BIOMARKER EVALUATION OF THERAPUETIC CARDIOTOXICITY?

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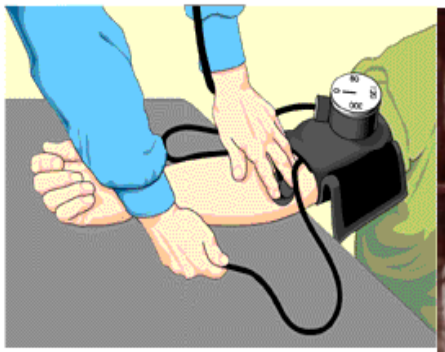
Cardiovascular Side Effects of Cancer Therapy

Arrhythmia
QT-Prolong

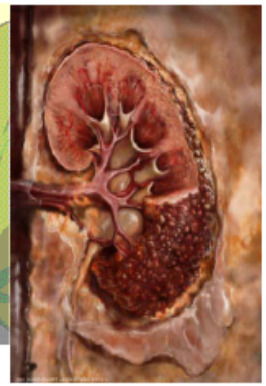
Cardiac Dysfunction

Thromboembolism

AP / MI



Hypertension



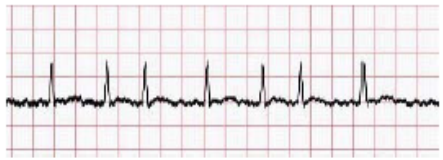
Renal Toxicity

Courtesy T Suter

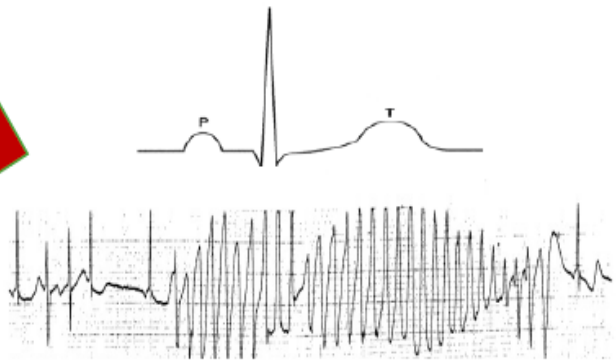
Cardiovascular Side Effects of Cancer Therapy - Arrhythmia

	Drug	Toxic Dose	Comments
Cytotoxic Chemotherapeutics	**Anthracyclines** • Doxorubicin • Epirubicin	> 450 mg/m² (total dose) > 720 mg/m²	Cardiomyopath
	Taxols • Paclitaxel	Conventional dose	Bradycardia, Heart Failure ? (with trastuzumab)
	Cyclophosphamide	>100–120 mg/kg	Heart Failure;,Myocarditis/Pericarditis
	Antimetabolites • 5-FU / Capecitabine	Conventional dose	Myocardial Ischemia / MI
	Cisplatin	Conventional dose	Myocardial Ischemia / MI
signaling inhibitors	**Anti-HER2** • Trastuzumab (Herceptin®) • Lapatinib (Tykerb®)	Conventional dose	Contractile Dysfunction, Heart Failure QTc-Prolongation
	Anti-VEGF/Angiogenics • Bevacizumab (Avastin®) • Sunitinib (Sutent®) • Sorafenib (Nexavar®)	Conventional dose	Hypertension Contractile Dysfunction, Heart Failure QTc-Prolongation
	BCR-ABL targeted • Imatinib • Dasatinib • Nilotinib	Conventional dose	Heart Failure, QTc-Prolong

(Supraventricular) Arrhythmia



QTc Prolongation
Torsade



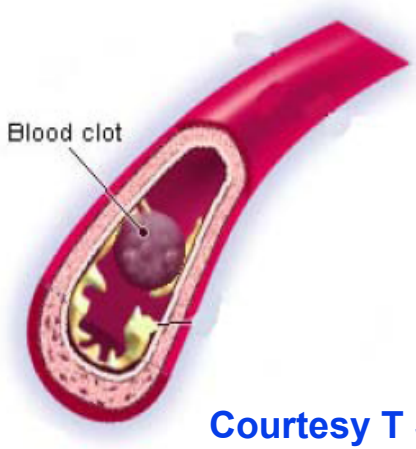
Courtesy T Suter

Cardiovascular Side Effects of Cancer Therapy - Ischemia

	Drug	Toxic Dose	Comments
Cytotoxic Chemotherapeutics	Anthracyclines • Doxorubicin • Epirubicin	> 450 mg/m² (total dose) > 720 mg/m²	Cardiomyopathy; Heart Failure; Arrhythr
	Taxols • Paclitaxel	Conventional dose	Bradycardia, Heart Failure ? (with trastuzumab)
	Cyclophosphamide	>100–120 mg/kg	Heart Failure; Myocarditis/Peri
	Antimetabolites • 5-FU / Capecitabine	Conventional dose	Myocardial Isc
	Cisplatin	Conventional dose	Myocardial Ischemia / MI
signaling inhibitors	Anti-HER2 • Trastuzumab (Herceptin®) • Lapatinib (Tykerb®)	Conventional dose	Contractile Dysfunction, Heart Failure QTc-Prolongation
	Anti-VEGF/Angiogenics • Bevacizumab (Avastin®) • Sunitinib (Sutent®) • Sorafenib (Nexavar®)	Conventional dose	Hypertension Contractile Dys Heart Failure QTc-Prolongation
	BCR-ABL targeted • Imatinib • Dasatinib • Nilotinib	Conventional dose	Heart Failure, QTc-Prolongation

Vasoconstriction

Thrombosis



Courtesy T Suter

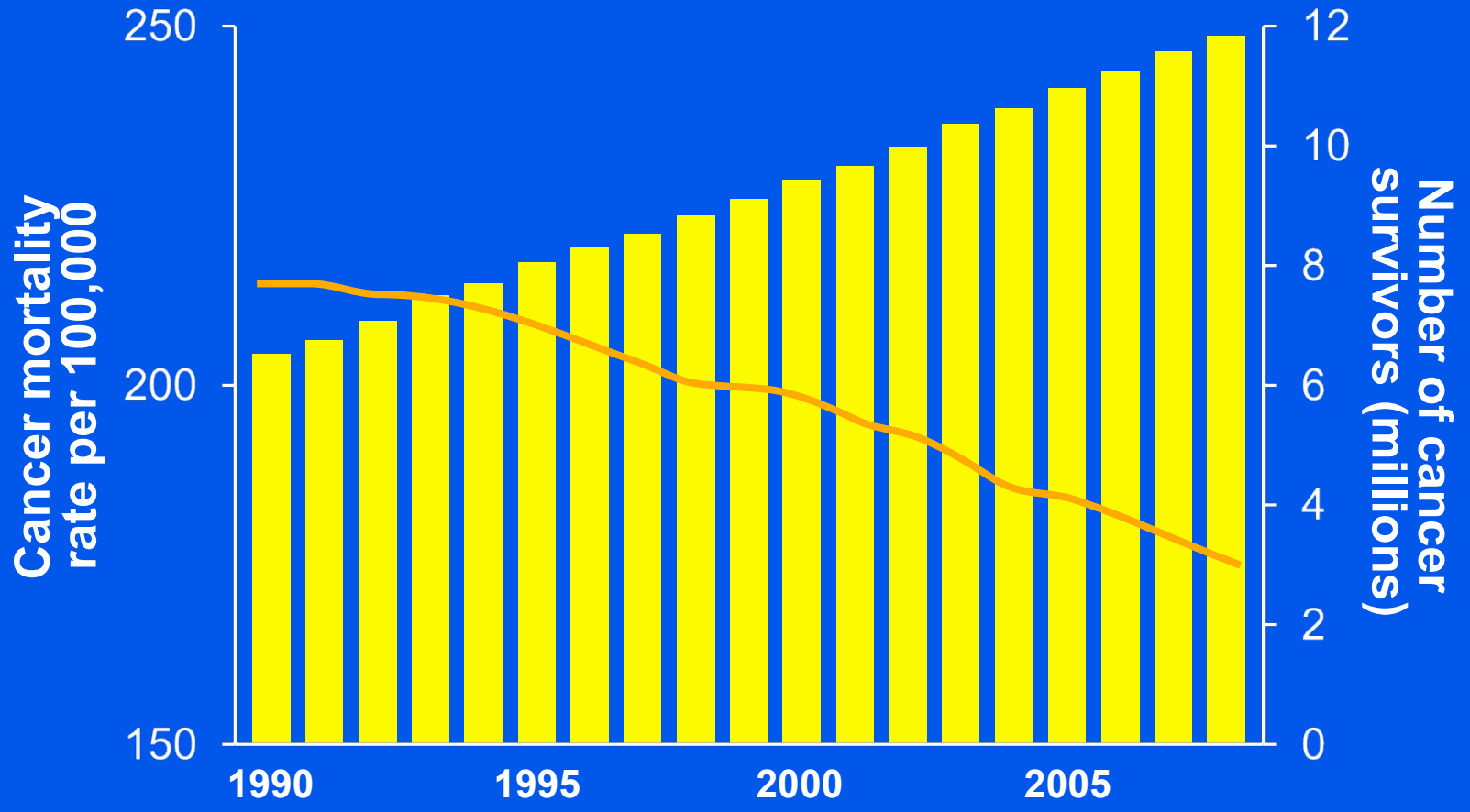
Cardiovascular Side Effects of Cancer Therapy Cardiac Dysfunction – Heart Failure

Anthracyclines	Cardiac Dysfunction	Heart Failure
Anthracyclines - Doxorubicin - Epirubicin / Mitoxantrone		 2 – 12 % 4 – 15 %
Paclitaxel		
Cyclophosphamide		1 %
Signaling Inhibitors		
Trastuzumab (Herceptin®)	3-18 %	4 %
Lapatinib (Tykerb®)	10 %	2 %
Bevacizumab (Avastin®)	1-3 %	
Sunitinib (Sutent®)	8 -15 %	10 %
Sorafenib (Nexavar®)		
Imatinib (Gleevec®)	2 %	1 %

Courtesy T Suter

Cancer Statistics USA – 1990-2008

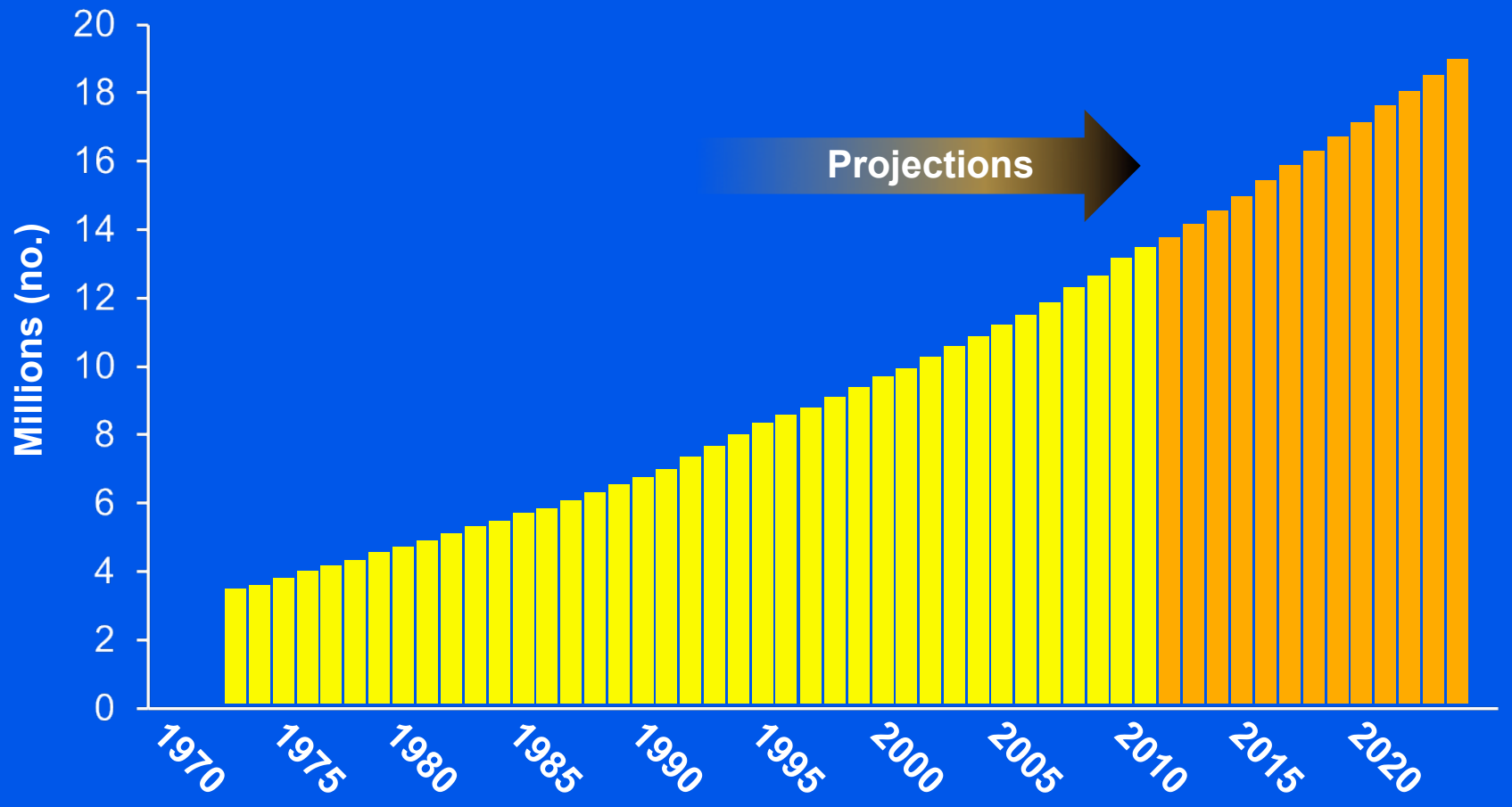
Surviving Rising, Mortality Decreasing



Data from National Cancer Institute on estimated number of cancer survivors and age-adjusted cancer deaths/100,000 people

