How to Mitigate Cardiotoxicity: Statins and Proton Therapy for All Childhood and Adult Cancer Patients and Survivors?

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Disclosures

- Ehrhardt
  - Nothing to disclose
- Hundley
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  - Stockholder: Prova, Inc.

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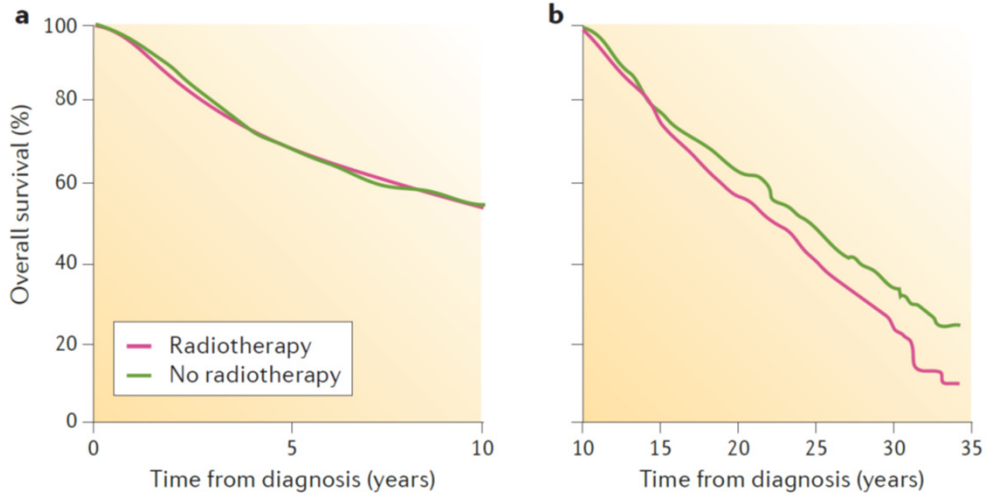
Outline

- Epidemiology of CV disease related to XRT
- Mechanisms of CV disease after XRT
- Risk factors associated with XRT and CVD
- Review of techniques/research to mitigate XRT associated CVD
- Suggested management and unanswered questions related to XRT associated CVD

Early suggestion of XRT associated CV disease

- 7941 individuals randomized to receive post-mastectomy XRT before 1975.
- Excess CV events after: cobalt source, left breast area XRT.



Cuzick, et al. J Clin Oncol. 1987.

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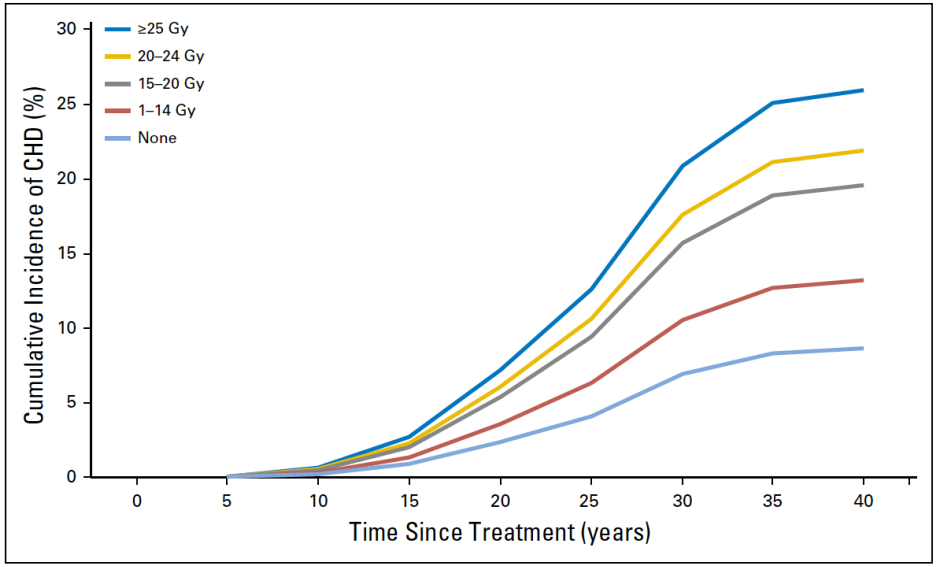
Latent, dose dependent occurrence of XRT related CVD

- Nested case-control study of 325 Hodgkin lymphoma survivors (Aged 26 to 50 years, Rxed from 1965-1995) compared to 1204 matched controls.
- CHD (myocardial infarction or angina requiring intervention)



van Nimwegen, et al. J Clin Oncol. 2016.

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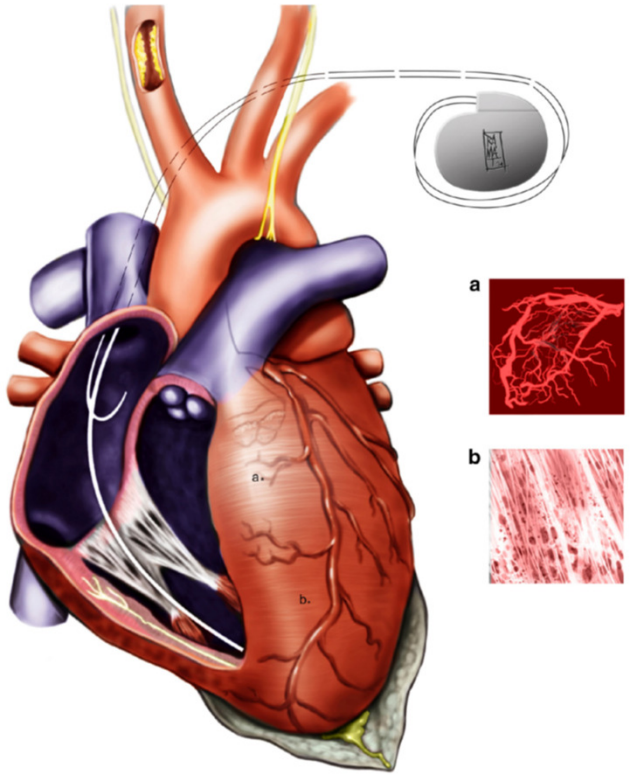
CVD associated with radiation treatment

- Pericarditis
- Pericardial fibrosis
- Diffuse myocardial fibrosis
- Coronary artery disease
- Myocardial ischemia
- Valvular heart disease
- Conduction disease
- Heart innervation injury
- Implantable device issues



Santoro, et al. Clin Research Cardiol. 2014.

Differences in coronary artery disease patterns after XRT

Table 3 Difference between typical coronary artery disease and radiation-induced coronary injury

Lesion characteristics	Radiogenic coronaritis	Typical CAD
Prevalent anatomical site	Main ostia	Branching sites
Wall orientation	Concentric since the beginning	Initially eccentric
Onset time	Younger age (<50 years)	Elder age (>50 years)
Fibrous component	Prevalent	Variable
Lipid component	Less represented	Typically present
Length extension	Longer	Focal
Treatment of choice	PTCA or CABG	PTCA > CABG

Santoro, et al. Clin Research Cardiol. 2014.

Potential mechanisms of myocardial ischemia after XRT

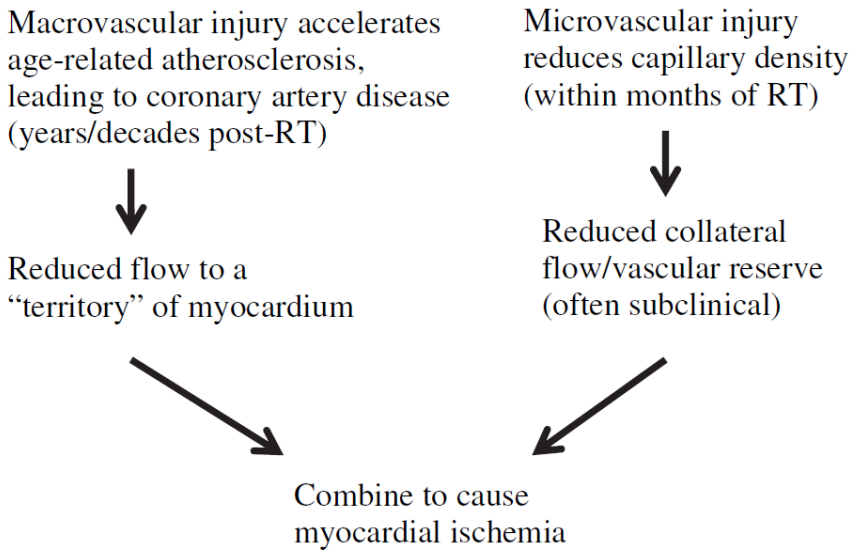


Fig. 4. An outline of how microvascular and macrovascular radiation-related cardiac injury could theoretically combine to cause myocardial ischemia after RT.

Darby, et al. Int. J. Rad Onc & Biophys. 2010.

