	
Total events	7		18				
Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 2 (P = 0.64); I² = 0%							
Test for overall effect: Z = 0.36 (P = 0.72)							
Test for subgroup differences: Chi² = 2.56, df = 1 (P = 0.11), I² = 60.9%							



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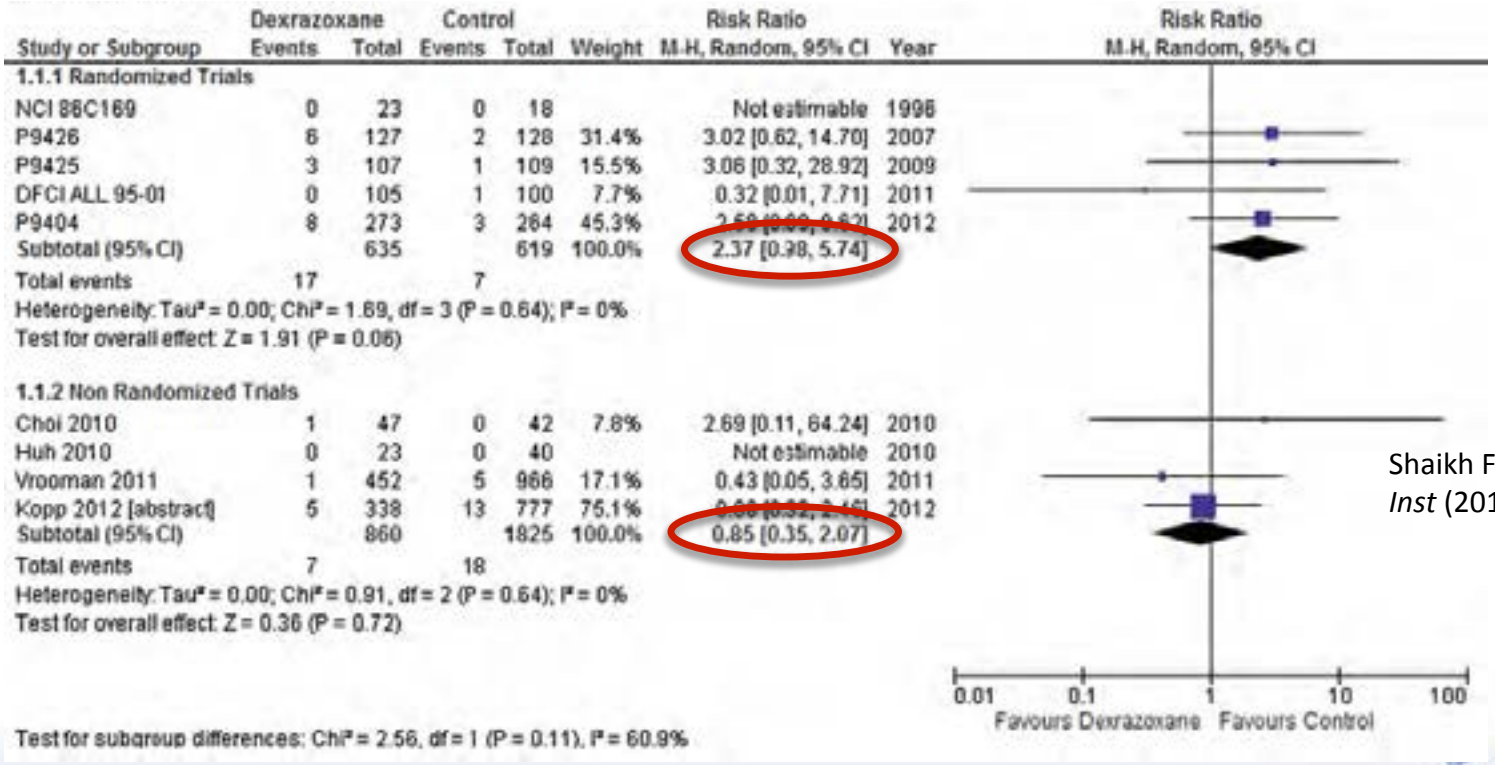
DXZ: Pediatric SMNs



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DXZ: Risk Factor Analysis

- Nationwide Korean study: 1,453 pts received anthracycline
  - 15 hospitals
  - 1,035 received DXZ with each anthracycline
  - 418 did not received DXZ
- DXZ improved cardiac event-free survival rates among $\geq$ 400mg/m^2
- SMNs not related to DXZ in multivariate analysis
  - 6 yr SMN incidence rate 0.67 $\pm$ 0.24%