Cancer Survivors Statistics USA

"Nearly 20 (M) by 2020"



DeSantis C, Chunchieh L, Mariotto AB, et al (2014); Cancer Treatment and Survivorship Statistics, 2014, CA: A Cancer Journal for Clinicians, In press

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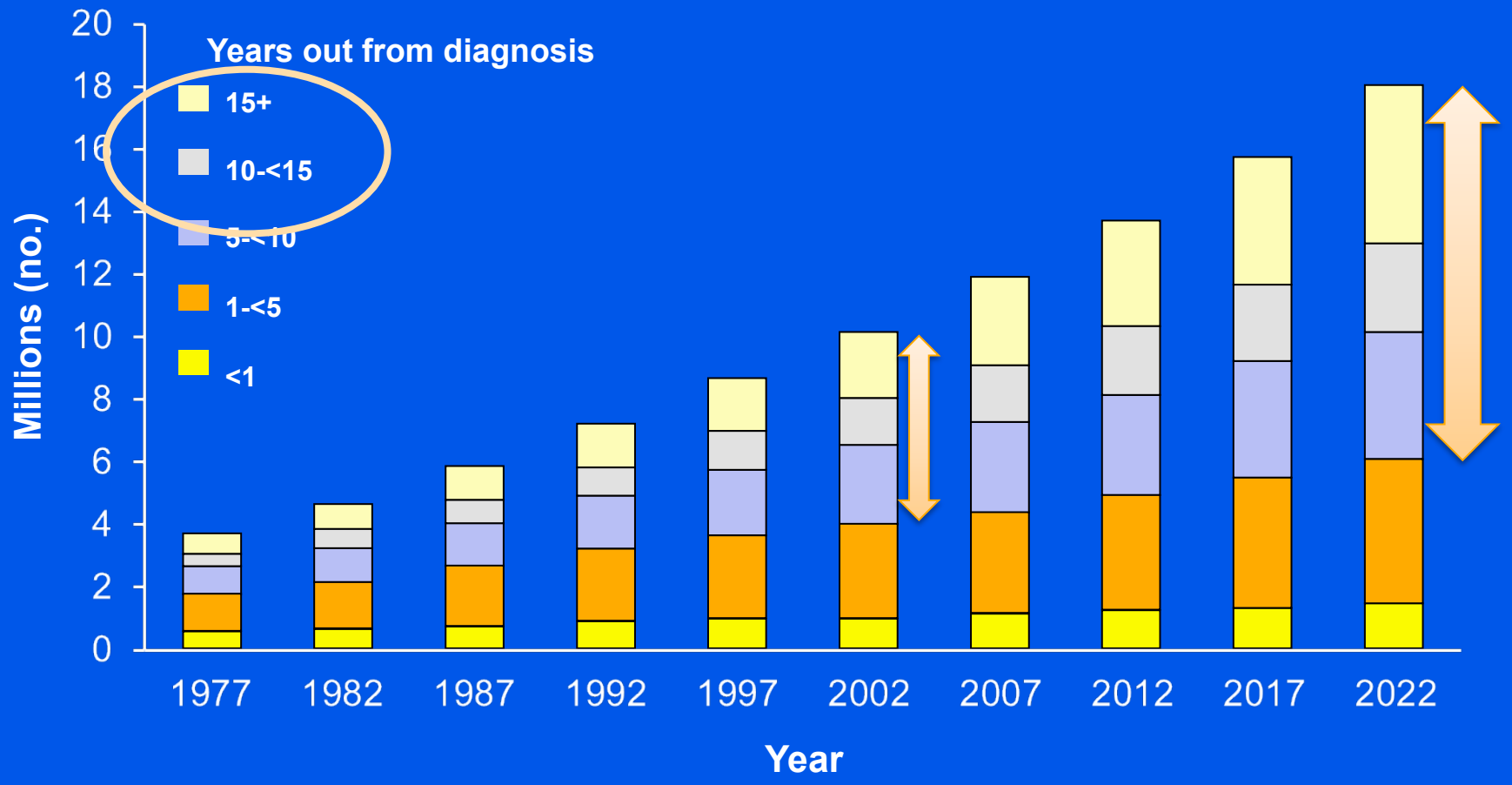
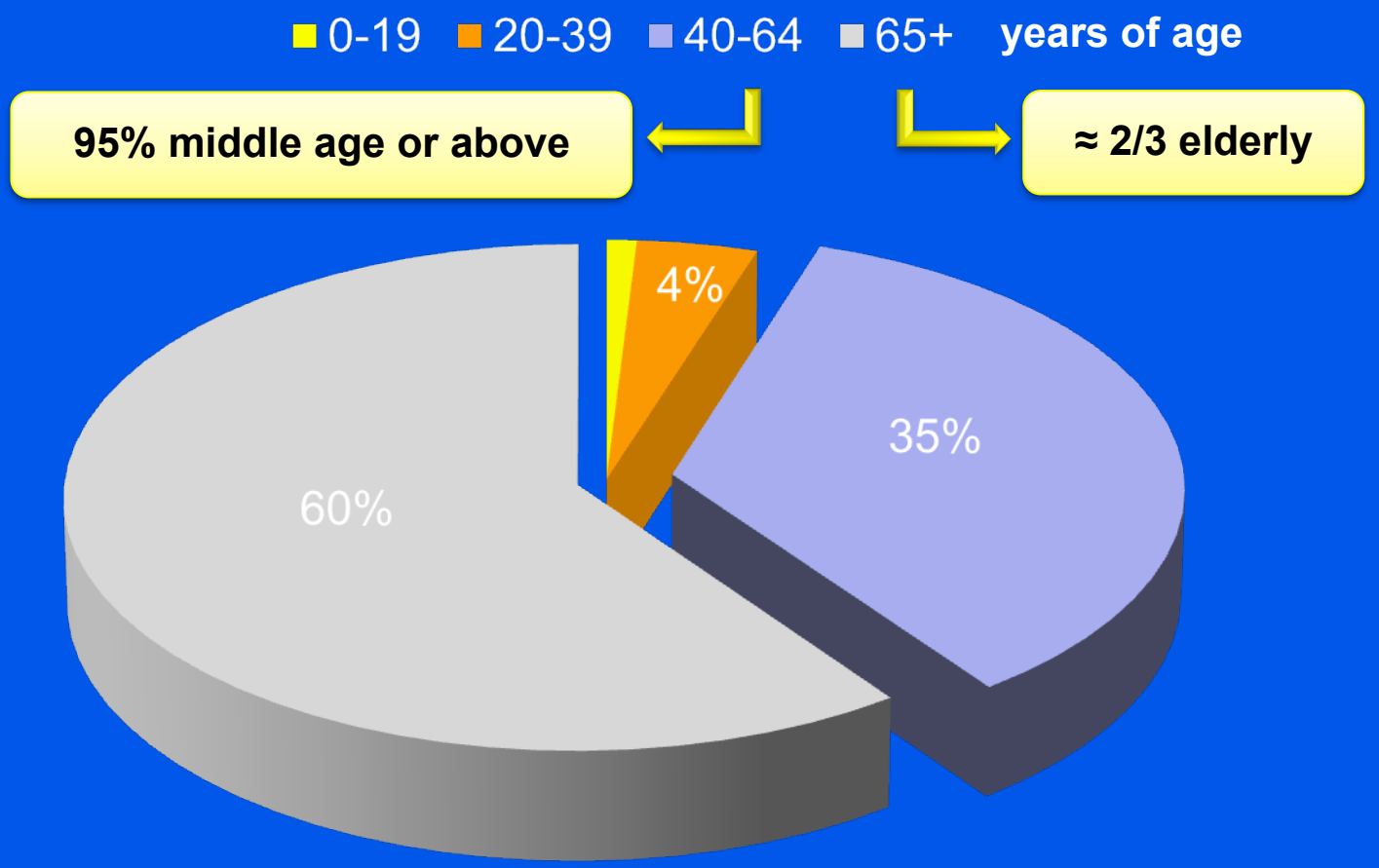
Cancer Survivors Statistics USA

Greatest Increase in Long-term Survivors



De Moor JS, Mariotto AB, Parry C, Alfano CM, Padgett L, Kent EE, Forsythe L, Scoppa S, Hachey M, and Rowland JH;
cancer survivors in the United States: Prevalence across the Survivorship Trajectory and Implications for Care;
Cancer Epidemiol Biomarkers Prev. 2013 Apr;22(4):561-70. doi: 10.1158/1055-9965.EPI-12-1356. Epub 2013 Mar 27

Cancer Survivors in the USA - 2014
Stratified by Age



DeSantis C, Chunchieh L, Mariotto AB, et al. (2014). Cancer Treatment and Survivorship Statistics, 2014. CA: A Cancer Journal for Clinicians, In press

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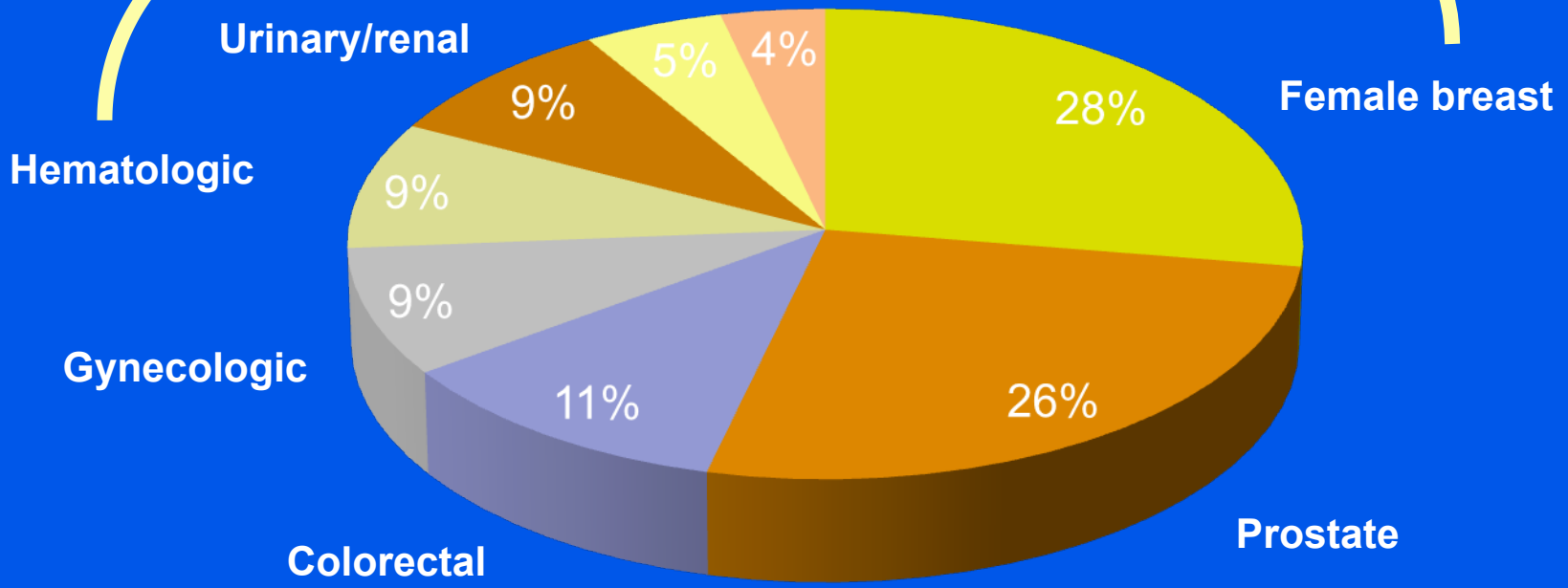
Cancer Survivors in the USA - 2014
Stratified by Site

Total: 14.5 M

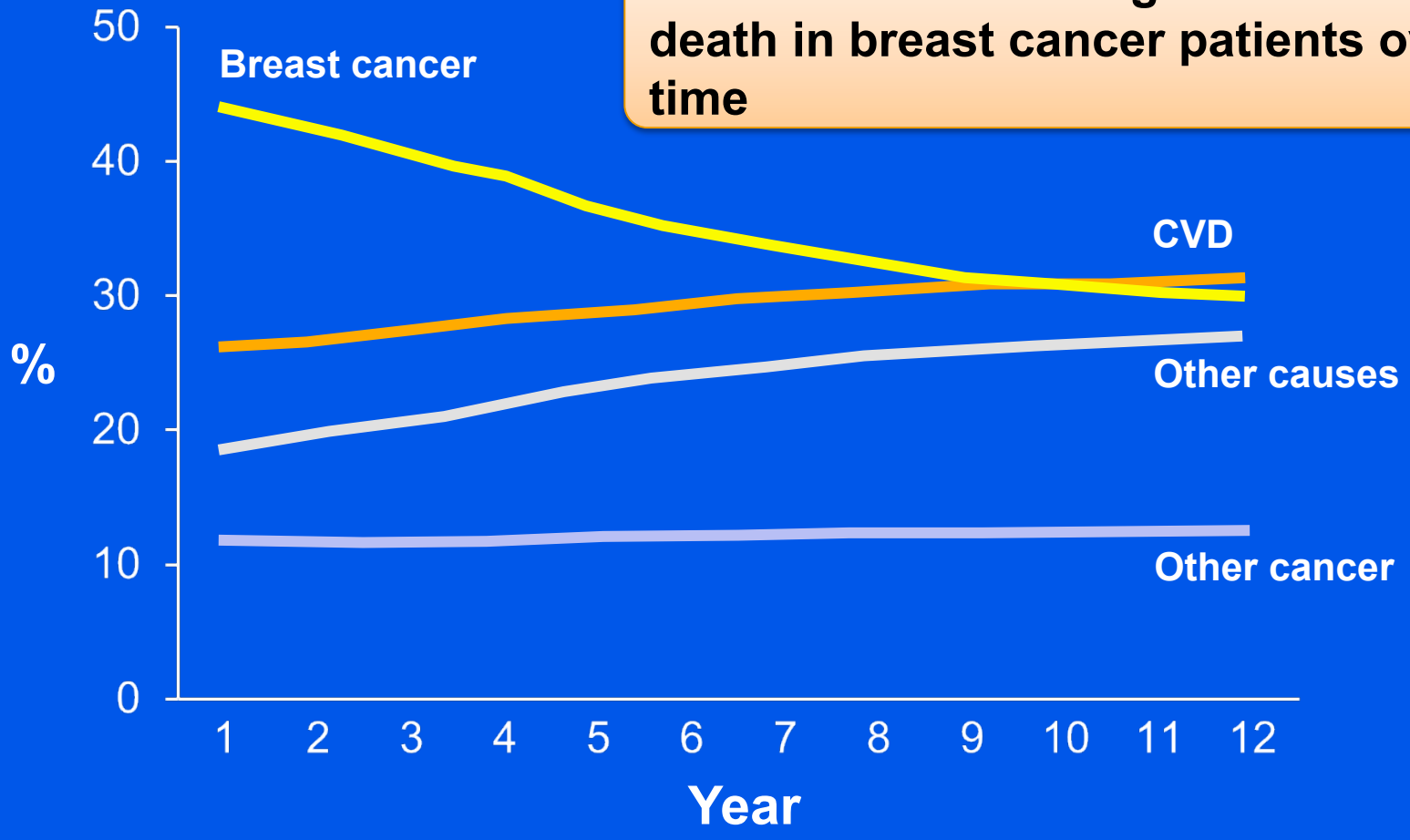
High lifetime cardiotoxicity risk: 5.3 M