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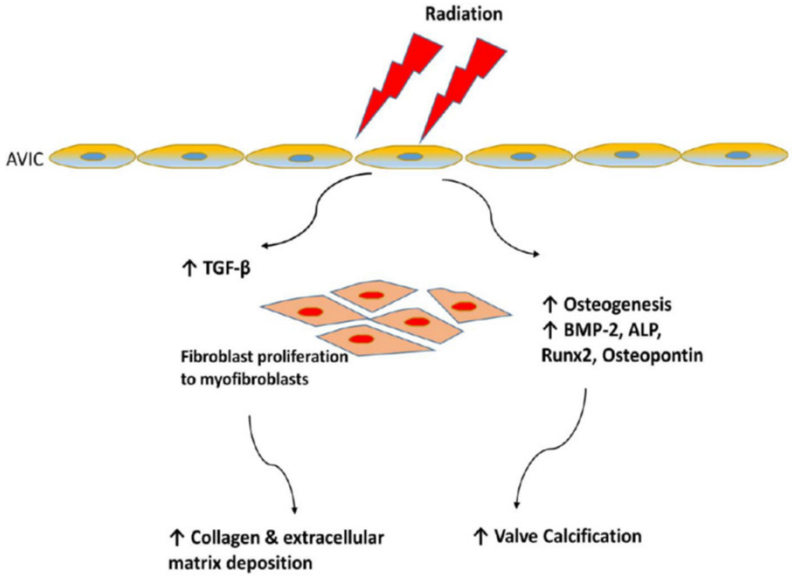
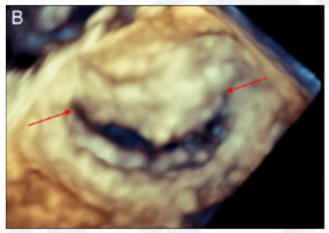
Valvular heart disease after XRT

- 40% to 43% experience valve thickening
- 3% to 17% experience valve dysfunction

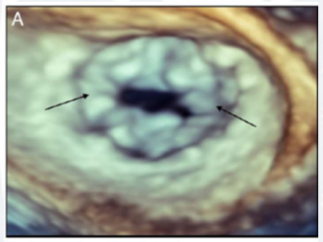


Gujral, et al. Heart. 2016.

Radiation (no fusion of commisures)



Rheumatic (fusion of commisures)



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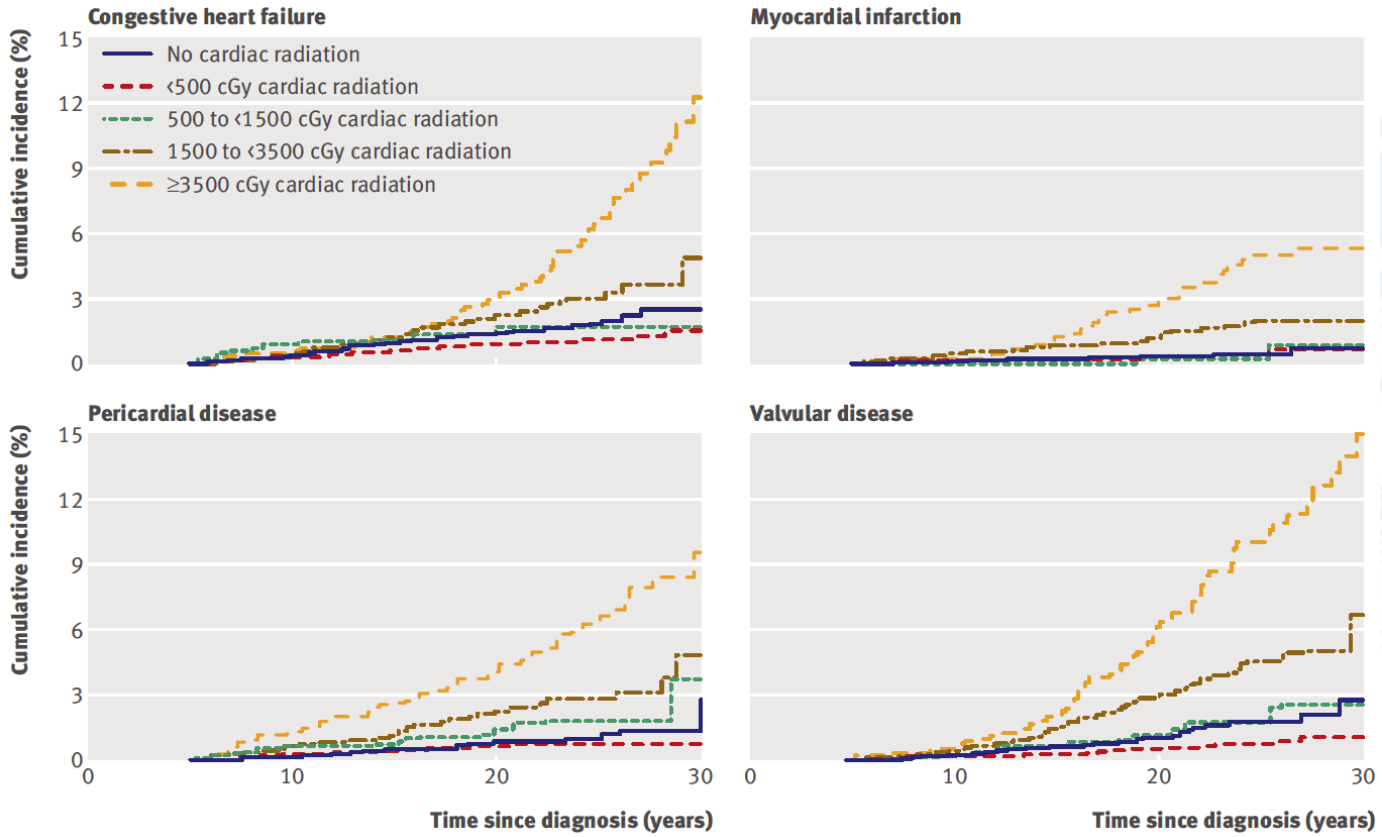
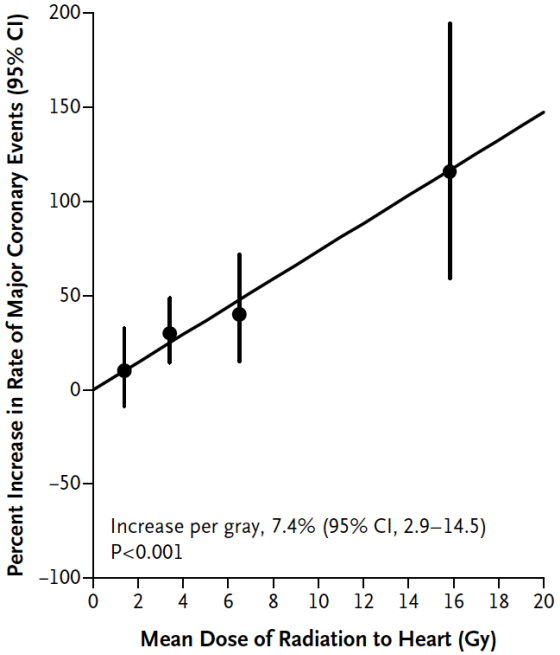
RT and heart disease in childhood cancer survivors



Mulrooney, et al. Brit Med J. 2009.

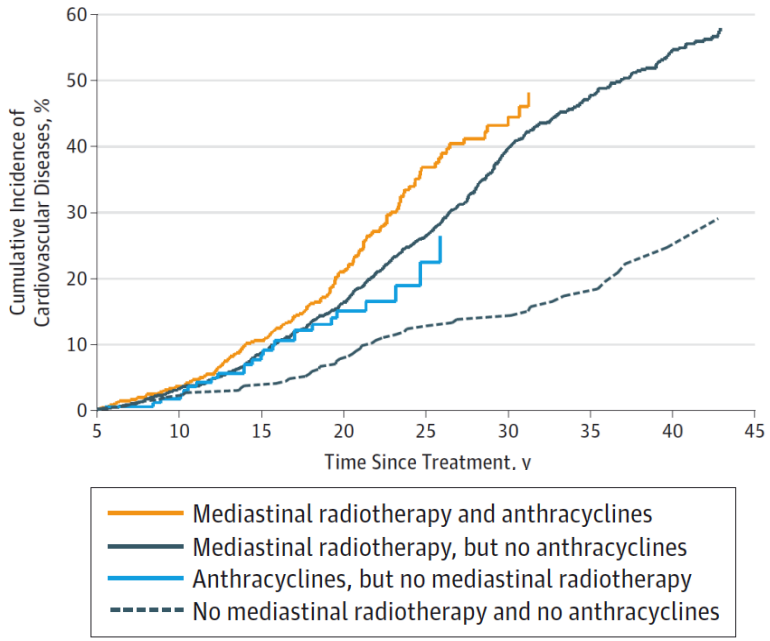
RT and heart disease in adult cancer survivors

Major Coronary Event



Darby, et al. N Engl J Med. 2013.