Kim et. Al, Korean Cancer Association, 2018

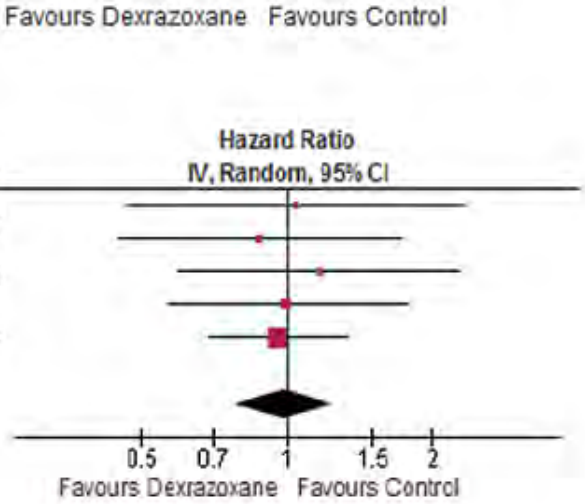
DXZ: Pediatric EFS

Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.37), I² = 0%

D Event-Free Survival

Study or Subgroup	log[Hazard Ratio]	SE	Dexrazoxane Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
NCI 86C169	0.04	0.41	23	18	8.5%	1.04 [0.47, 2.32]	1996
P9426	-0.13	0.34	127	128	12.4%	0.88 [0.45, 1.71]	2007
P9425	0.15	0.34	107	109	12.4%	1.16 [0.60, 2.26]	2009
DFCI ALL 95-01	0	0.29	105	100	17.0%	1.00 [0.57, 1.77]	2011
P9404	-0.04	0.17	273	264	49.6%	0.96 [0.69, 1.34]	2012
Total (95% CI)			635	619	100.0%	0.99 [0.78, 1.25]	

Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 4 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.91)

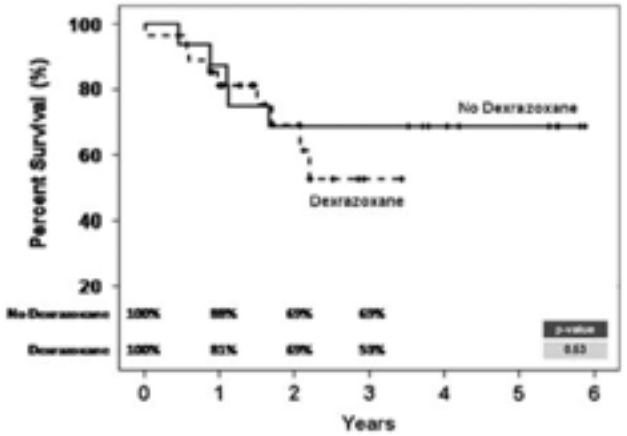


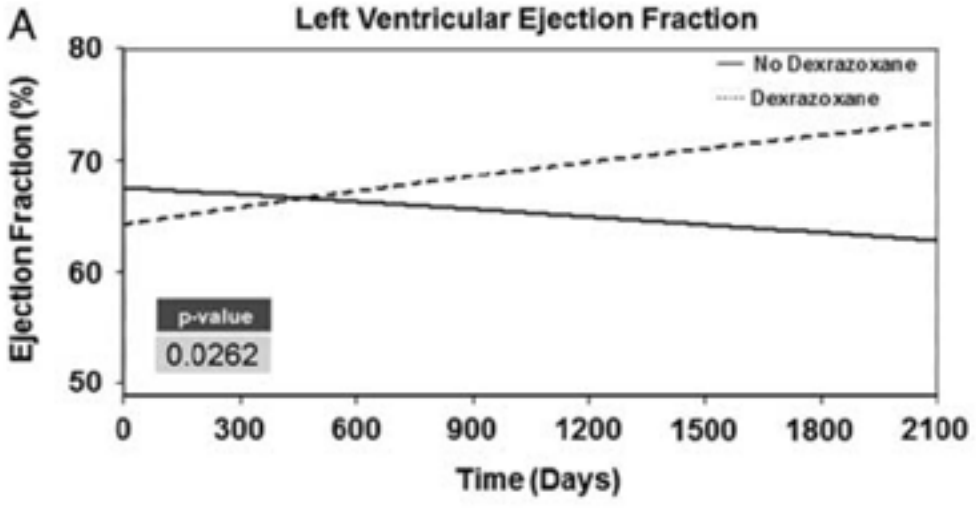
Shaikh F et.al, *JNCI J Natl Cancer Inst* (2016) 108(4): djv357

DXZ in AML

- 44 pts AML dx 0-21 yrs at single institution 2008-2011
- Adopted dexrazoxane prior to anthracyclines 2011
- No difference in event rate or OS
- Improved cardiac function

(Schloemer et.al, J Pediatr Hematol Oncol, 2017)





DXZ: Antitumor Effects

- Cochrane meta-analysis of PR or CR not different in RCTs with DXZ randomly assigned (van Dalen, Cochrane Database Syst, 2011)
  - PFS not different between groups +/- DXZ
- Among women with breast CA, response rates not different +/- DXZ (Abdel-Qadir, Ann Oncol, 2017)