DeSantis C, Chunchieh L, Mariotto AB, et al. (2014). Cancer Treatment and Survivorship Statistics, 2014. CA: A Cancer Journal for Clinicians, In press

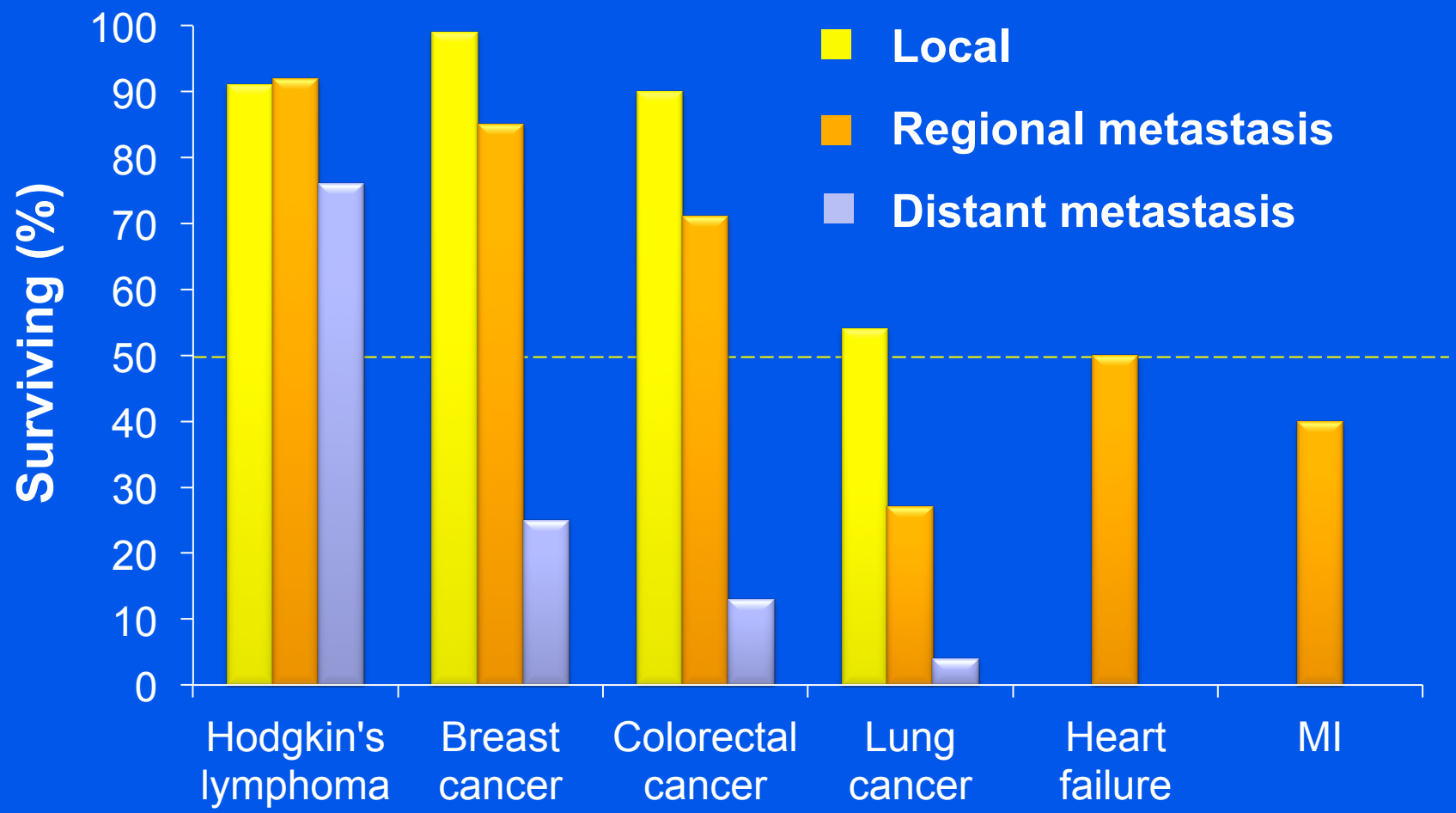
Breast Cancer Patients
Cause of Death

CVD becomes leading cause of death in breast cancer patients over time



Patnaik JL et al: Breast Cancer Res 13:R64, 2011

5-year survival rates
Heart Failure, Myocardial Infarction vs. Cancer



SEER Cancer Statistics Review 1975-2011 - National Cancer Institute

Heart Disease and Strokes Statistics – 2014 update – American Heart Association

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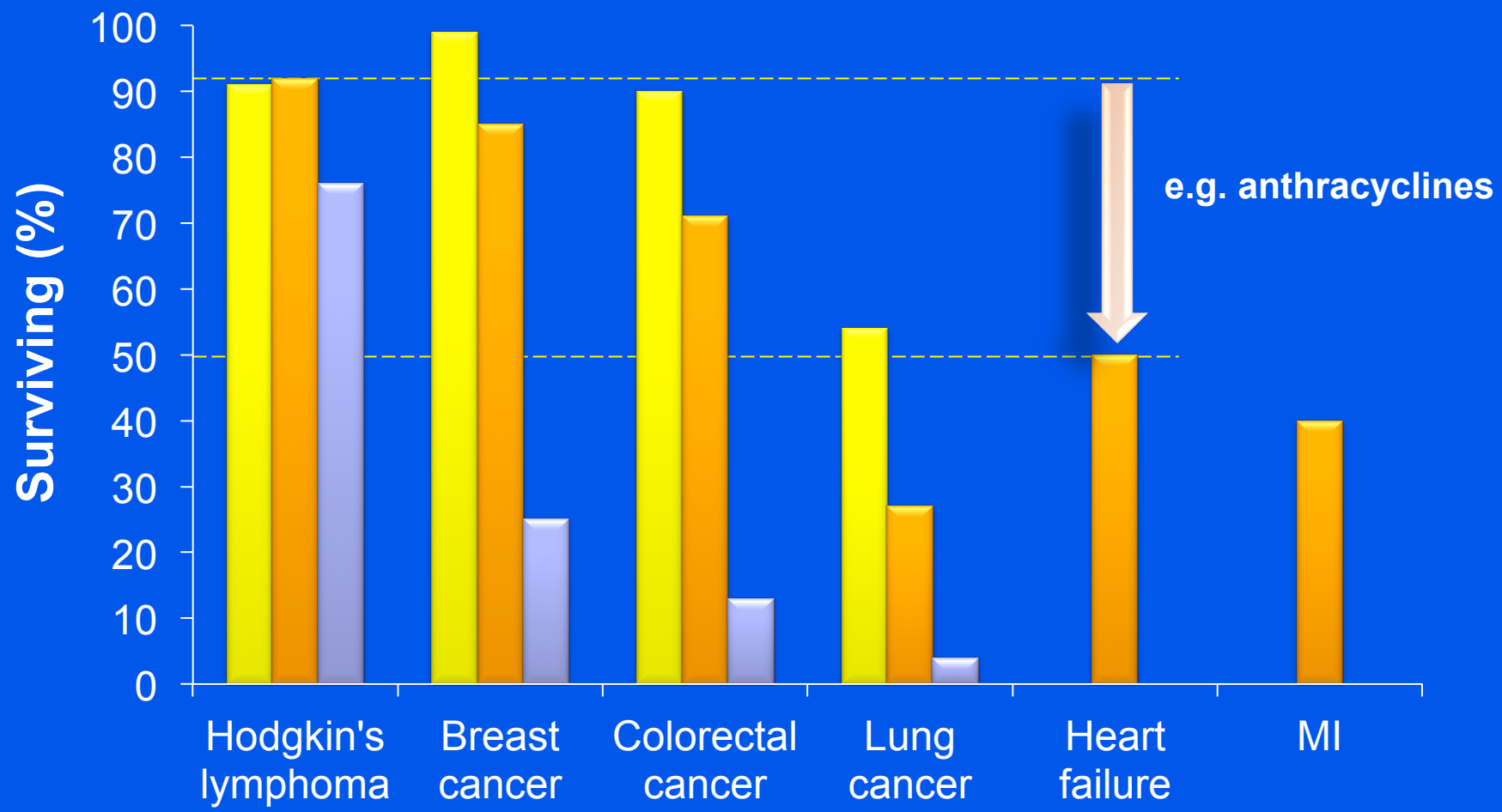
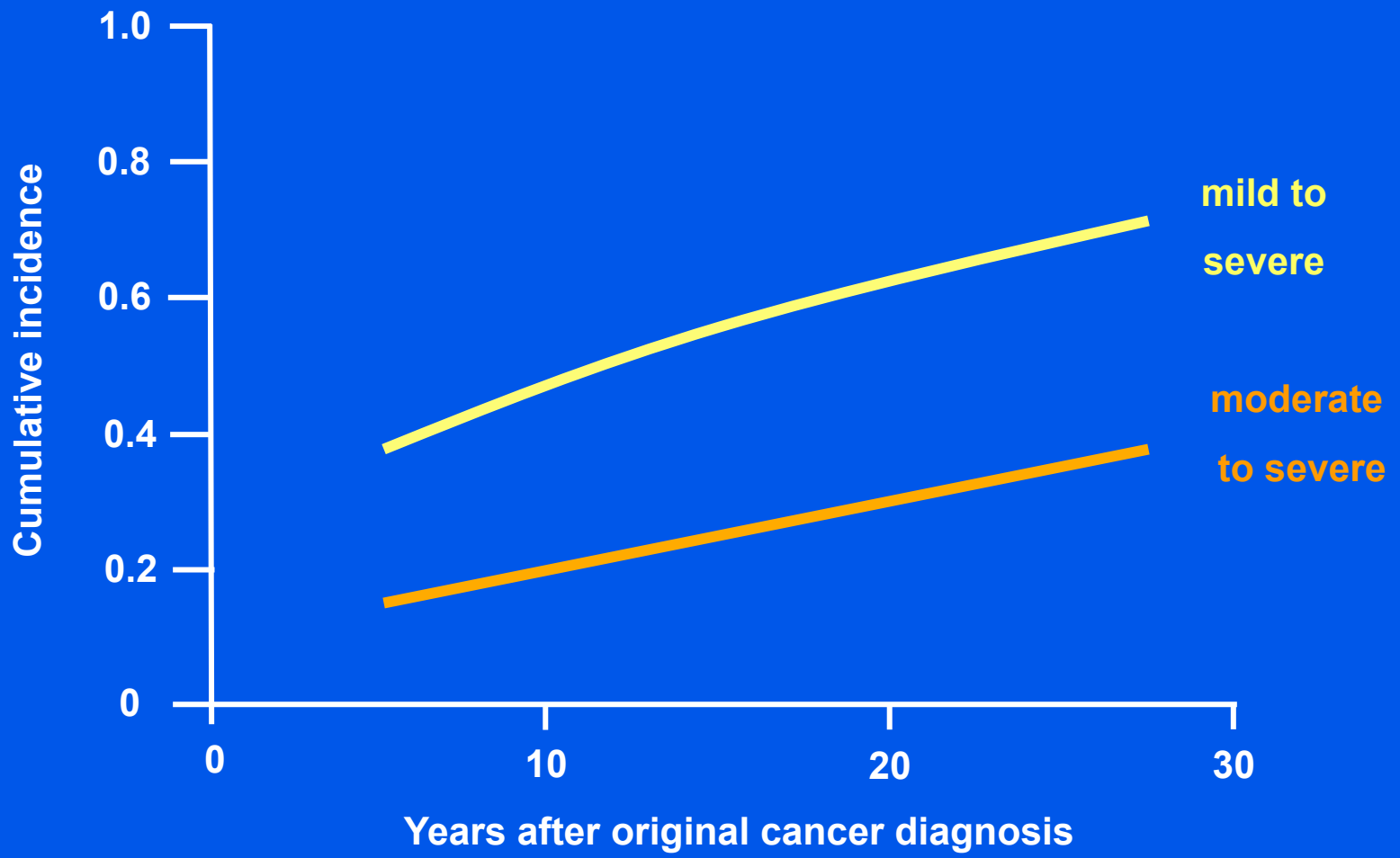
5-year survival rates
Heart Failure, Myocardial Infarction vs. Cancer



SEER Cancer Statistics Review 1975-2011 - National Cancer Institute

Heart Disease and Strokes Statistics – 2014 update – American Heart Association

Childhood Cancer Survivors
Incidence of Chronic Health Conditions



Oeffinger KC et al. NEJM 2006;355:1572-82

Cardiac implications of Chemotherapy

Epidemiology of Anthracycline Cardiotoxicity in Children and Adults

Michelle A. Grenier and Steven E. Lipshultz

Long-term survivors of cancer represent one of the largest and ever-increasing groups of patients at risk for premature cardiovascular disease.[8,9] A

Semin Oncol 1998

Cardiac implications of Chemotherapy

VOLUME 22 · NUMBER 5 · MARCH 1 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

INTRODUCTION

Nearly 70% of all children diagnosed with a malignancy become long-term survivors, and can reasonably be described as cured [1]. However, this impressive cure rate has been achieved at a significant cost in terms of side effects associated with the intense treatment needed to achieve these results. Consequently, there are now approximately 250,000 long-term survivors of pediatric cancer [1] at risk for a wide variety of medical late effects of therapy [2], with half of these patients having been exposed to anthracyclines. It is estimated that more than half of all patients exposed to anthracyclines (ie, more than 60,000 patients) will show cardiac abnormalities on two-dimensional echocardiography or gated nuclear angiography (GNA) testing at 10 to 20 years from diagnosis [3-5]. Of these, possibly 5% could develop congestive heart failure. Arrhythmias are also noted to occur in approximately 40% of patients by 20 years from diagnosis [3,6], and the incidence of cardiac abnormalities increases with time [3,7-10].