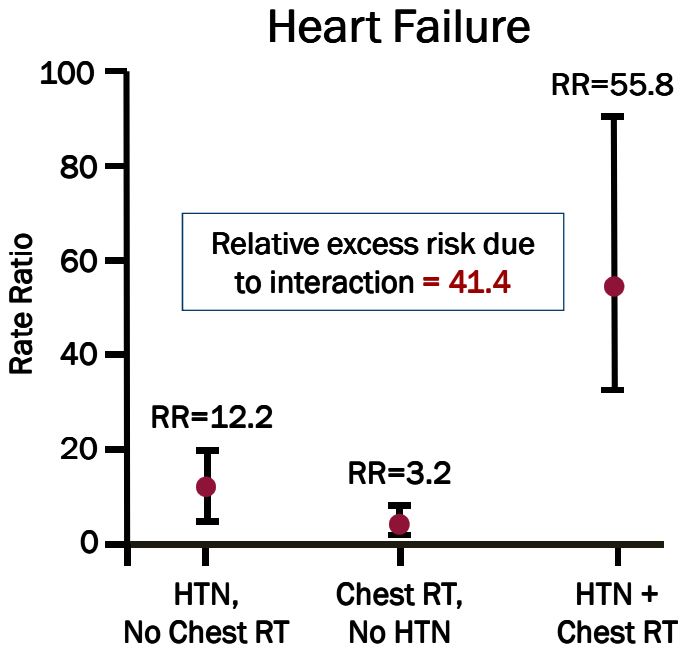
Any Cardiovascular Event



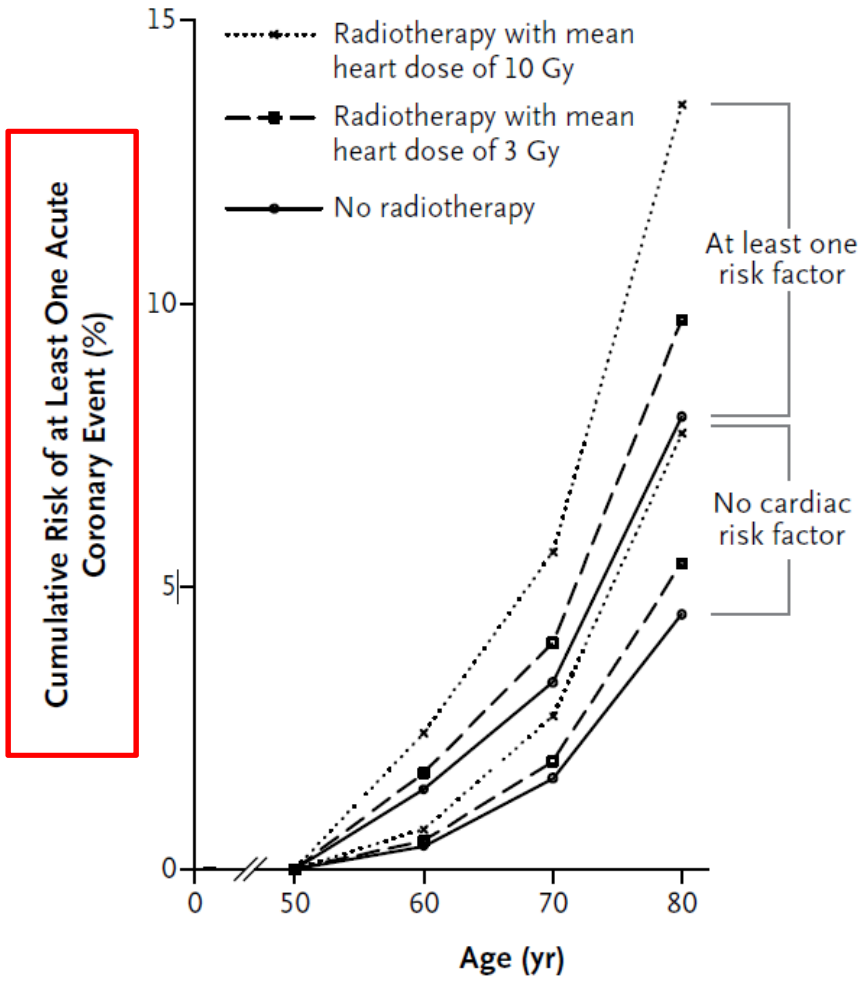
van Nimwegen, et al. JAMA Intern Med. 2015.

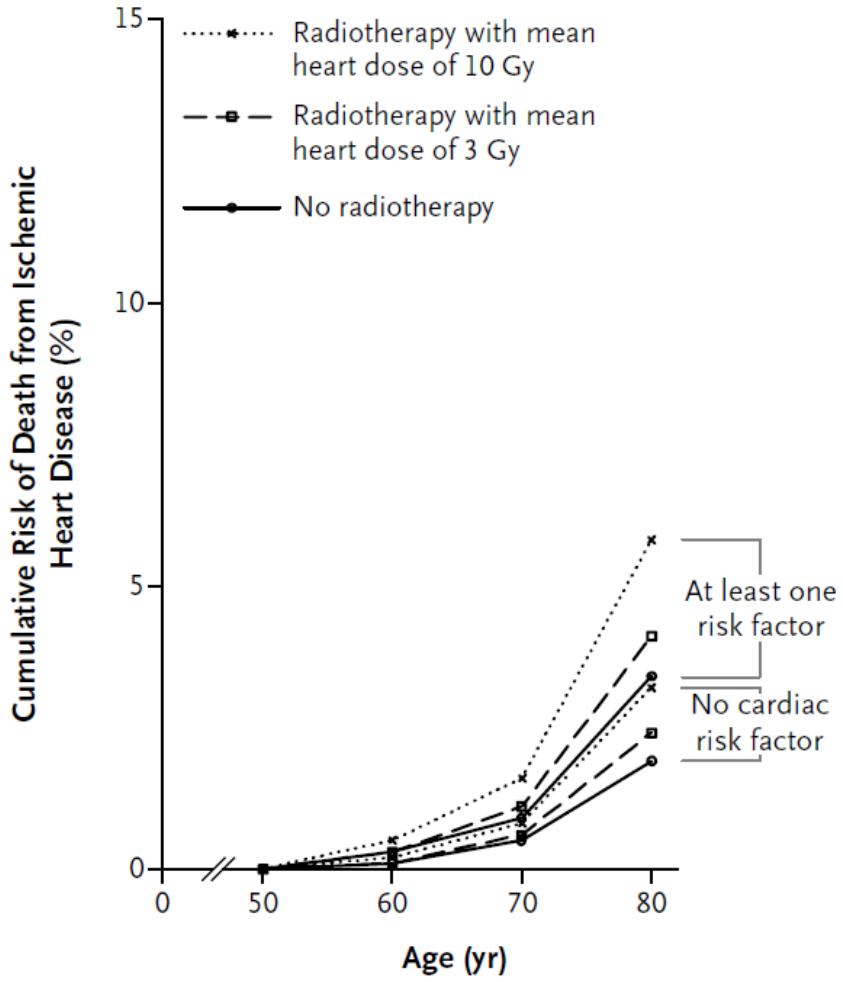
CVRFs potentiate RT-associated HF

- Evaluate relative contribution of CV risk factors towards heart failure
  - Longitudinal evaluation
  - 10,724 survivors, CCSS
  - Is risk simply additive?
  - Hypertension potentiates radiation-associated risk for heart failure
  - Multiple traditional CV risk factors increase risk