DXZ: Cytopenias

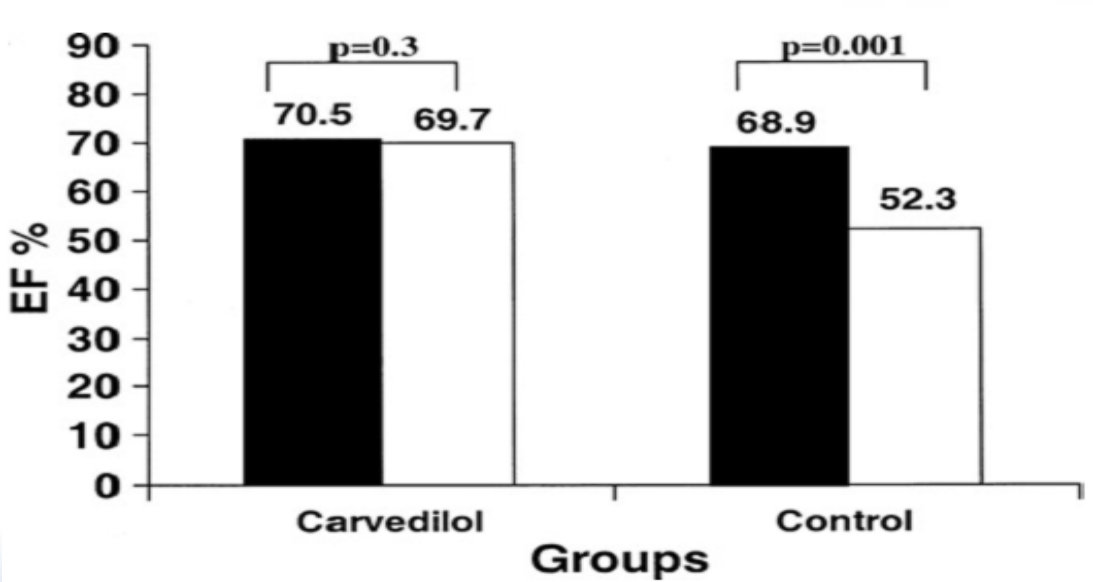
- Common in children receiving chemotherapy
- Hematological events likely due to chemotherapy
- 1 RCT with grade 3 or 4 hematological toxicity identical (89.0% with DXZ vs 89.8% without DXZ; p = 0.26) (Asselin, JCO, 2016)
- Routine hematological testing & blood product support

Liposomal Anthracyclines

- Concentrates drug in tumor cells
  - ↓ blood concentration
- Decreased cardiotoxicity 5x with same efficacy (O'Brien, Ann Oncol, 2004)
- Limited pediatric studies
  - COG study AAML1421 (CPX-351)

Carvedilol : Chemoprophylaxis

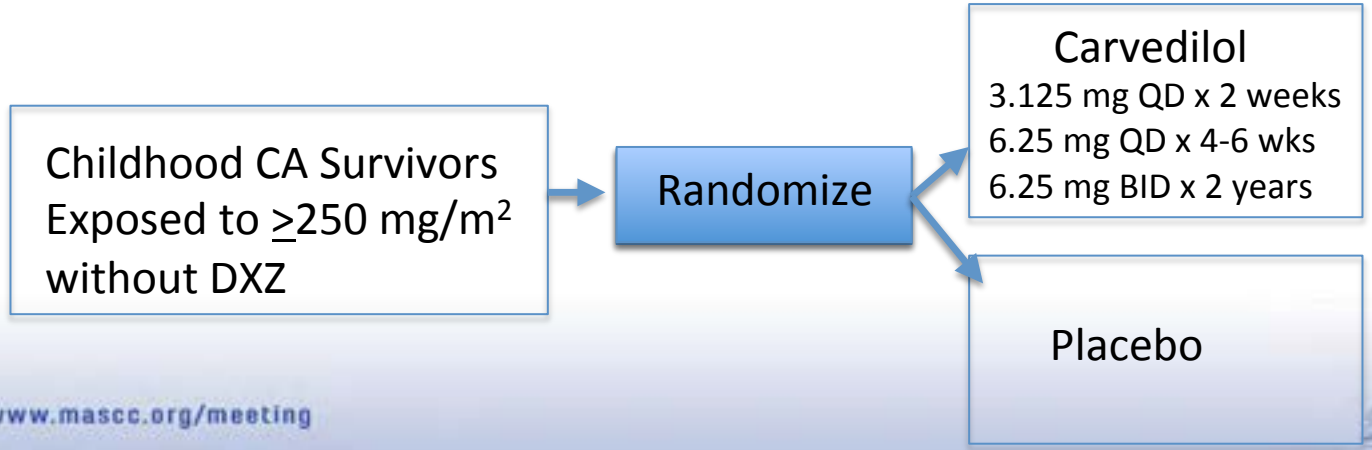
- N=50 (25 each group of RCT)
- Anthracycline Rx
- Carvedilol 12.5 mg vs placebo
- Started before chemo and continued 6 mos later
- Echo @ baseline & 6 mos post