The Cardiac Implications of Chemotherapy

Long-Term Outcomes of Adult Survivors of Childhood Cancer

Results from the Childhood Cancer Survivor Study

TABLE 2
Summary of Published Results from the Childhood Cancer Survivor Study

Reference	Outcome	Study population	Selected findings
Mertens et al. (2001)[9]	Mortality	Full CCSS cohort	10-fold excess in overall mortality; SMR for second cancer, cardiac and pulmonary, 19.4, 8.2, and 9.2, respectively.
Neglia et al.[10]	Second malignancy	Full CCSS cohort	6.4-fold excess in cancer occurrence; SIR highest for bone and breast cancers, 19.1 and 16.2, respectively.
Sklar et al. (2000)[16]	Thyroid function	Hodgkin disease	Relative risk of hypothyroidism (17.1) and hyperthyroidism (8.0); cumulative risk of hypothyroidism for those treated with 4500 cGy or more was 50% at 20 yrs from dia gnosis.

8.2-fold higher cardiovascular mortality

Cardiovascular Morbidity in Long-Term Survivors of Metastatic Testicular Cancer

By M.T. Meinardi, J.A. Gietema, W.T.A. van der Graaf, D.J. van Veldhuisen, M.A. Runne, W.J. Sluiter, E.G.E. de Vries, P.B.H. Willemse, N.H. Mulder, M.P. van den Berg, H. Schraffordt Koops, and D.Th. Sleijfer

Purpose: To determine whether long-term survivors of metastatic testicular cancer have an increased risk of cardiovascular morbidity more than 10 years after chemotherapy.

Patients and Methods: Eighty-seven patients treated with cisplatin-containing chemotherapy before 1987 who were in remission for at least 10 years and whose ages were ≤ 50 years at the time of analysis were evaluated for the occurrence of cardiovascular events. Sixty-two of 87 patients were additionally evaluated for cardiac damage and cardiovascular risk factors. Their

found. In addition, one patient experienced a cerebrovascular accident. Exercise ECG did not reveal cases of subclinical coronary artery disease. Echocardiography showed normal systolic left ventricular function in most patients, but diastolic left ventricular function was disturbed in 33% of the patients. Of 62 chemotherapy patients, 79% had hypercholesterolemia, 39% had hypertension, 25% still experienced Raynaud's phenomenon, and 22% had microalbuminuria. Compared with patients with stage I disease, the chemotherapy patients had higher blood pressure and higher total cho-

Conclusion: **In long-term survivors of metastatic testicular cancer, we observed a significantly increased risk for occurrence of cardiac events accompanied by a persisting unfavorable cardiovascular risk profile. Accurate follow-up, focused on cardiovascular complications and aimed at intervention in these young cancer survivors, seems to be important.**

J Clin Oncol 18:1725-1732.

Cumulative Incidence of Heart Failure or Cardiomyopathy During First 3 Years After Diagnosis by Cancer Therapy

	All cancer patients	Anthracycline + trastuzumab n=431	Anthracycline n=5,257	Trastuzumab n=437	Other chemotherapy n=2,712	None n=36,700
Observed cumulative incidence (%)						
1 year	7.2	16.4*†	7.7‡	15.7*	7.8	6.8
2 years	12.3	23.8*†	11.9	20.7*	12.4	12.1
3 years	16.9	28.2*†	15.3‡	26.7*	17.0	16.9
Adjusted cumulative incidence (%)						
1 year	7.5	22.0*†	9.8*	16.7*	8.4*	7.0
2 years	13.3	33.2*†	15.3*	23.2*	13.7*	12.8
3 years	18.7	41.9*†	20.2‡	32.1*	19.2	18.1

***P<0.001 vs no adjuvant therapy group; †P<0.001 vs anthracycline group, only in the model containing anthracycline + trastuzumab and anthracycline adjuvant therapy; ‡P<0.05 vs no adjuvant therapy group**

Chen et al: JACC 60(24):2504, 2012

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Cumulative Incidence of Heart Failure or Cardiomyopathy During the First 3 Year in Breast Cancer Patients Without Adjuvant Therapy vs Cancer-Free Controls

	Breast cancer, no adjuvant therapy n=36,700	Cancer-free Medicare controls n=36,700
Observed (%)		
1 year	6.8	8.0*
2 years	12.1	13.7*
3 years	16.9	18.7*
Adjusted (%)		
1 year	6.7	7.0
2 years	12.2	12.4
3 years	17.2	17.2

*P<0.001

Chen et al: JACC 60(24):2504, 2012

CORRESPONDENCE

Serum Troponin T Levels in Adults Undergoing Anthracycline Therapy

Among the wide variety of cytotoxic agents used for anticancer chemotherapy today, anthracyclines are agents with an extremely broad spectrum of activity. The use of anthracyclines, however, is limited by their cardiotoxic potential both in children and in adults.

Recently, the first encouraging results with cardioprotective agents to overcome this obstacle to a certain extent have been published (*1-3*). Despite these promising data, the exact mechanisms underlying anthracycline-related cardiotoxicity have yet to be established. One of the most commonly accepted hypotheses focuses on the generation of free radicals with subsequent oxidative damage to membranes of myocardial cells (*4,5*).

In view of the fact that serum troponin T levels become elevated even in patients with minimal myocardial cell damage, i.e., unstable angina pectoris (*6*) or after catheter ablation (our unpublished data), we performed serial measurements of troponin T serum levels in adult patients undergoing their initial cycle of anthracycline therapy; these patients did not have a history of cardiac disease or risk factors. Five patients were administered doxorubicin (50 mg/m^2) as a part of combination chemotherapy for malignant lymphoma (three patients) or small-cell lung cancer (two patients), while five patients received epirubicin (100 mg/m^2) for pancreatic cancer (three patients) or gastric or breast cancer (one patient each). Given the results obtained in patients with myocardial damage (*6*), blood samples were drawn immediately before and 1, 4, 8, 24, and 48 hours after administration of therapy in order to cover the time of most probable change in serum levels.

In all 10 patients, no change in troponin T serum levels, as analyzed by a commercially available enzyme-linked immunosorbent assay (Enzymun Troponin T; Boehringer Mannheim Corp., Indianapolis, IN), could be detected; the cutoff level was 0.2 ng/mL. The mean values (in nanograms per milliliter) were as follows: 0.02 (95% confidence interval [CI] = 0.00-0.04) at baseline and 0.02 (95% CI = 0.00-0.04), 0.015 (95% CI = 0.00-0.03), 0.015 (95% CI = 0.00-0.03), 0.04 (95% CI = 0.00-0.08), and 0.025 (95% CI = 0.00-0.05) after 1, 4, 8, 24, and 48 hours, respectively.

These data are consistent with a report about breast cancer patients undergoing irradiation to the left breast wall (*7*); that report also demonstrated no rise in serum troponin T levels, which thus decreases the likelihood of acute minimal cell disruption as the underlying cause of cardiotoxicity observed in such patients. Our preliminary results suggest that acute damage to myocardial cells is not likely to be implicated in cardiotoxicity due to anthracycline application. Thus, confirmation of our results in larger studies and attempts to further elucidate potential mechanisms responsible for cardiac sequelae of cytotoxic treatment are clearly warranted.

MARKUS RADERER
GABRIELA KORNEK
GEORG WEINLÄNDER
JOHANNES KASTNER

References

(*1*) Wexler LH, Andrich MP, Venzon D, Berg SL, Weaver-McClure L, Chen CC, et al. Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. J Clin Oncol 1996;14:362-72.

(*2*) Lipshultz SE. Dexrazoxane for protection against cardiotoxic effects of anthracyclines in children [editorial]. J Clin Oncol 1996;14:328-31.

(*3*) Hellmann K. Anthracycline cardiotoxicity prevention by dexrazoxane: breakthrough of a barrier—sharpens antitumor profile and therapeutic index [editorial]. J Clin Oncol 1996;14:332-3.

(*4*) Doroshow JH. Anthracycline antibiotic-stimulated superoxide, hydrogen peroxide, and hydroxyl radical production by NADH dehydrogenase. Cancer Res 1983;43:4543-51.

(*5*) Myers C, Gianni L, Zweier J, Muindi J, Sinha BK, Eliot H. Role of iron in adriamycin biochemistry. Fed Proc 1986;45:2792-7.

(*6*) Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljungdahl L, et al. The prognostic value of serum troponin T in unstable angina. N Engl J Med 1992;327:146-50.

(*7*) Hughes-Davies L, Sacks D, Rescigno J, Howard S, Harris J. Serum cardiac troponin T levels during treatment of early-stage breast cancer. J Clin Oncol 1995;13:2582-4.

Notes

Affiliations of authors: M. Raderer, G. Kornek, G. Weinländer (Department of Internal Medicine, Division of Oncology) and J. Kastner (Department of Internal Medicine, Division of Cardiology), University of Vienna, Austria.

Correspondence to: Markus Raderer, M.D., Department of Internal Medicine, Division of Oncology, University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria.

Re: *Healthy People 2000* Review: Women's Cancers

The Alliance for Lung Cancer Advocacy, Support, and Education (ALCASE) would like to express its great concern over the *Stat Bite* (*1*) in the "News" section of the October 16 issue of the Journal that lists the cancer-related objectives for *Healthy People 2000*: Women's Cancers. Lung cancer is the leading cancer-related killer of women and is one cancer that can, in most cases, be directly attributed to a specific cause, yet there is no mention of reducing the rate of lung cancer in the objectives. This only reinforces our concern that lung cancer is truly the disease with an invisible patient population.

I was privileged to attend the recent meeting in Washington that focused on smoking in women, especially the rising rates in adolescent girls and to see a preview of the wonderful programs to come. However, the brief overview in the Journal makes it appear that the only organs in women worth saving from cancer are those involved with reproduction.

PEGGY MCCARTHY

Reference

(*1*) Kolin R. *Stat Bite: Healthy People 2000* review: women's cancers. J Natl Cancer Inst 1996;88:1427.

Note

Correspondence to: Peggy McCarthy, ALCASE, 1601 Lincoln Ave., Vancouver, WA 98660.

In all 10 patients, no change in troponin T serum levels, as analyzed by a commercially available enzyme-linked immunosorbent assay (Enzymun Troponin T; Boehringer Mannheim Corp., Indianapolis, IN), could be detected; the cutoff level was 0.2 ng/mL. The mean values (in nanograms per milliliter) were as follows: 0.02 (95% confidence interval [CI] = 0.00-0.04) at baseline and 0.02 (95% CI = 0.00-0.04), 0.015 (95% CI = 0.00-0.03), 0.015 (95% CI = 0.00-0.03), 0.04 (95% CI = 0.00-0.08), and 0.025 (95% CI = 0.00-0.05) after 1, 4, 8, 24, and 48 hours, respectively.

Sampling at 1, 4 8, 24 and 48 hours

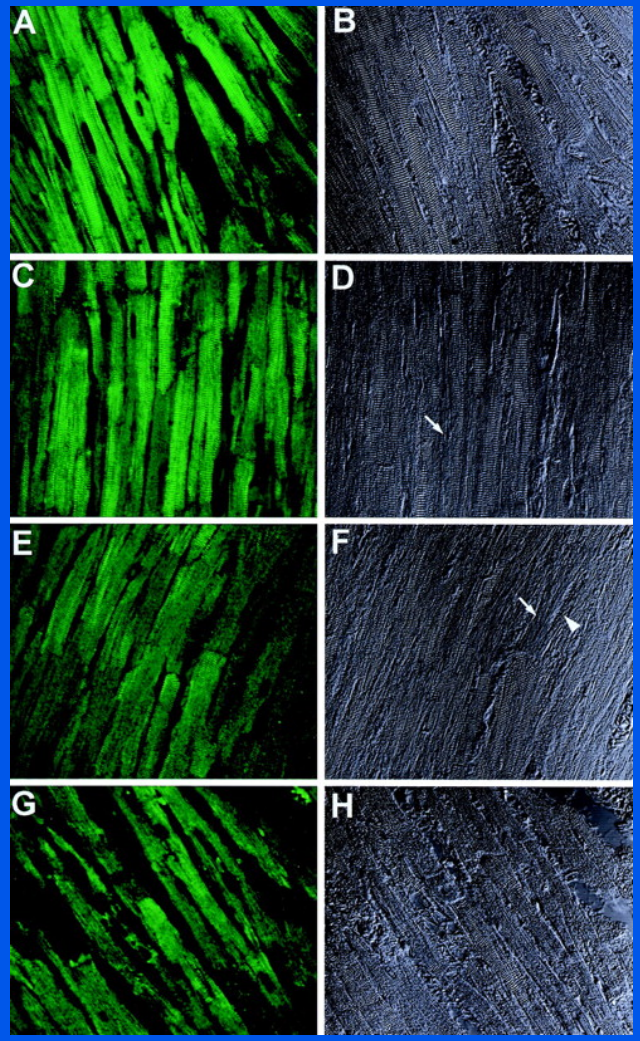
cTnT and histological Changes in Myocardium of SHR