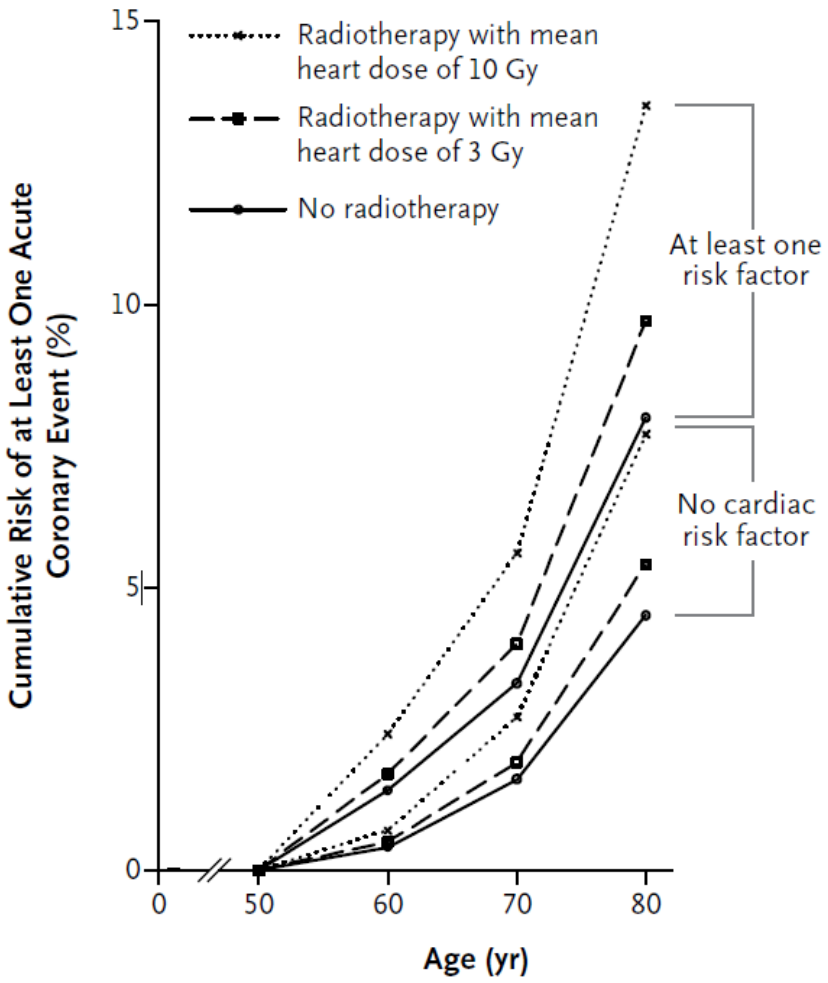


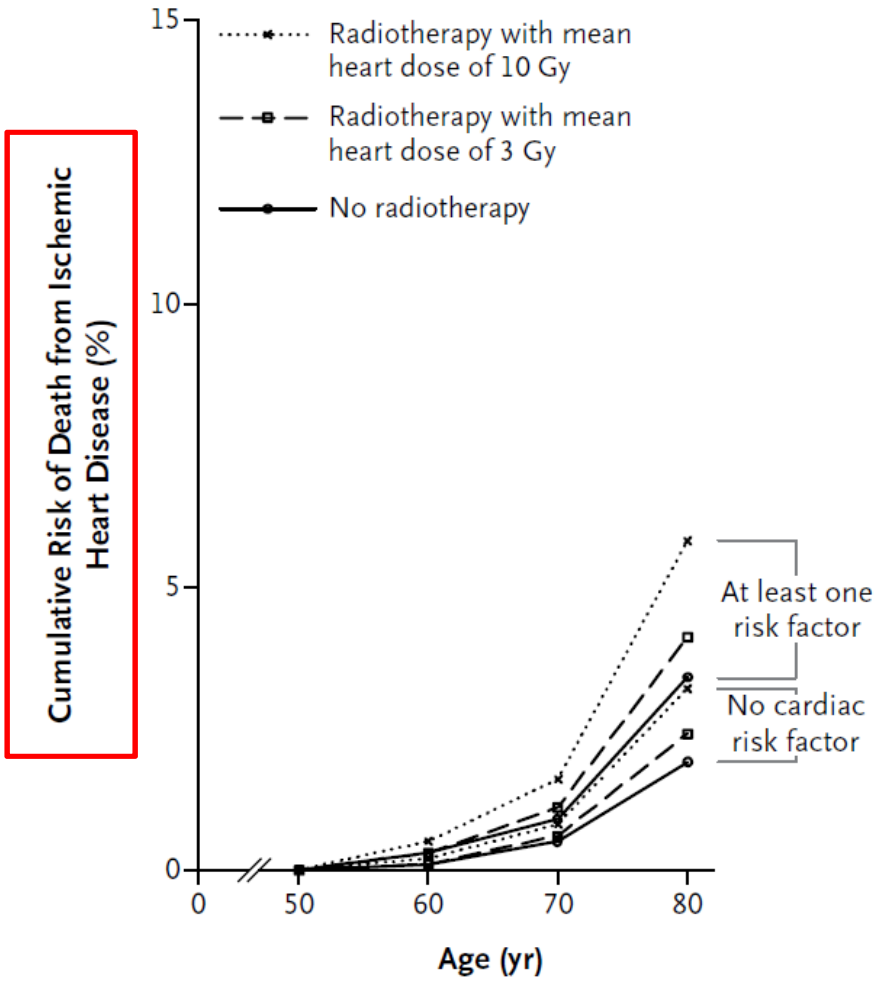
Armstrong, et al. J Clin Oncol. 2013.





Darby, et al. N Engl J Med. 2013.





Darby, et al. N Engl J Med. 2013.

Risk factors for CV disease after receipt of XRT

Table 1 Radiation-induced heart disease depends on other factors related to whole cancer therapy, patients' characteristics and clinical history

Additional risk factors for radiotherapy cardiovascular disease
Total dose >30 Gy or fractioned dose >2 Gy/day [4, 7]
Heart volume exposed [4, 7, 17]
Time since exposure [19–21, 41]
Adjunctive chemo/hormone therapy [101, 111–115]
Presence of general risk factors [38, 54, 75, 76] (dyslipidemia, obesity, diabetes, hypertension, smoking)
Younger age [7, 19–21, 41]
Absence of irradiation shields and protective techniques [7]

Santoro, et al. Clin Research Cardiol. 2014.

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Protection of the heart during XRT

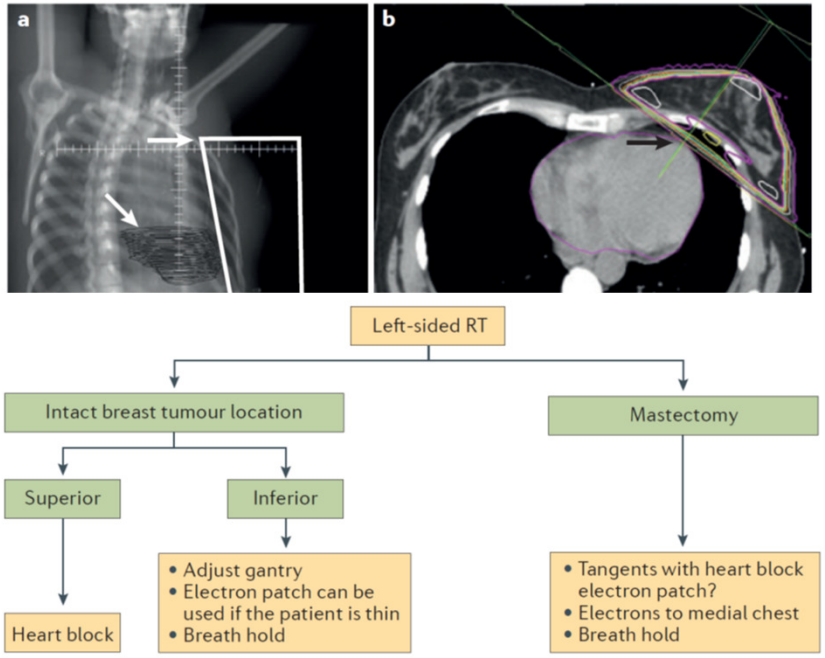
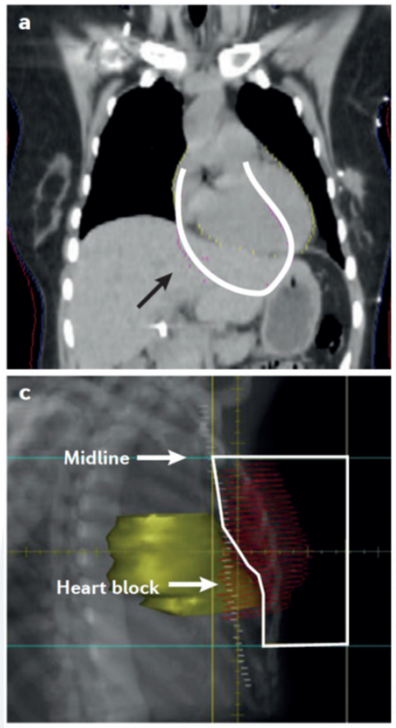


Figure 7 | **Algorithm used to select methods to minimize cardiac exposure during radiation therapy in patients with left-sided breast tumours.** Strategies such as a deep inspiratory breath hold or heart block can be routinely employed to minimise the risk of exposing the patient's heart to radiation.

Zagar, et al. Nat Rev Clin Oncol. 2015.



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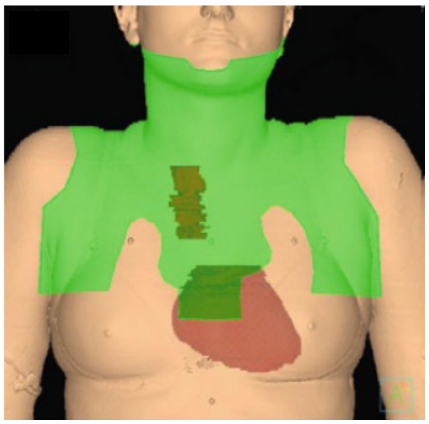
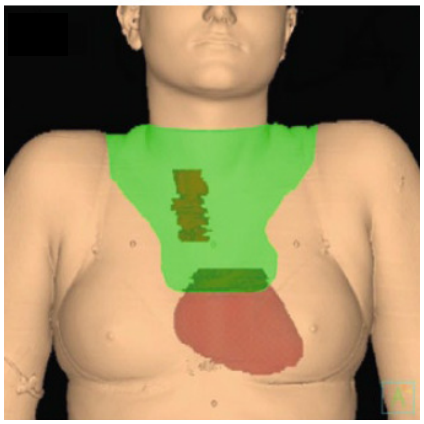
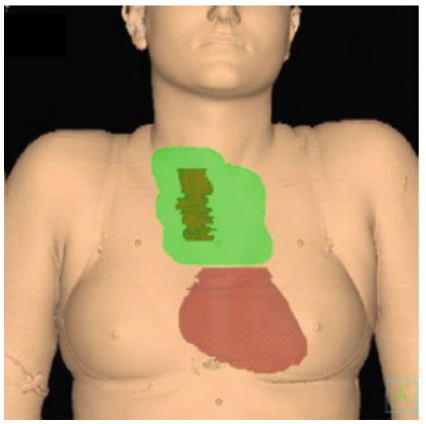
Mantle RT