Kalay N et.al. *J Am Coll Cardiol* 2006;48:2258–62

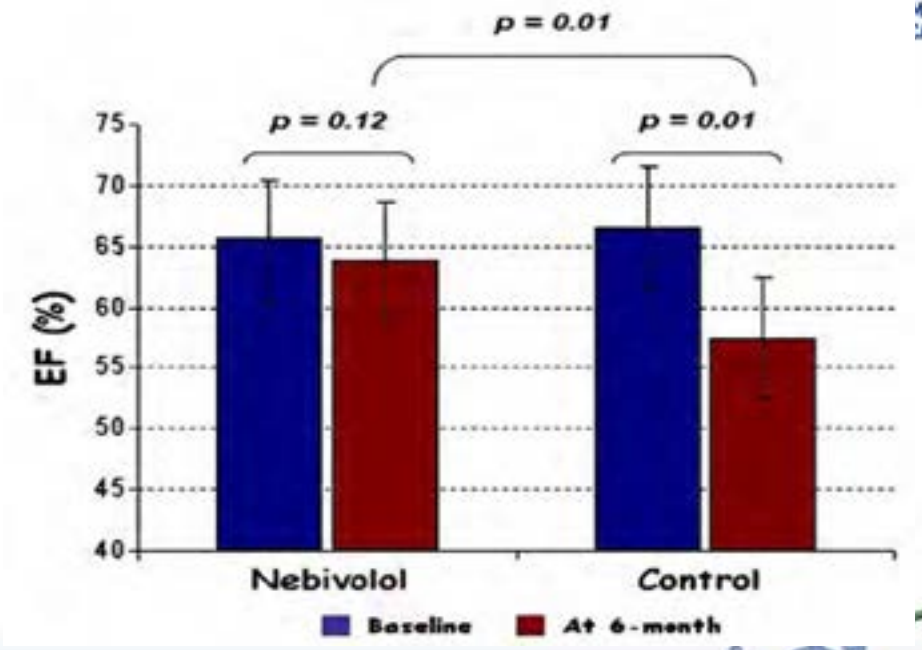
Carvedilol: COG ALTE1621

- PREVENT-HF: Pharmacologic Reversal of Ventricular Remodeling in Childhood Cancer Survivors at Risk for Heart Failure
- Phase 2b RCT of Carvedilol vs Placebo
- Outcomes: LV thickness (echo) & biomarker



Nebivolol: Chemoprophylaxis

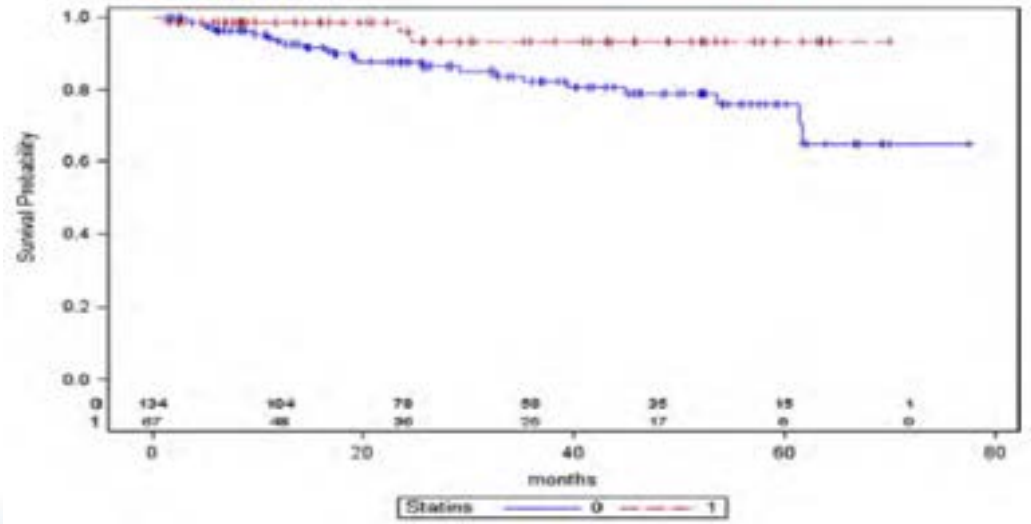
- N= 45 (27/18)
- Breast CA
- Nebivolol 5 mg daily or placebo
- TTE data at baseline and 6 months



Kaya, *Int J of Card, 2013.*

Statins as Protective Therapy

- Preclinical data: ↓oxidative stress, pro-inflammatory cytokines & caspase-mediated apoptosis (Riad, Cancer Res, 2009)
- N=628, breast CA
- 67 on statins during anthracycline Rx vs 134 propensity matched controls
- HR 0.3 (CI 0.1-0.9) for development of symptomatic heart failure



Seicean, *J Am Coll Cardiol 2012.*

Statins as Protective Therapy

- RCT of 40 pts
- 40 mg/day atorvastatin vs placebo x 6 mo
- No ↓ LV EF in atorvastatin group