cTnT Control

4 mg/kg of DXR

8 mg/kg of DXR

10 mg/kg of DXR



Nomarski control

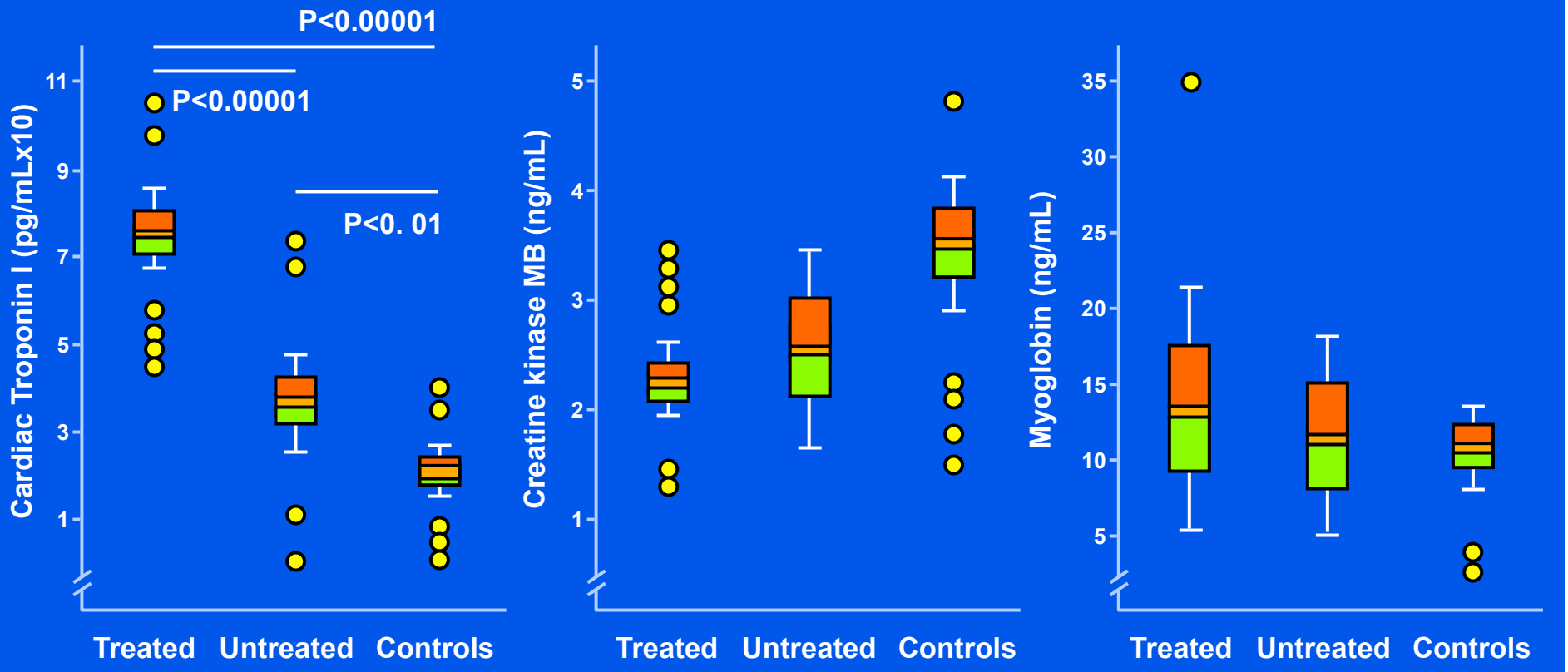
Focal disruption of cross striations

Cytoplasmic vacuoles, loss of I bands

Cytoplasmic vacuoles and myofibrillar disruption

Herman, E. H. et al. J Clin Oncol; 17:2237 1999

Levels of cTnI in Patients Treated with Adriamycin



Cor Art Dis 8:537-541, 1997

Left Ventricular Dysfunction Predicted by Early Troponin I Release After High-Dose Chemotherapy

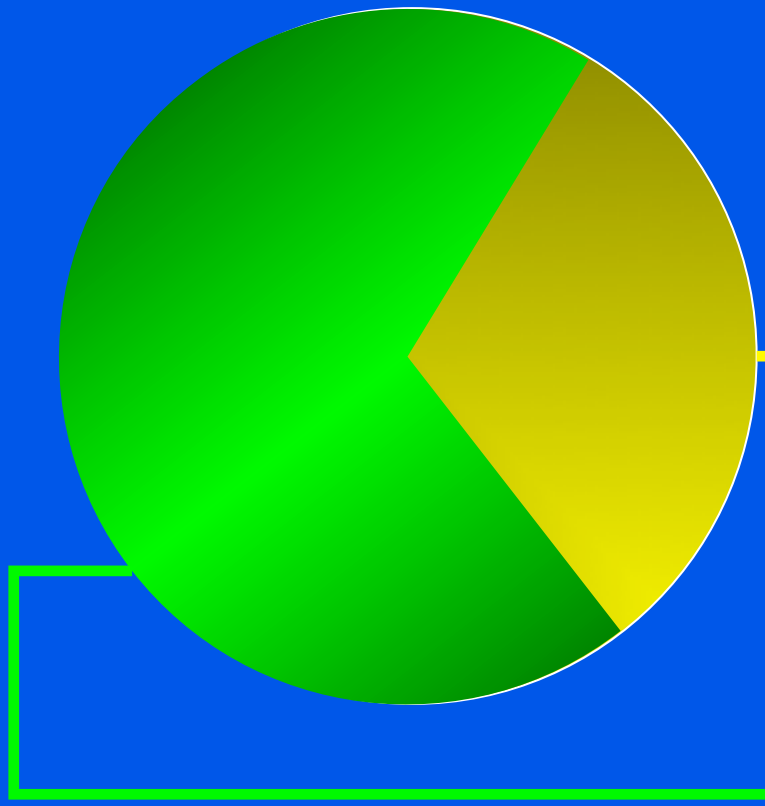
Daniela Cardinale, MD, Maria Teresa Sandri, MD,† Alessandro Martinoni, MD, Alessio Tricca, LabTech,† Maurizio Civelli, MD, Giuseppina Lamantia, MD, Saverio Cinieri, MD,* Giovanni Martinelli, MD,* Carlo M. Cipolla, MD, Cesare Fiorentini, MD

Milan, Italy

- 204 patients (661 cycles of high-dose CT)
- 39 males e 165 females (age 45±10 years).
- Poor-prognosis cancer diseases:
  - advanced or primary-resistant breast cancer
  - refractory ovarian carcinoma
  - Small-cell lung cancer
  - high- grade non Hodgkin's lymphoma
  - refractory Hodgkin's disease
- High-dose chemotherapy

J Am Coll Cardiol 2000

Results
Troponin I Positivity



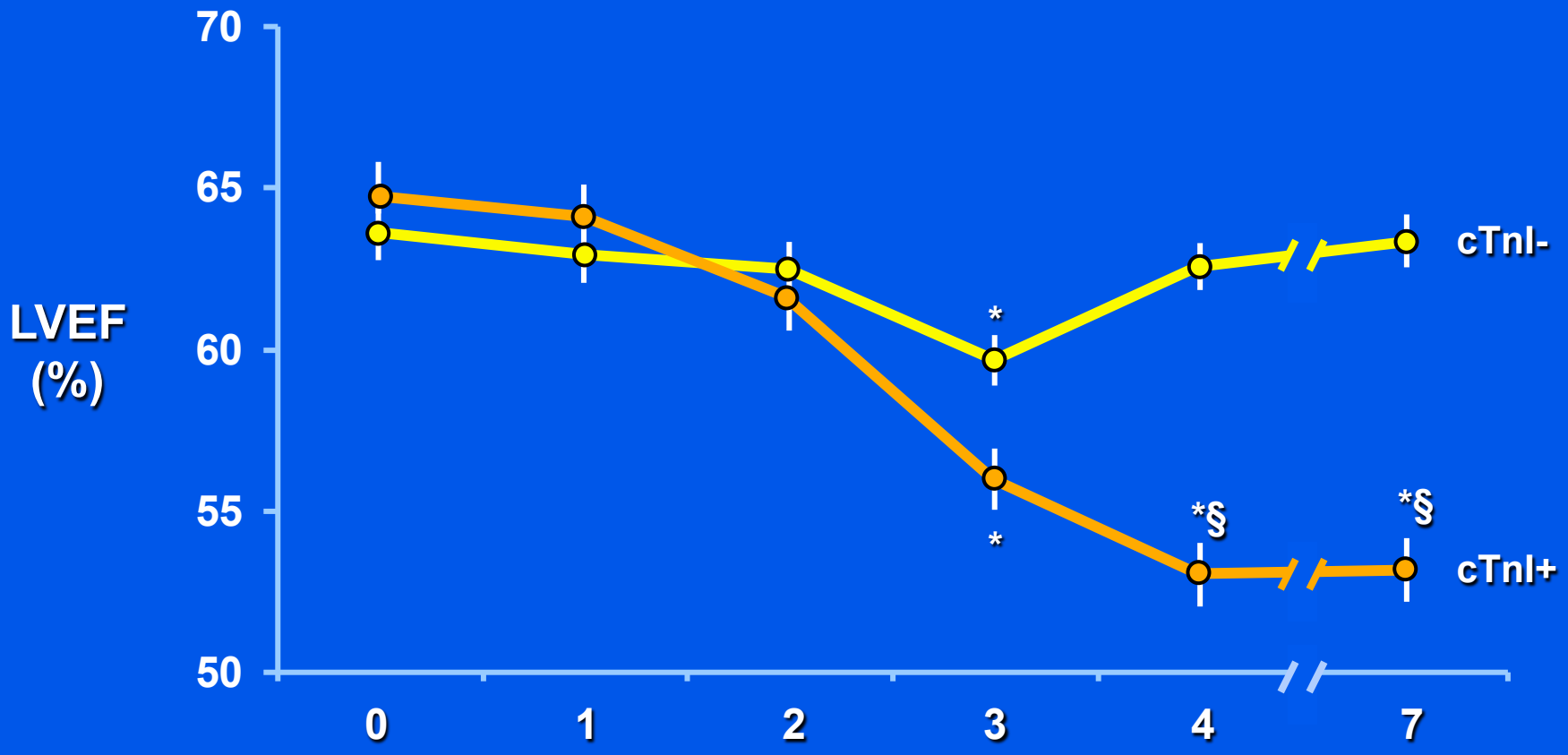
n = 65 pts (32%)
TnI pos

n = 139 pts (68%)
TnI neg

Range = 0.5 - 2.0 ng/ml
Mean = 1.0 ± 0.5 ng/ml

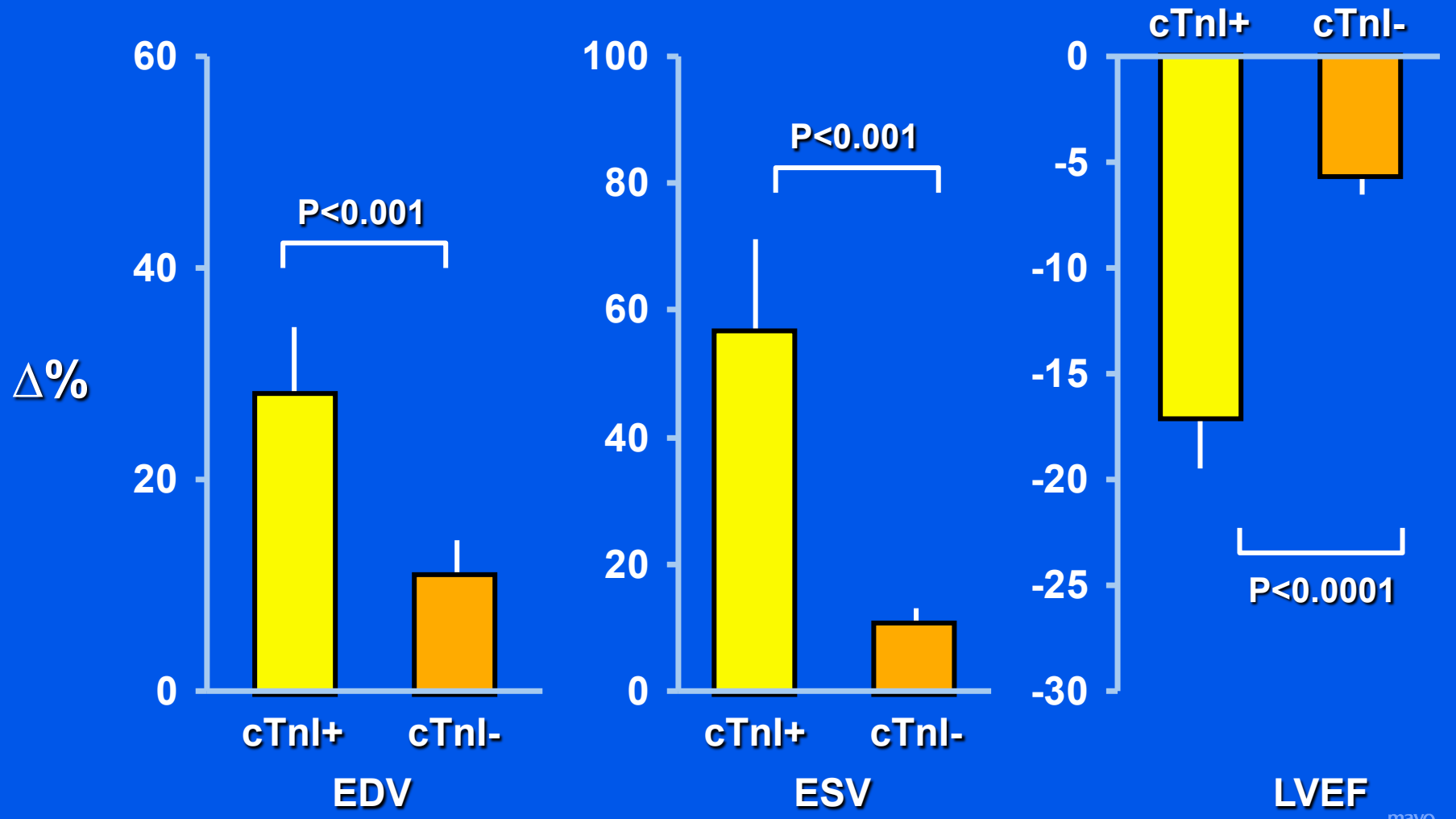
Cardinale D et al. J Am Coll Cardiol 2000