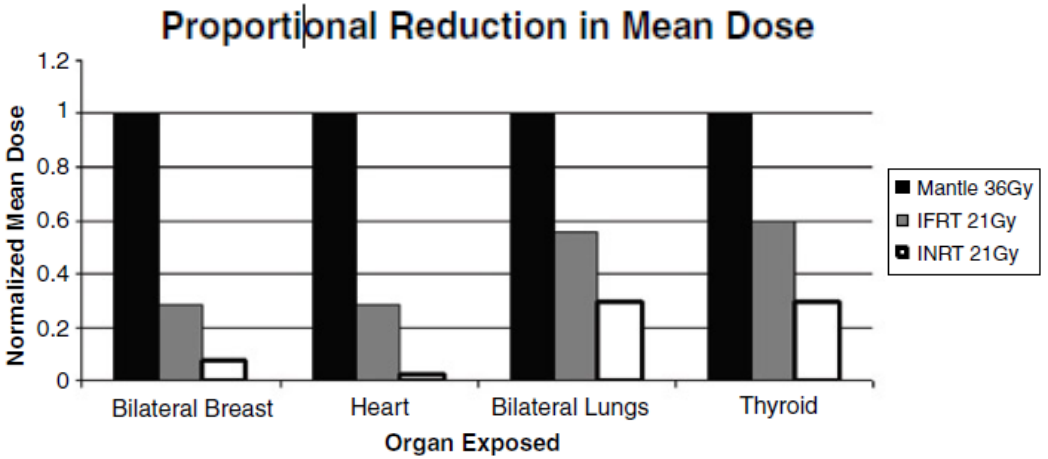


Involved Field RT



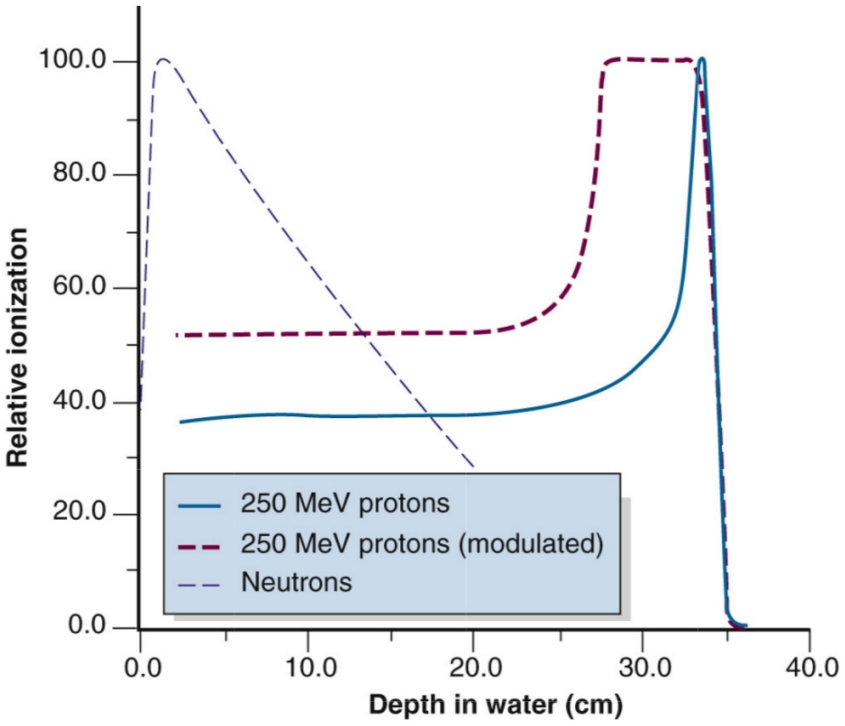
Involved Node RT





Specht and Yahalom. Radiotherapy for Hodgkin Lymphoma. 2011.

Advantages of proton therapy



Gunderson and Tepper, Clinical Radiation Oncology. 2016.

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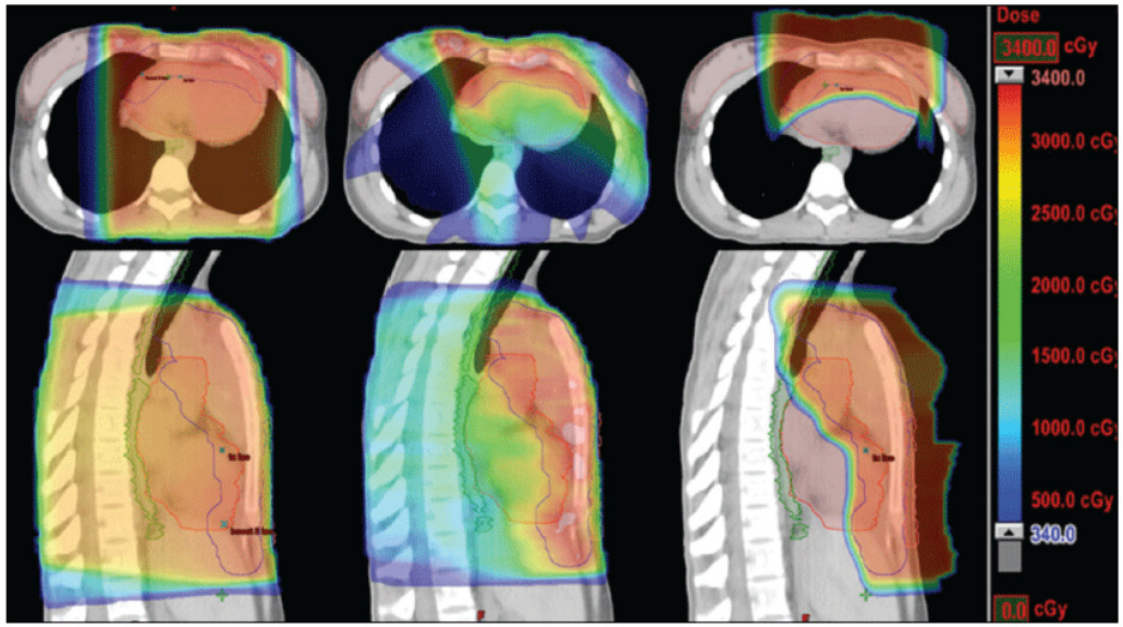
Conformal RT approach and advantages of proton therapy

AP Field IMRT AP Proton



Hoppe, et al. Oncol. 2012.

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RadComp

PATIENT POWERED

- A randomized pragmatic trial funded by PCORI
- Aim: To assess the effectiveness of proton vs. photon therapy in reducing major cardiovascular events (MCE)
- Primary hypothesis: For patients with locally advanced breast cancer, proton therapy will reduce the 10-year MCE rate after radiation from 6.3% to 3.8%
- Sample size: 1,716 patients
- Accruing sites: >30 proton centers and >50 participating radiation treatment centers across US
- Large, simple trial approaches: Passive and active follow-up techniques

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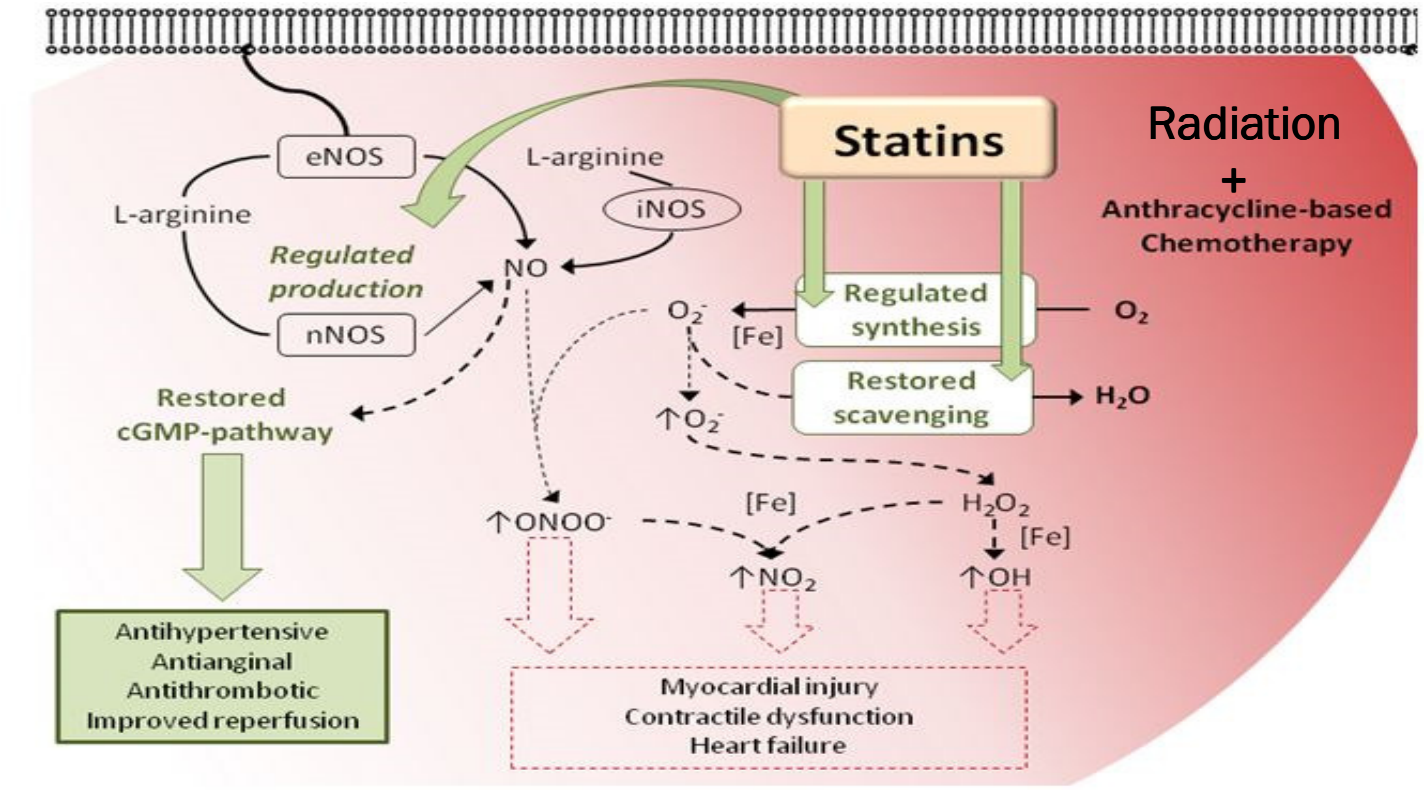


Statins work to prevent myocardial injury through Anth-bC by regulating the production of nitric oxide (NO), regulating synthesis and restoring scavenging of superoxide free radicals (O_2^-). Question if statins can also mitigate the effect of radiation therapy.