Acar, J Am Coll Cardiol, 2011

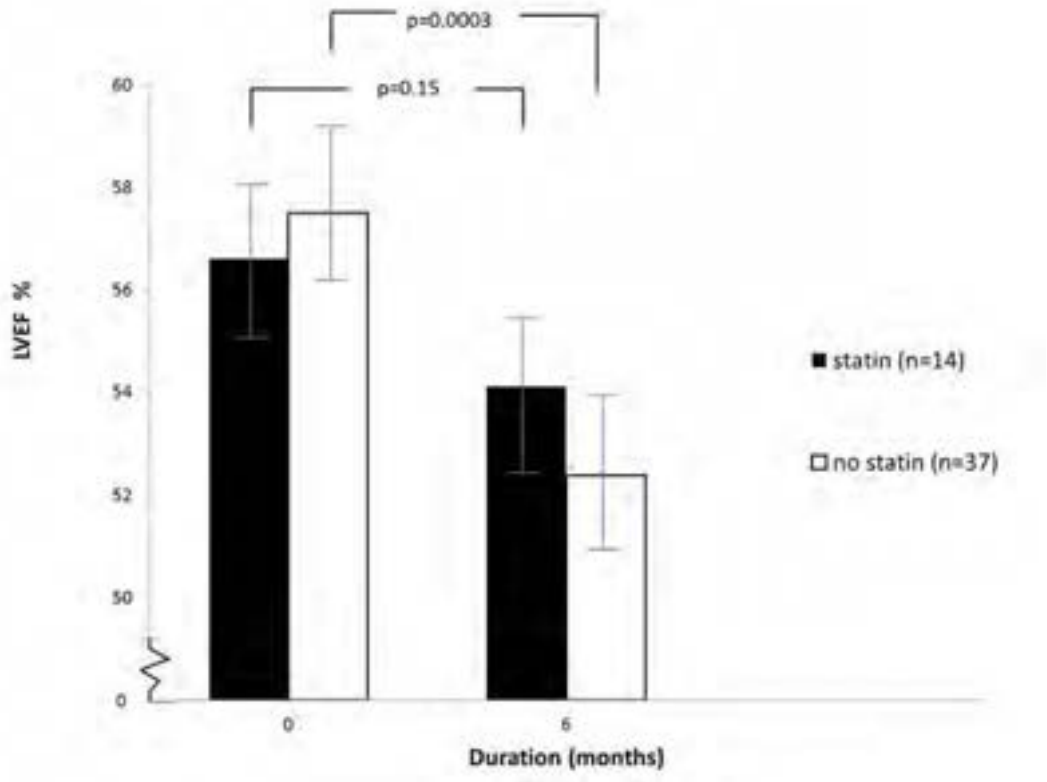
Table 1 Comparison of Echocardiographic Parameters in the Study Group Between Baseline and Follow-Up Values

	Statin Group (n = 20)	Control Group (n = 20)	p Value
LVEF (%)			
Baseline	61.3 ± 7.9	62.9 ± 7.0	
After 6 months	62.6 ± 9.3	55.0 ± 9.5	
Mean change	1.3 ± 3.8	−7.9 ± 8.0	<0.001
LVEDD (mm)			
Baseline	46.5 ± 7.2	47.2 ± 5.2	
After 6 months	46.3 ± 6.8	49.2 ± 6.2	
Mean change	−0.15 ± 4.0	2.0 ± 3.3	0.021
LVESD (mm)			
Baseline	30.9 ± 7.2	30.3 ± 5.4	
After 6 months	29.6 ± 6.1	32.3 ± 5.4	
Mean change	−1.35 ± 4.0	2.1 ± 1.8	<0.001

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter.

Statins as Protective Therapy

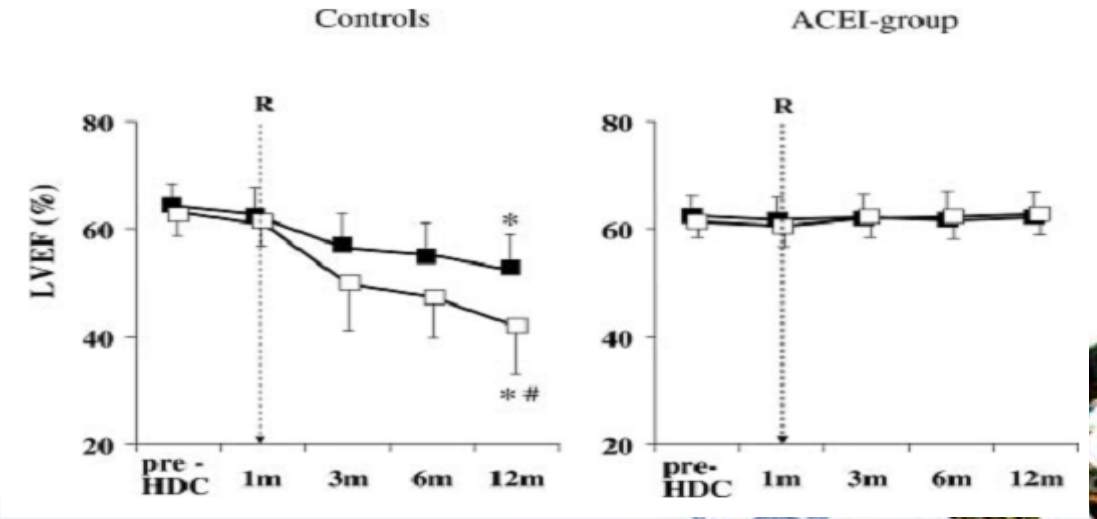
- 51 pts
  - Breast CA, lymphoma, leukemia
- 14 statins, 37 no statins
- LF EF did not decrease in statin group



Chotenimitkhun et al, Can J Cardiol, 2015.