Change in LVEF



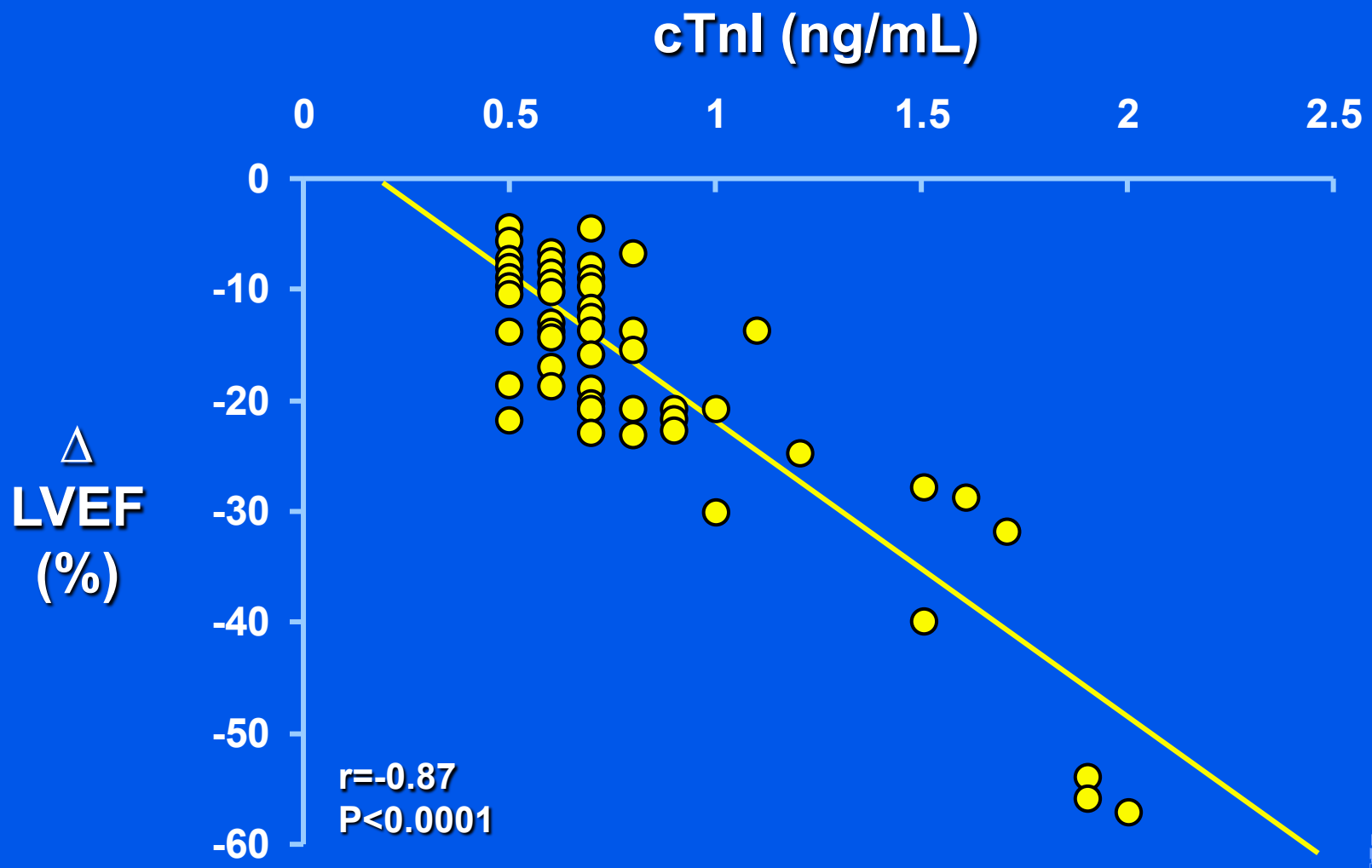
*P<0.001 vs baseline
§P<0.001 vs cTnI-group
J Am Coll Cardiol 36:517-22, 2000

Change in Volumes and LVEF



J Am Coll Cardiol 36:517-22, 2000

Relationship of Elevations of cTnI and LVEF



Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy

Daniela Cardinale, MD; Maria T. Sandri, MD; Alessandro Colombo, MD; Nicola Colombo, MD; Marina Boeri, MD; Giuseppina Lamantia, MD; Maurizio Civelli, MD; Fedro Peccatori, MD; Giovanni Martinelli, MD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

- ①703 patients (216 males)
- ①age 47±12 years
- ①treated with HDC
- ①poor prognosis malignancies

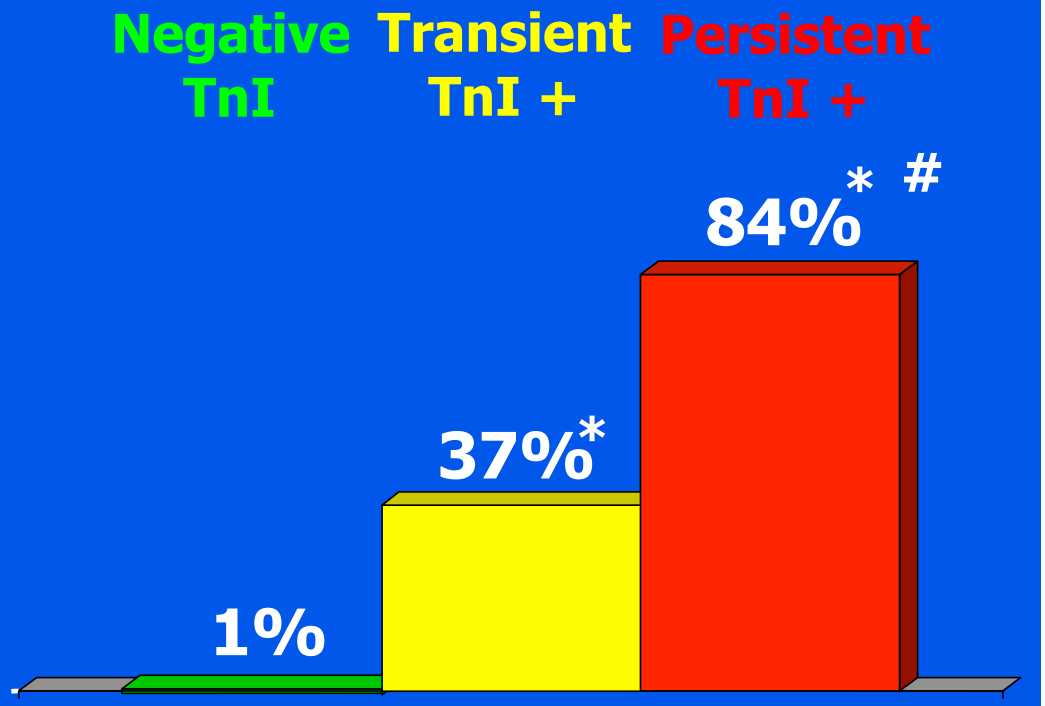
- ♫ Follow-up = 48 months
- ♫ MACE incidence

- ✓ TnI serum determination:
  - Baseline = before HDC
  - Early = soon after HDC (0,12,24,36,72 hours)
  - Late = 1 month after HDC

Circulation 2004

Cardiac Events
3.5 year-follow-up

Sudden death
Cardiac death
Acute pulmonary edema
Heart failure
Asymptomatic↓ LVEF >25%
Life-threatening arrhythmias
Conduction disturbances
requiring PM implantation



*= p<0.001 vs. TnI - #= p<0.001 vs. TnI +-

Circulation 2004

Cardiac risk stratification

Persistent TnI+ = High risk

Transient TnI+ = Intermediate risk

Negative TnI = Low risk

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Positive predictive value = 84%

Negative predictive value = 99%

Jpn. J. Pharmacol. **88**, 183 – 188 (2002)

Beneficial Effects of Angiotensin-Converting Enzyme Inhibition in Adriamycin-Induced Cardiomyopathy in Hamsters

In adriamycin induced cardiomyopathic hamster.....

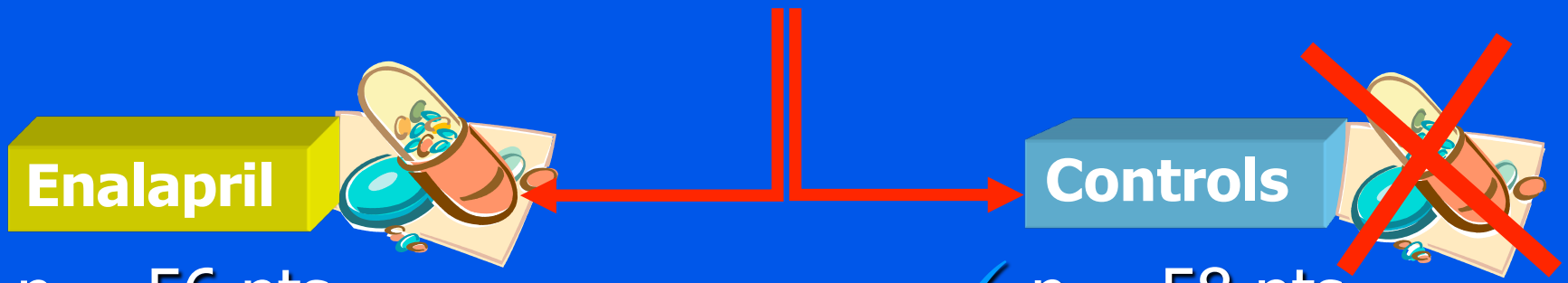
....cardiac ACE activity was increased...

....indicating that cardiac ACE plays a pivotal role in the development of adriamycin-induced cardiomyopathy.

ABSTR
enzymes, angiote
ria mycin-induced c
i.p., three times we
20 mg/kg per day, p
e vehicle- and ACE
-matched ha nsters
t increase in the rat
diac ACE activity, but not the chymase activity, in the vehicle hamsters was significantly increased in comparison to that in the control hamsters. In the ACE inhibitor-treated group, the increased ACE activity was reduced significantly, and the cardiac hypertrophy and dysfunction were improved significantly. In adriamycin-induced cardiomyopathic hamsters, cardiac ACE activity was increased and ACE inhibition significantly improved cardiac function and survival rate, indicating that cardiac ACE, but not the chymase, plays the pivotal role in the development of the adriamycin-induced cardiomyopathy.

Troponin I Early Positivity

443 pts
High-dose CT
TnI + = 114 pts (24%)



- ✓ n = 56 pts
- ✓ started 1 month after HDC
- ✓ continued for 1 year

✓ n = 58 pts

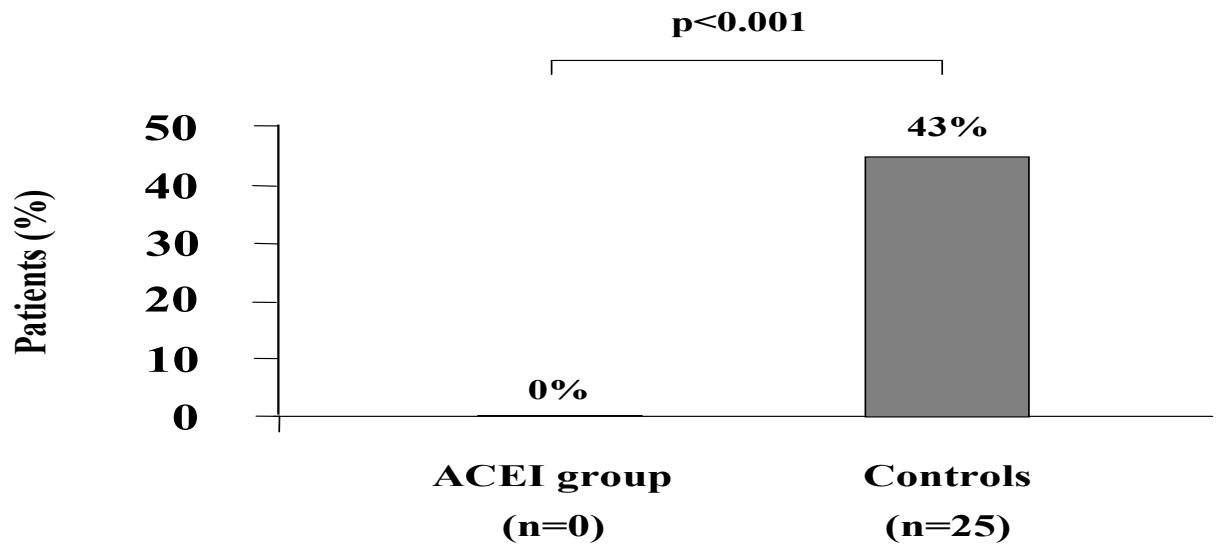
✓ physical examination, ECG, ECHO: b,1,3,6,12 months

Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

Daniela Cardinale, MD; Alessandro Colombo, MD; Maria T. Sandri, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Maurizio Civelli, MD; Giovanni Martinelli, MD; Fabrizio Veglia, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