Observational Study

- 628 women with breast cancer (BrC); Mean age 51.5 ± 10.8 years
- Followed for 2.55 ± 1.68 years
- Propensity matching 2:1
- 67 patients received statins and 134 controls received no statins
- Statin use was associated with lower risk for heart failure (HF)

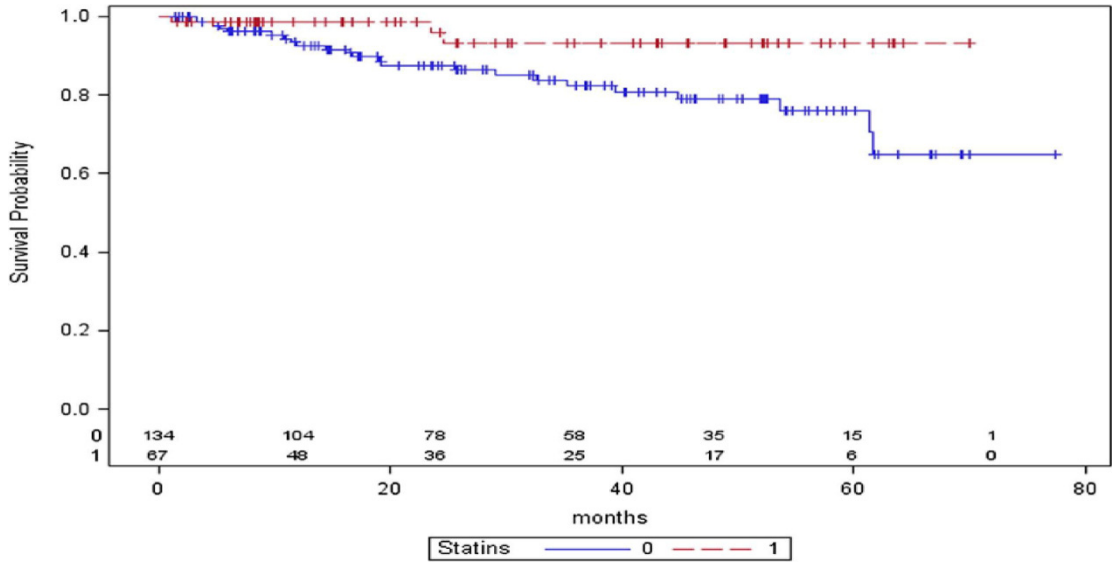
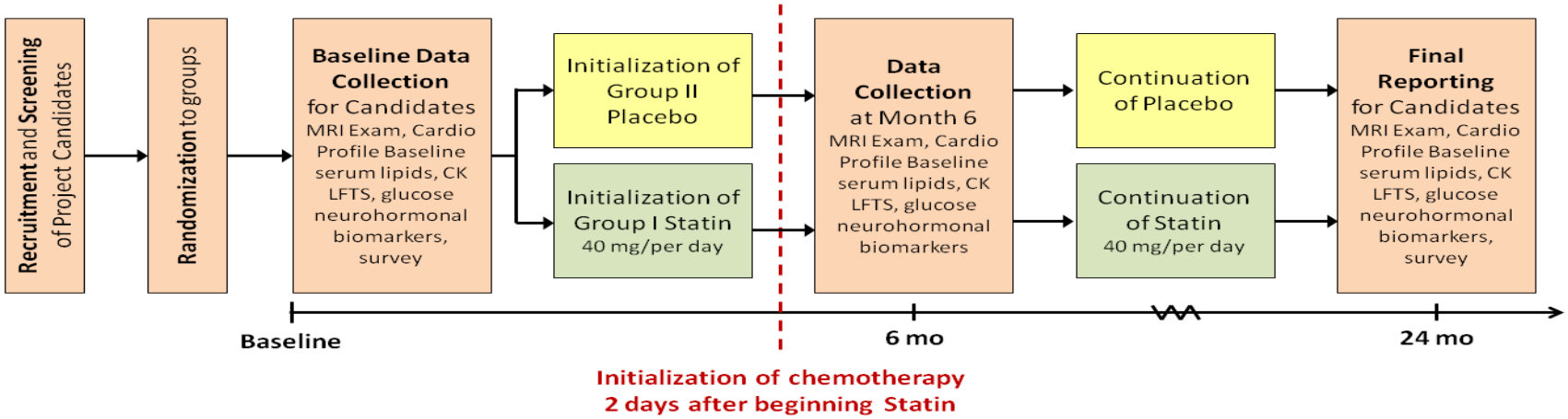


Chart illustrates survival in statin users (red) and non-statin users (blue). Figures above abscissa relate to number surviving without heart failure at each 12 month interval.

Seicean S, et al. Effect of statin therapy on the risk for incident heart failure in patients with chemotherapy breast cancer receiving anthracycline chemotherapy. *JACC* 2012; 60:2384-90.

PREVENT: NCI and NHLBI multi-center randomized, double-blind placebo controlled clinical trial testing the efficacy of generic atorvastatin among 250 women with stage I-III Breast Cancer scheduled to receive Anthracycline-based chemotherapy



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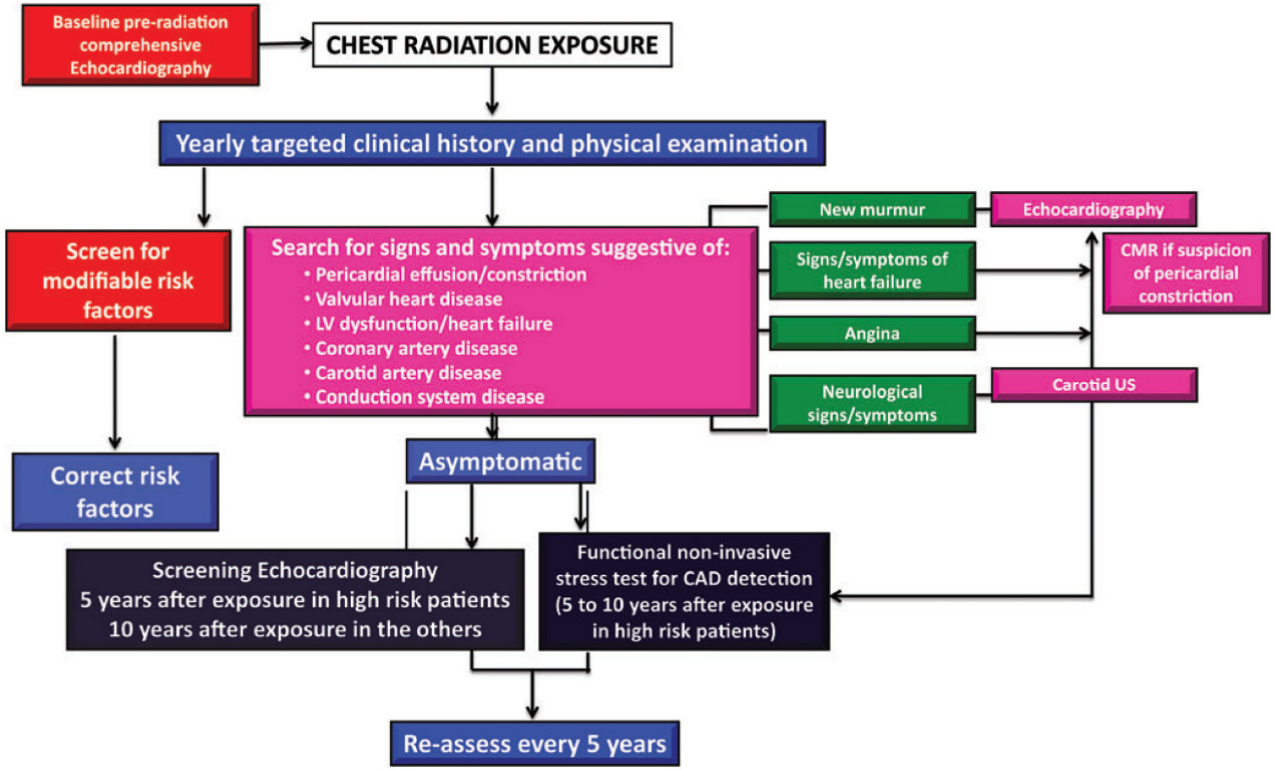
Potential suggestion for management of individuals previously receiving XRT



Lancellotti, et al. Eur Ht J-Cardiovasc Imaging. 2013.

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Unanswered questions related to cardio-protective strategies during XRT

- Do recently implemented cardioprotection strategies forestall the development of long-term cardiac sequelae?
- Are there adverse consequences from XRT exposure to other "non-heart" cardiovascular structures (e.g., the aorta)?
- Are there adverse, general systemic effects from the receipt of XRT that promote CVD (e.g., systemic inflammation)?