ACE-Inhibitors

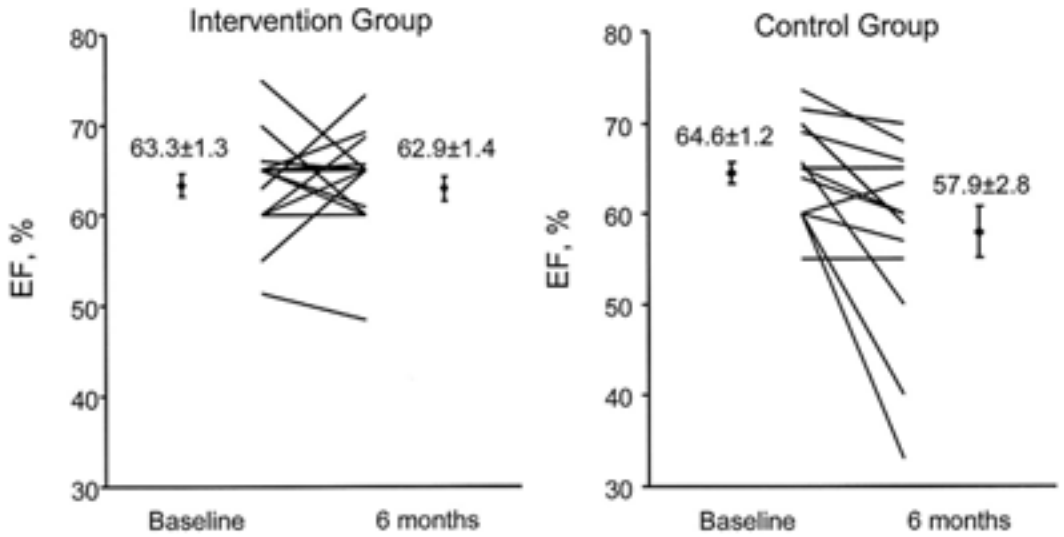
- N=114
- Early cTnI after high dose chemo
- Enalapril vs placebo
- 1 month after chemo to 1 year



Cardinale, *Circulation*. 2006.

ACE-I & Carvedilol

- N=90 (36 leukemia, 54 HSCT)
- Randomized to Control (45) vs Enalapril + Carvedilol (45)
- TTE + CMRI, 6 mos before and after randomization
- Combined treatment prevented left ventricular systolic dysfunction



Bosch et.al, *J am Coll Card,* 2013.

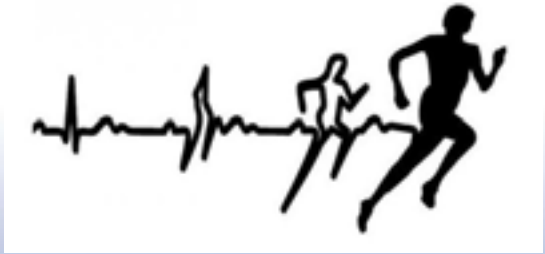
L-Carnitine

- L-Carnitine alterations in cancer survivors
  - ↓ plasma carnitine & ↑ essential & long chain fatty acids (LCFA) associated with decreased systolic function
  - Primary & secondary carnitine deficiency results in cardiomyopathy & arrhythmias due to accumulation of LCFA & acylcarnitines
  - Etiology & timing/onset of depletion is unclear
- Preliminary studies suggest role in primary and secondary prevention of cardiotoxicity
- Larger RCTs are needed

Armenan, Ann Nutr Metab, 2016.

Fitness in Childhood Cancer Survivors

- 30-50% meet CDC guidelines for physical activity (Gilliam, 2013)
- Physical activity similar or lower than sedentary general population (Stolley, 2010 & Hocking 2013)
- More sedentary than siblings (Zhang, 2013)
- ↓ Exercise capacity, ↓ Endurance & ↓ Anaerobic threshold (Miller, 2013)
  - Females had high CRP & proBNP
    - Consistent with inflammation & neurohormonal activation of cardiomyopathy
    - Greater risk for late effects than males