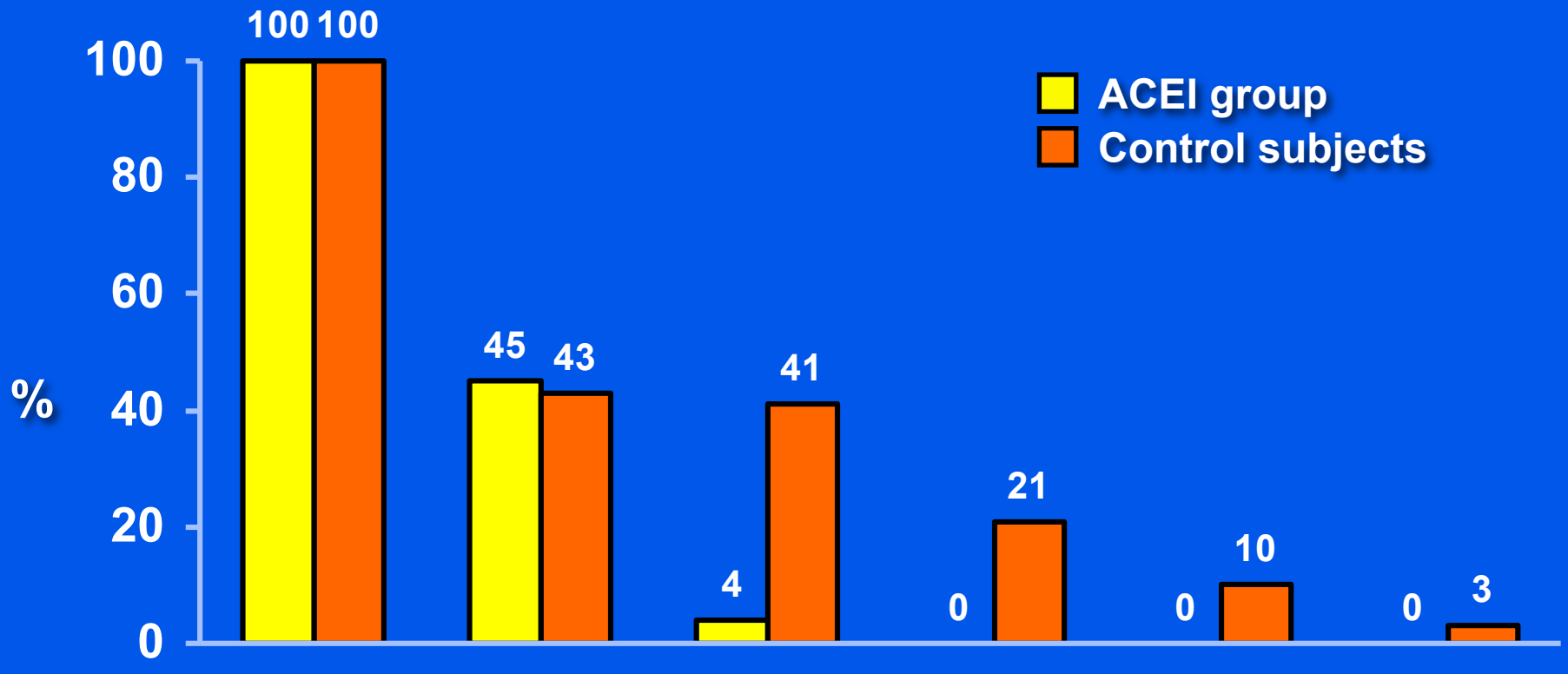
Primary end-point:

LVEF decrease >10 percent units + <50%



Circulation 2006

TnI Values in Both Groups



	Early	M1	M2	M3	M6	M12
No.	56	56	56	56	56	55
TnI (ng/mL)	0.18±0.38	0.15±0.34	0.02±0.02	0.01±0.01	0.01±0.01	0.00±0.01
No.	58	58	58	58	57	55
TnI (ng/mL)	0.23±0.44	0.14±0.31	0.10±0.17	0.09±0.29	0.03±0.06	0.01±0.02

Circ 114:2474, 2006

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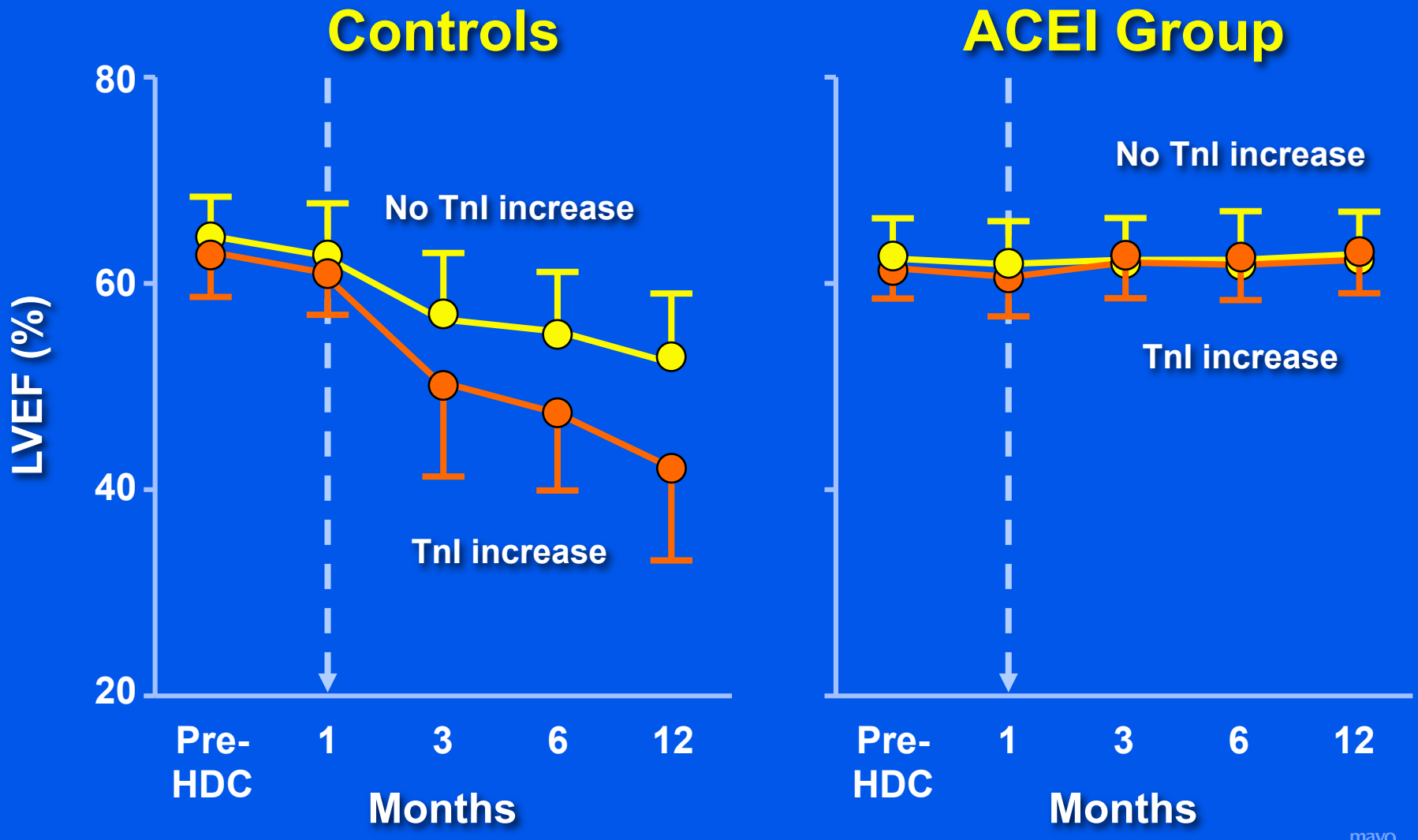
CP1252755-8

LVEF with and Without ACEI



Circ 114:2474, 2006

mayo

CP1252755-7

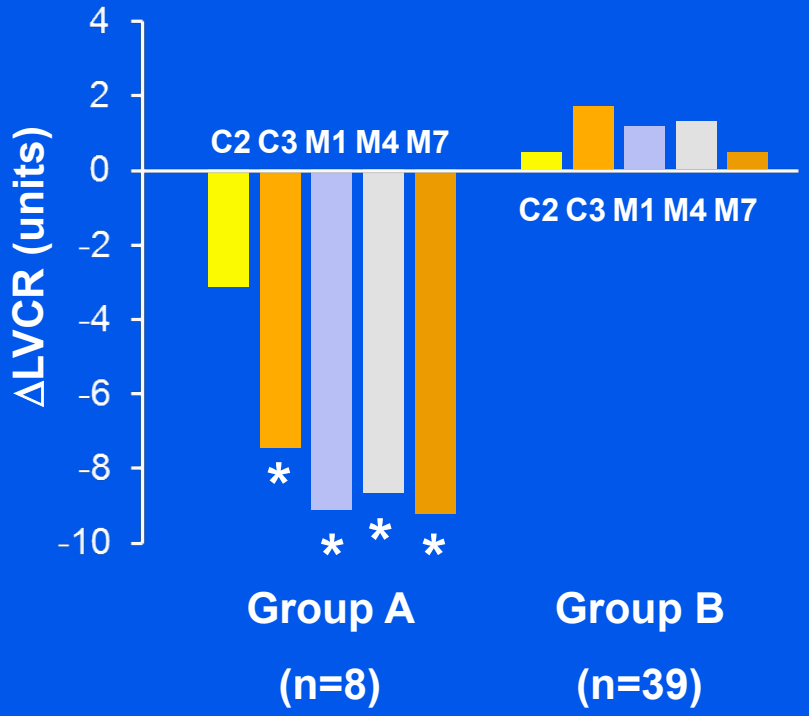
Secondary end-points
follow-up 12 months

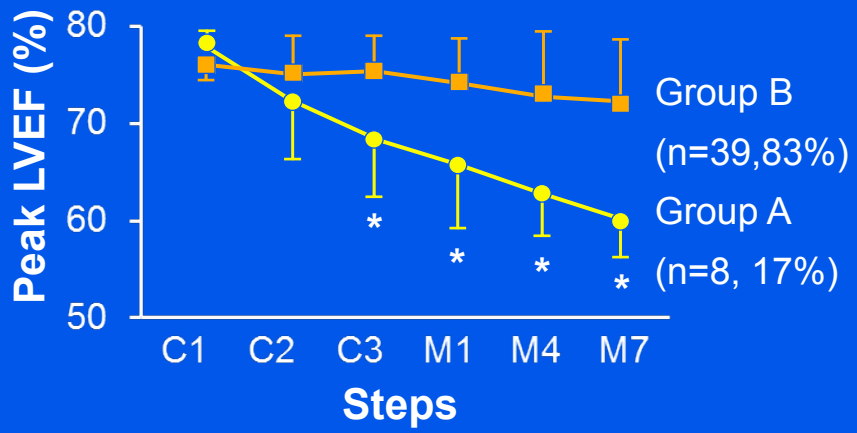
	Total n=112	ACEI n=54	Controls n=58	P
Sudden death	0 (0%)	0 (0%)	0 (0%)	NS
Cardiac death	2 (2%)	0 (0%)	2 (3%)	NS
Acute pulmonary edema	4 (2%)	0 (0%)	4 (3%)	NS
Heart failure	14 (12%)	0 (0%)	14 (22%)	<0.001
Life-threatening arrhythmias	11 (10%)	1 (2%)	10 (16%)	0.01
CUMULATIVE EVENTS	**31** (28%)	**1** (2%)	**30** (52%)	**0.001**