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Potential myocardial ischemia after left breast XRT

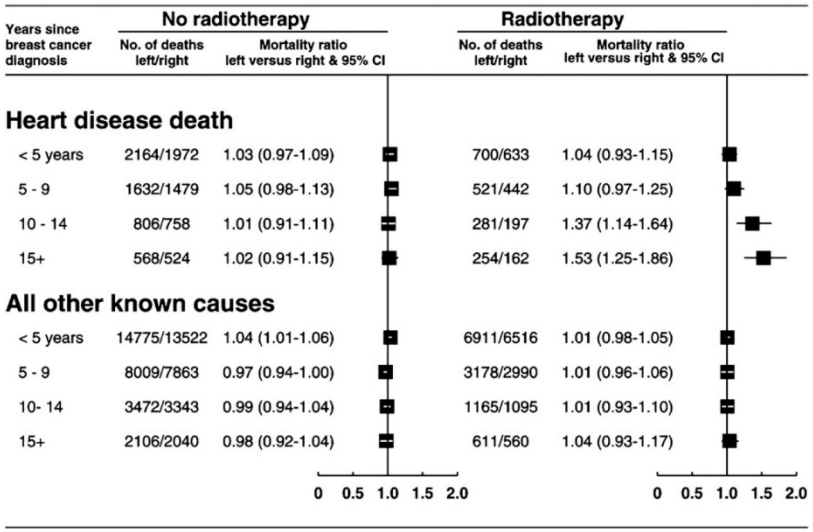

Fig. 5. Left-sided vs. right-sided breast cancer. Mortality ratios by radiotherapy status, cause, and years since diagnosis in 300,000 women with breast cancer and registered in the Surveillance Epidemiology and End Results (SEER) cancer registries, 1973 to 2001 (*From* Darby SC, McGale P, Taylor CW, *et al*. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 2005;6:557-565; *with permission*.)

Darby, et al. Int J Rad Onc & Biophys. 2010.

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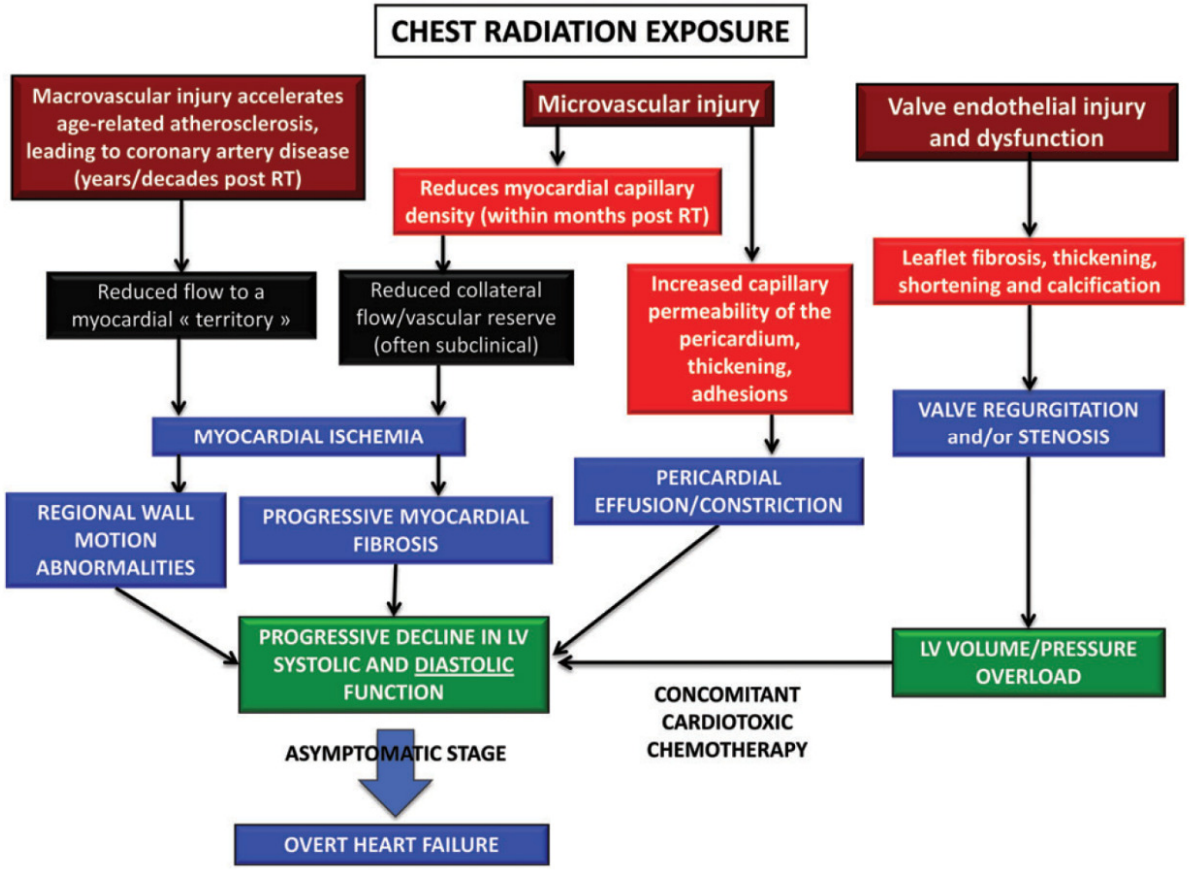
Cardiovascular disease associated with radiation treatment



Lancellotti, et al. Eur Ht J-Cardiovasc Imaging. 2013.

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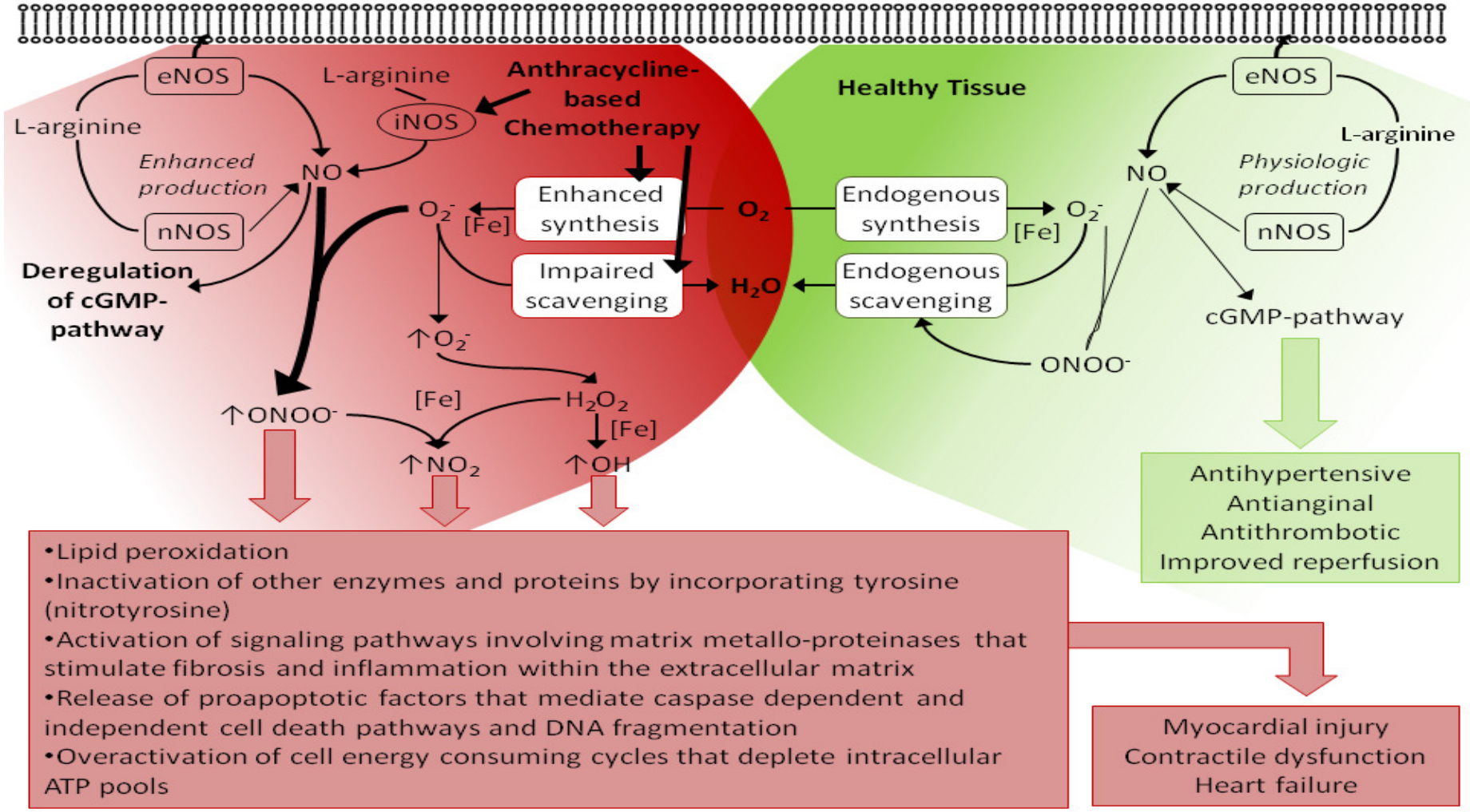

eNOS
L-arginine
iNOS
Anthracycline-based Chemotherapy
L-arginine
Enhanced production
NO
nNOS
Deregulation of cGMP-pathway
O_2^-
[Fe]
Enhanced synthesis
O_2
Impaired scavenging
H_2O
$\uparrow O_2^-$
$\uparrow ONOO^-$
[Fe]
H_2O_2
[Fe]
$\uparrow NO_2$
$\uparrow OH$
Healthy Tissue
eNOS
L-arginine
Physiologic production
NO
nNOS
cGMP-pathway
Endogenous synthesis
O_2^-
[Fe]
Endogenous scavenging
$ONOO^-$
Antihypertensive
Antianginal
Antithrombotic
Improved reperfusion
•Lipid peroxidation
•Inactivation of other enzymes and proteins by incorporating tyrosine (nitrotyrosine)
•Activation of signaling pathways involving matrix metallo-proteinases that stimulate fibrosis and inflammation within the extracellular matrix
•Release of proapoptotic factors that mediate caspase dependent and independent cell death pathways and DNA fragmentation
•Overactivation of cell energy consuming cycles that deplete intracellular ATP pools
Myocardial injury
Contractile dysfunction
Heart failure