Aerobic Exercise (ET) Attenuates Dox-induced changes in Mouse

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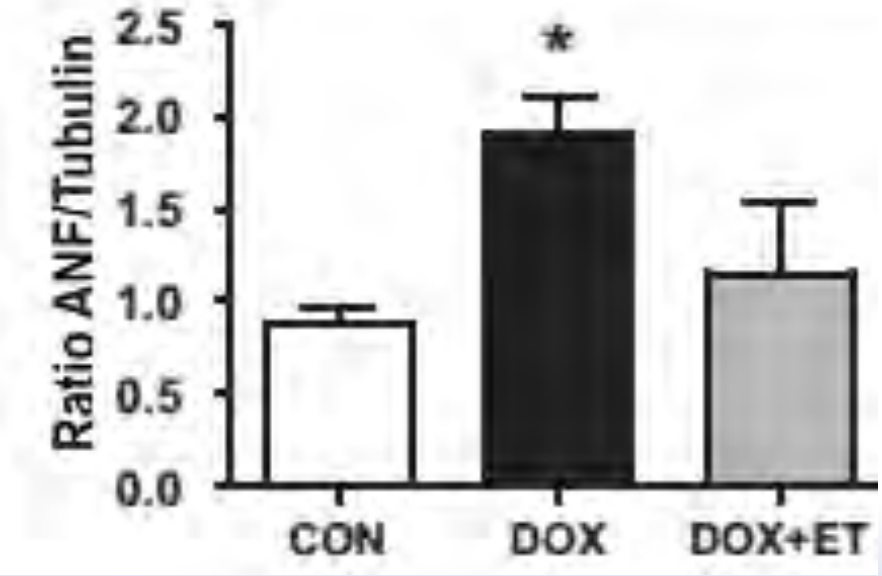
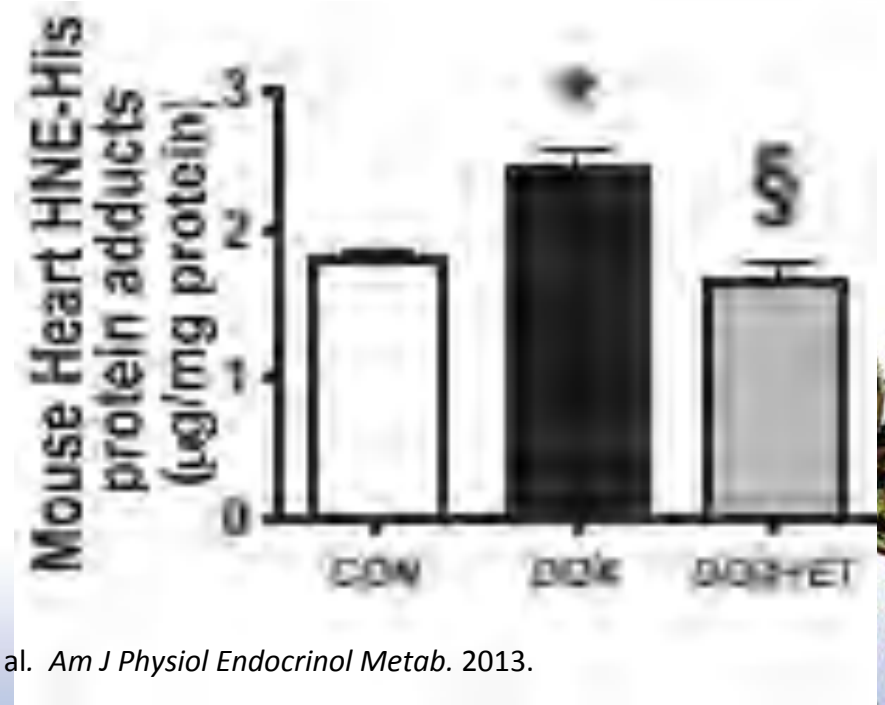
SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE





Dolinsky, VW, et al. *Am J Physiol Endocrinol Metab.* 2013.

Clinical Exercise Interventions in Pediatric Oncology

- Feasible & safe
- No adverse effects described
- Positive effects:
  - ↓ Fatigue
  - ↑Muscle Strength
  - ↑Quality of Life

Baumann FT et al. Pedatric Research,2013.

Exercise Improves Cardiac Function of Childhood ALL Survivors

- 21 long-term survivors of ALL (age 16-30 years) & matched controls
- Home based exercise for 12 weeks
  - 8 muscle strength exercises 3-4x/wk
  - 30 min aerobic exercise at least 3x/week
- ↑ early diastolic mitral inflow velocity
- Improved peak circumferential systolic & diastolic strain rates at mid-level

Jarvela LS, et al. PBC, 2016.

Can Exercise During or After Treatment Protect Against Cardiotoxicity?

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SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

- Innovative & tailored physical activity programs are needed to improve cardiac conditions of cancer survivors
- Exercise programs with close monitoring
- Inclusion of family members

Children's Oncology Group (COG): Long Term Follow-up Guideline of Physical Activity

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SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

- Promptly report to physicians symptoms of tiredness or difficulty in breathing that do not resolve with rest.
- Aerobic exercise is generally **safe** & should be **encouraged**.

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

POEM

PEDIATRIC ONCOLOGY EXERCISE MANUAL

Major Risk Categories

- Age
- Gender
- Radiation
- Alkylating Agents
- Anthracycline
- High dose Cyclophosphamide
- Previous Heart Disease
- Iron Overload
- Hypertension
- Bone Marrow Transplant
- SF<29% or SVEF <55% During Treatment

Age ☐
- ≥5 years: 0
- 1-4 years: 1
- <1 year: 2

Gender ☐
- Male: 0
- Female: 1

Radiation (to heart region) ☐
- None: 0
- <30 Gy: 1
- 30-40 Gy: 2
- >40 Gy: 3

Alkylating agents ☐
- None: 0
- Vinca alkyloids: 1

Anthracycline cumulative dose ☐
- < 101 mg/m^2: 0
- 101 to 150 mg/m^2: 1
- 151 to 200 mg/m^2: 2
- 201 to 250 mg/m^2: 3
- 251 to 300 mg/m^2: 5
- > 300 mg/m^2: 8

High dose Cyclophosphamide ☐
- None: 0
- Cyclophosphamide: 1

Previous heart disease ☐
- None: 0
- Not affecting myocardium: 1
- Affecting myocardium: 2