Statins in breast cancer

- Desai, et al., Women's Health Initiative
- Study population of 154,587 women aged 50-79 years[1]
- 7,430 cases of BrC
- Rate of BrC was 0.42% in statin users and 0.42% in non-statin users

- Ahern, et al., Danish Breast Cohort (n=66,000+)
- Denmark on women with Stage I-III BrC[2]
- 18,769 participants receiving statins for primary or secondary prevention CAD
- Simvastatin, a highly lipophilic statin, was associated with a reduced risk of BrC recurrence among participants, whereas no association between hydrophilic statin use and BrC recurrence was observed

1. Desai P, et al. Cancer Epidemiol Biomarkers Prev. 2013.
2. Ahern TP, et al. J Natl Cancer Inst. 2011.

Nitrotyrosine and statins

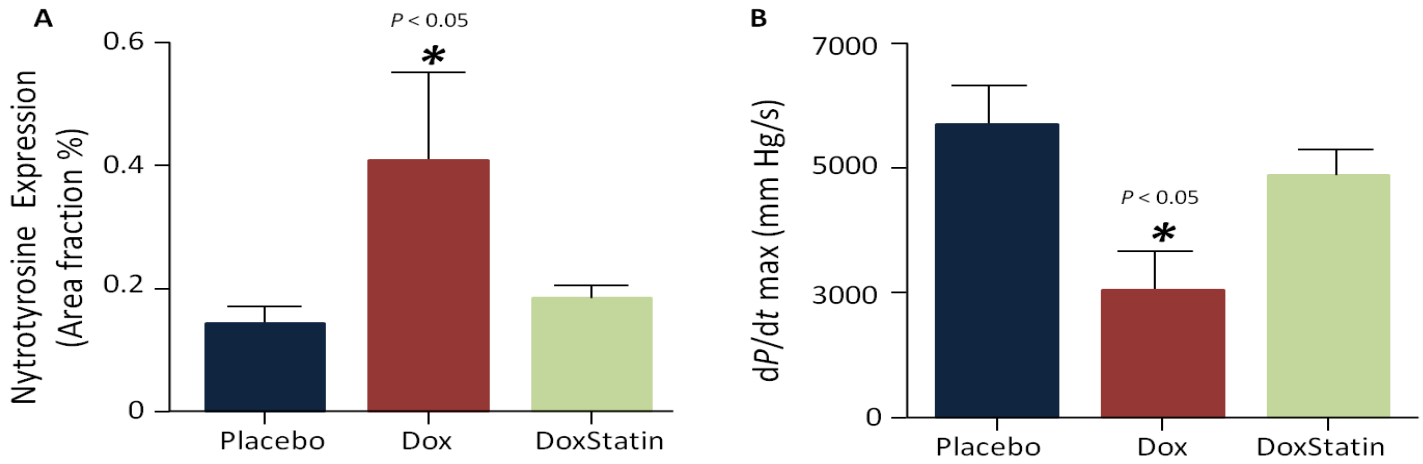
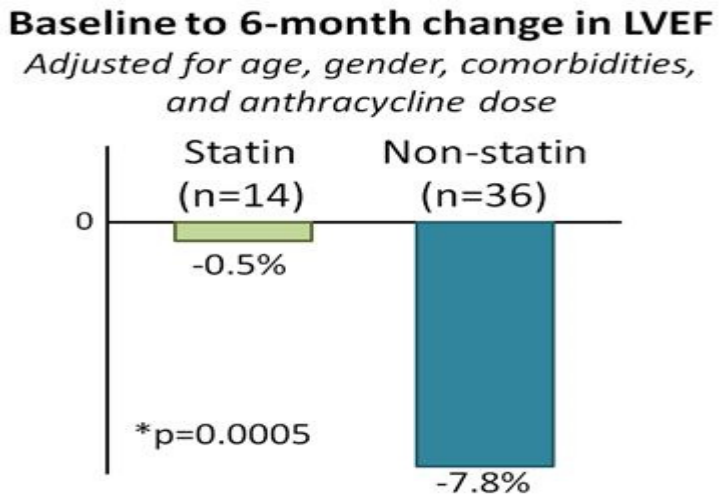


Figure 3: (A) Cardiac nytrotyrosine expression and (B) systolic LV function in 3 groups treated with placebo, Doxorubicin, and a combination of Fluvastatin and Doxorubicin. *Columns*, mean; *bars*, SE. Dox, doxorubicin (Riad. Cancer Res. 2009.)

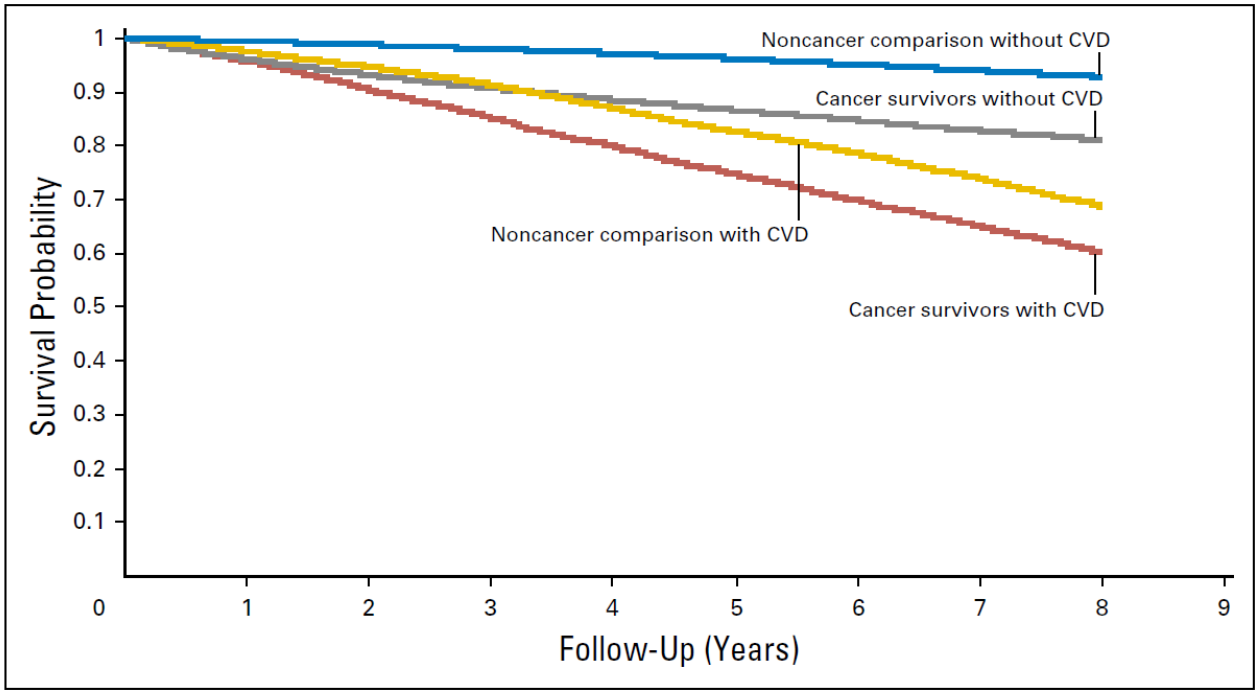
Table: Comparison of Echocardiographic Parameters: Baseline vs. Follow-Up Values in Pilot Study			
LVEF (%)	Statin Group (n=20)	Control Group (n=20)	p Value
Baseline	61±8	63±7	
After 6 months	63±9	55±10	
Mean change	+1±4	-8±8	<0.001

In a recent study of 40 patients scheduled to receive Anth-bC, those randomized to receive atorvastatin (40 mg per day before and during Anth-bC) had no decrease in LVEF at 6 months, but those randomized to receive Anth-bC without statins had an 8% reduction in LVEF.



In a multivariable model adjusted for age, gender, co-morbidities, and the anthracycline dose, those who received statin had an LVEF decline of -0.5% compared to the non-statin group at -7.8%.

CVD and cancer survivor mortality



Armenian, et al. J Clin Oncol. 2016.