Iron overload ☐
- No: 0
- Yes: 1

Hypertension (+1 per Hptn med) ☐
- Normal: 0
- Elevated/Pre-Hypertension: 1
- Stage 1: 2
- Stage 2: 3

Bone Marrow Transplant ☐
- None: 0
- Autologous: 1
- Allogenic: 2

SF<29 or SVEF<55 (During Tx) ☐
- No: 0
- Yes: 1

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SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

BMI
- BMI < 85th %ile: 0
- BMI 85th to < 95th %ile: 1
- BMI ≥95th %ile: 2
- BMI ≥ 120% of 95th %ile OR Absolute BMI ≥ 35, whichever is lower based on age and sex: 3

LIPIDS
- Normal (LDL-c <110, Non HDL-c <120, AND triglycerides <150): 0
- Low-Moderate Risk (LDL-c 110-129, OR Non HDL-c 120-144, OR triglycerides 150-199): 0.5
- High Risk (LDL-c ≥130, OR Non HDL-c ≥145, OR triglycerides ≥200): 1

Pre-diabetes/Diabetes
- Normal glucose/A1c (Fasting: <100, 2-hr OGTT: <140, or HA1c: <5.7%): 0
- Prediabetes (Fasting: 100-125, 2hr OGTT: 140-199, or HA1c: 5.7-6.4%): 0.5
- Diabetes (Fasting: ≥126, 2-hr OGTT: ≥200, or HA1c: ≥6.5%): 1

Sedentary lifestyle
- No sedentary lifestyle: 0
- Sedentary lifestyle: 1

Minor Risk Categories

- **BMI**
- **Lipids**
- **Prediabetes/Diabetes**
- **Sedentary Lifestyle**

CLINICAL CARE PATHWAY

Cardiac Care Guidelines for Chemotherapy Patients

This is a recommended algorithm that applies to patients receiving cardiotoxic chemotherapy medication

*Time of diagnosis: baseline echo:

To which risk category does the patient belong?

LOW RISK

- Obtain echocardiogram
- Encourage compliance with exercise regimens
- Complete fasting lipid profile following induction therapy
- Cardiac MRI, if indicated based on echo

MODERATE RISK

- High risk group: obtain echo every 150 mg/m^2 cumulative dose until 200 mg/m^2, then obtain every 50 mg/m^2
- Cardiac MRI, observation if needed
- Assess VO2 max, VO2 @ anaerobic threshold, VO2 pulse, VE/VCO2 at AT, exercise time (min), total work (METS)
- Determine if referral to PT is warranted based on results

HIGH RISK

- Obtain echocardiogram
- Dexrazoxane unless contraindicated
- Baseline stress testing:
  - *Performed following induction therapy for ambulatory patients*
  - *For ALL patients, it will be performed following induction and at start of maintenance*
  - *For solid tumor and AML patients, it will be performed off therapy*
- Fitnessgram (PACER)
- Encourage compliance with exercise regimens
- Complete fasting lipid profile following induction therapy

Minor risk categories:

BMI ☐
- BMI < 85th %ile: 0
- BMI 85th to < 95th %ile: 1
- BMI ≥95th %ile: 2
- BMI ≥ 120% of 95th %ile OR Absolute BMI ≥ 35, whichever is lower based on age and sex: 3

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- Diabetes (Fasting: ≥126, 2-hr OGTT: ≥200, or HA1c: ≥6.5%): 1

Sedentary lifestyle ☐
- No sedentary lifestyle: 0
- Sedentary lifestyle: 1

* Based on doxorubicin or equivalent doses

Major risk categories:

Age ☐
- ≥5 years: 0
- 1-4 years: 1
- <1 year: 2

Gender ☐
- Male: 0
- Female: 1

Radiation (to heart region) ☐
- None: 0
- <30 Gy: 1
- 30-40 Gy: 2
- >40 Gy: 3

Alkylating agents ☐
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Anthracycline cumulative dose ☐
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- 151 to 200 mg/m^2: 2
- 201 to 250 mg/m^2: 3
- 251 to 300 mg/m^2: 5
- > 300 mg/m^2: 8

High dose Cyclophosphamide ☐
- None: 0
- Cyclophosphamide: 1

Previous heart disease ☐
- None: 0
- Not affecting myocardium: 1
- Affecting myocardium: 2

True overload ☐
- No: 0
- Yes: 1

Hypertension (+1 per Hptn med) ☐
- Normal: 0
- Elevated/Pre-Hypertension: 1
- Stage 1: 2
- Stage 2: 3

Bone Marrow Transplant ☐
- None: 0
- Autologous: 1
- Allogenic: 2

SF<29 or SVEF<55 (During Tx) ☐
- No: 0
- Yes: 1

TOTAL SCORE ☐

Conclusions

- Dexrazoxane:
  - Effective as cardioprotectant in adults & children
  - Not associated with ↑ SMNs
  - Not associated with excess mortality
  - Does not impair antitumor efficacy of anthracyclines
  - Need more prospective long-term studies

Conclusions

- Further research needed for L-Carnitine, statins & neurohormonal antagonists
- Exercise established to be safe & feasible during treatment & survivors
  - In hospital & home
- RCTs needed to determine effect size, optimal exercise format & durability