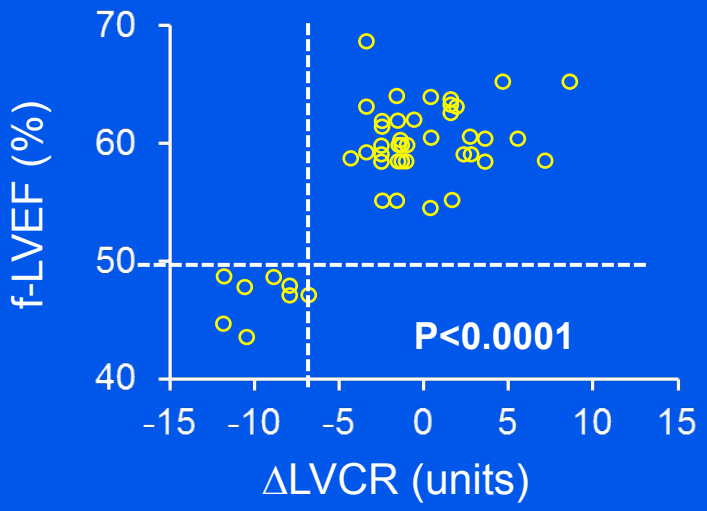
mayo

Cardinale et al. Circulation 2006

Dobutamine Stress Test







Civelli et al: Int J Cardiol 111:120, 2006

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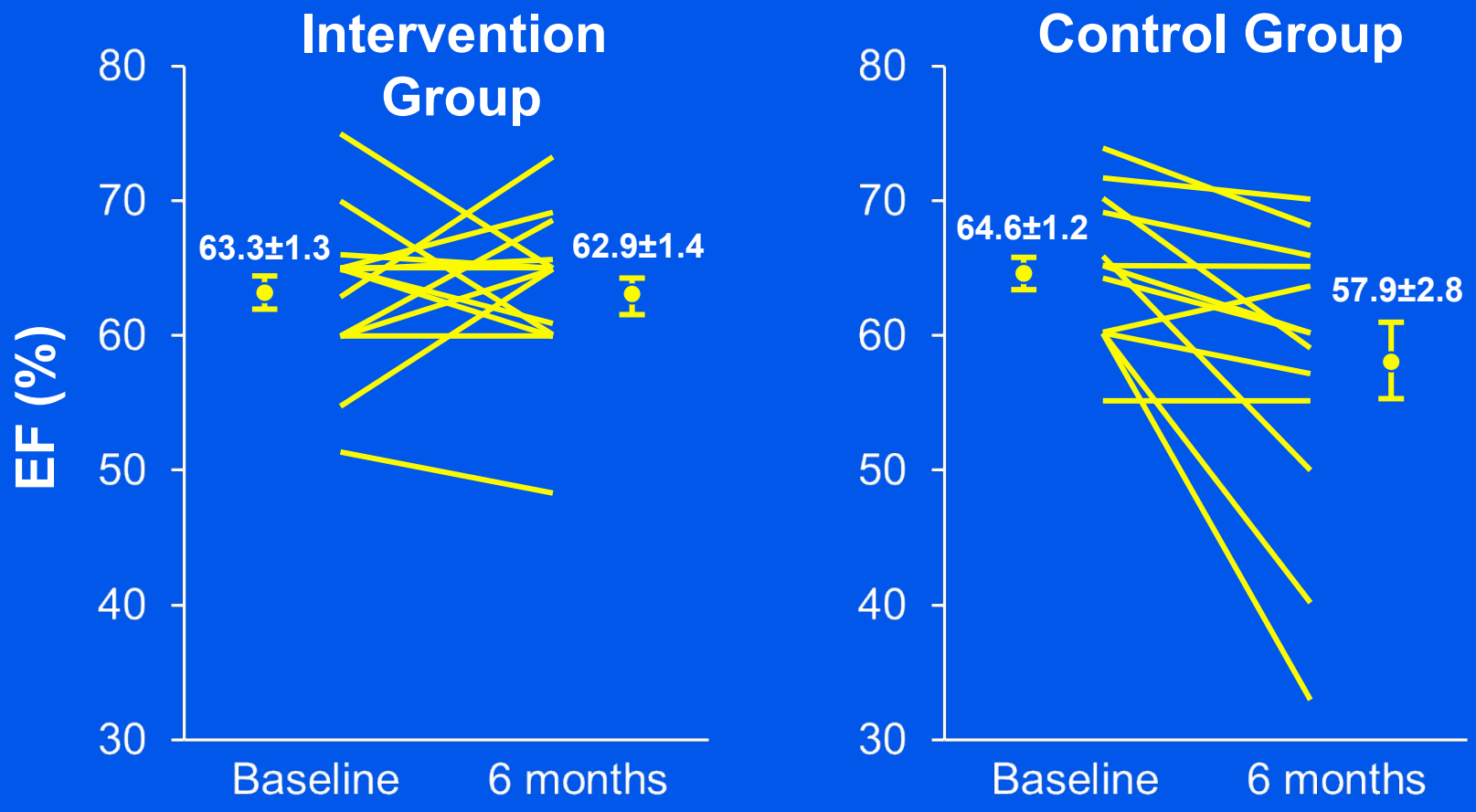
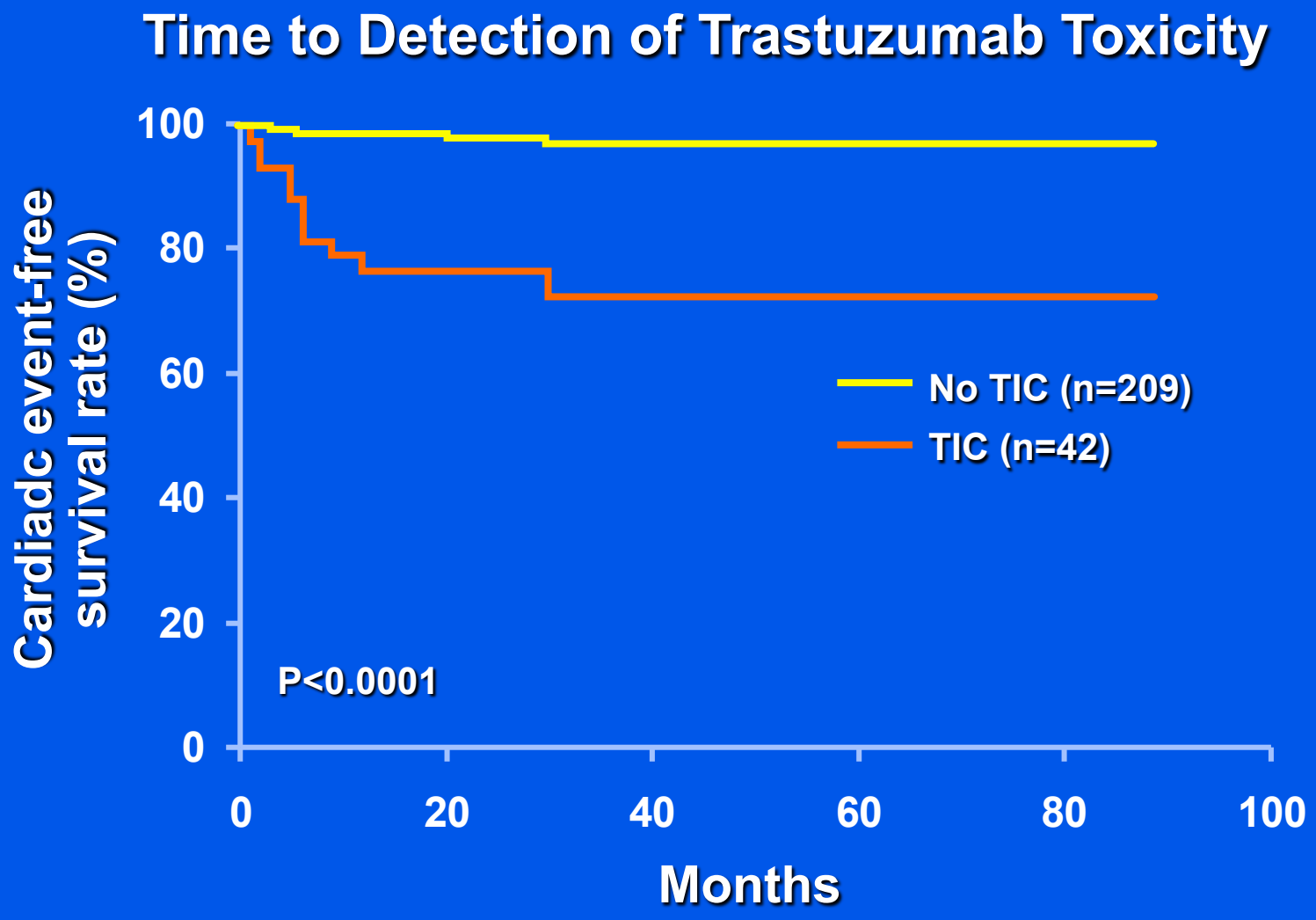
Changes in Ejection Fraction in Treated and Control Groups



Bosch et al: JACC, 2013

Timing of Clinical Effects of Trastuzumab



J Clin Oncology 28(25):3910, 2010

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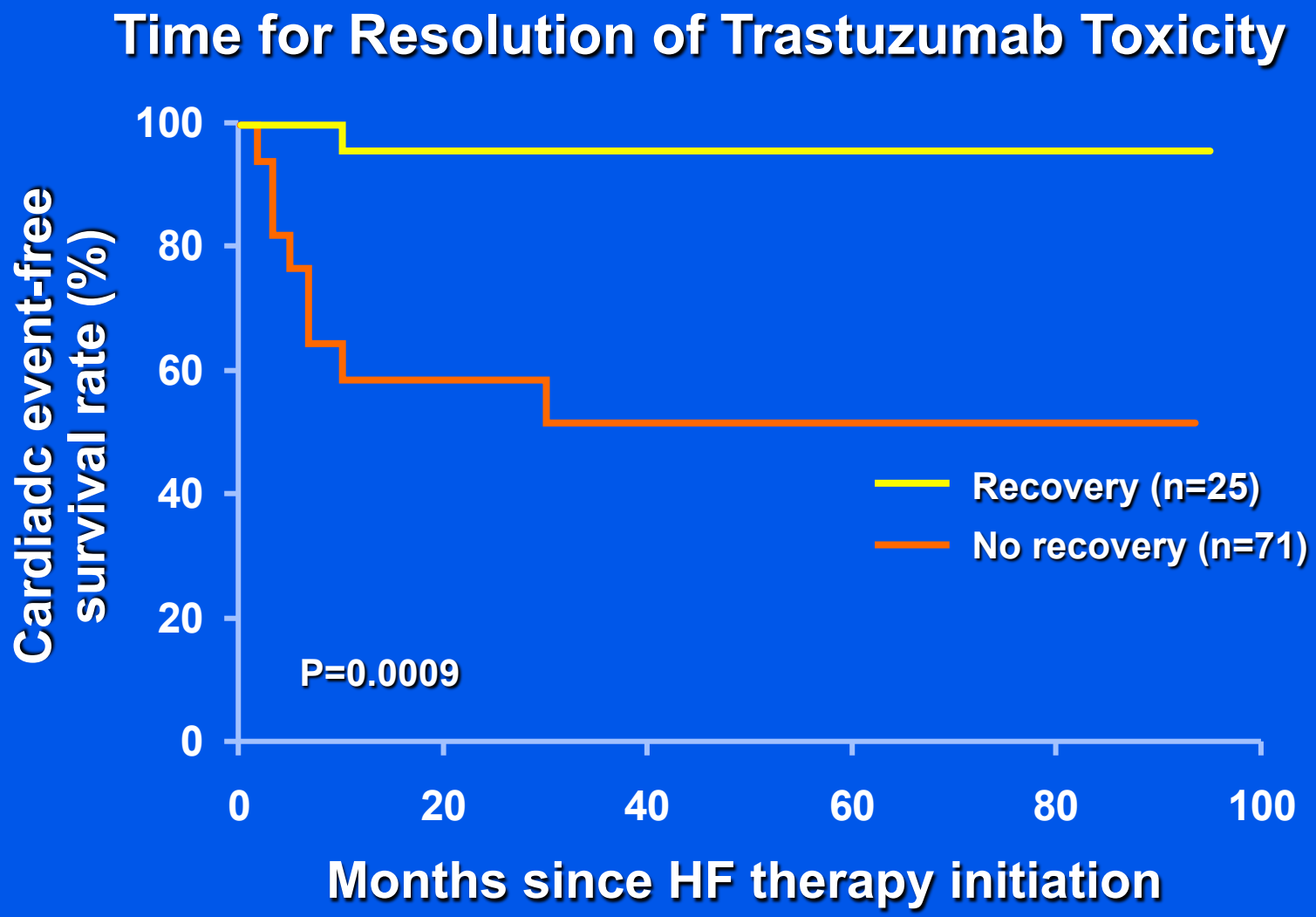
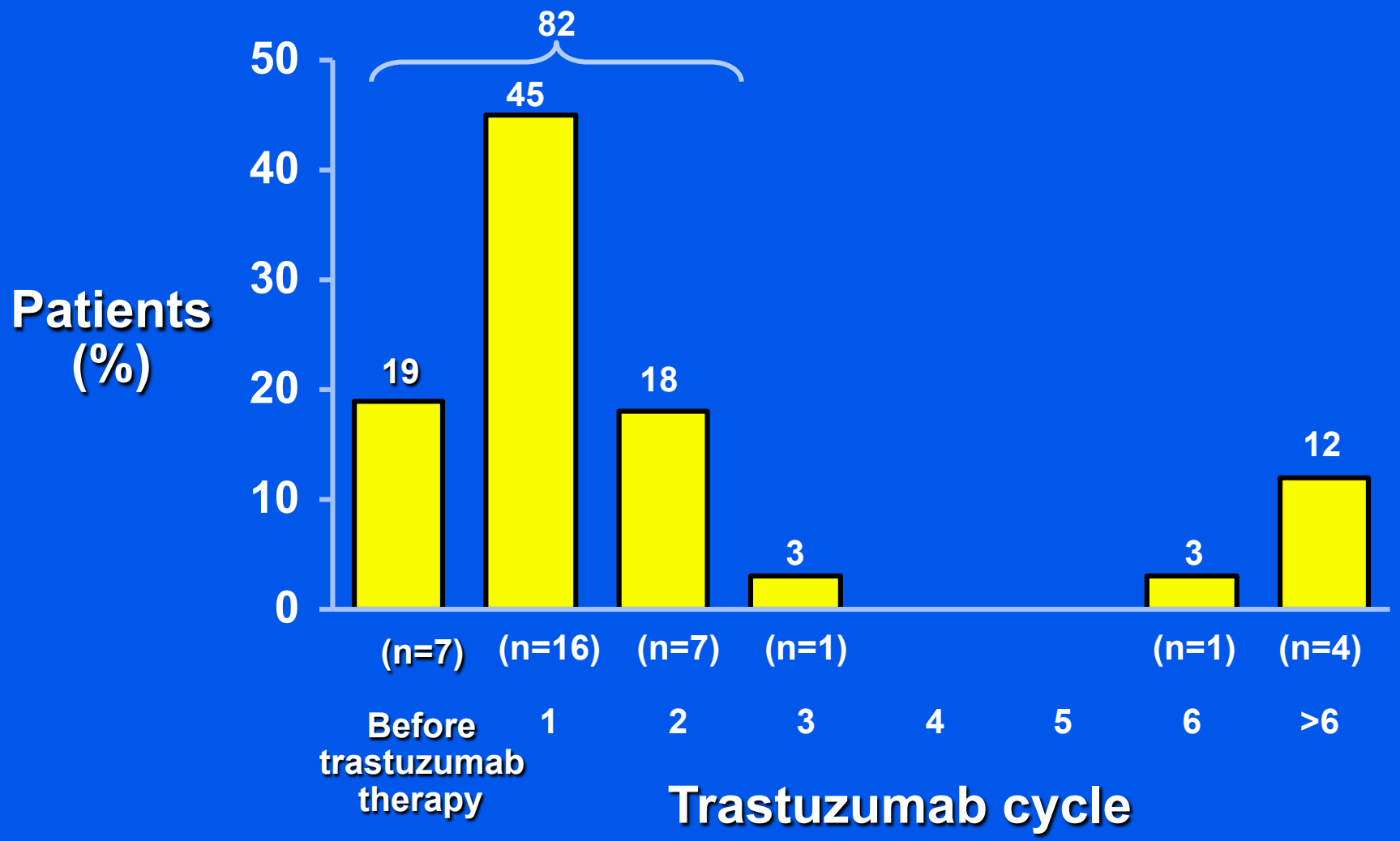
Timing of Clinical Effects of Trastuzumab



J Clin Oncology 28(25):3910, 2010

mayo

Timing of the Detection of Trastuzumab Toxicity



J Clin Oncology 28(25):3910, 2010

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CHARACTERISTICS OF PATIENTS RECOVERING OR NOT FROM CARDIAC DYSFUNCTION

Characteristics	LVEF Recovery (n = 25). No.	%	No LVEF Recovery (n = 17). No.	%	*P*
Age, years	50 ± 8		56 ± 11		.047
Hypertension	7	28	4	21	1.00*
Diabetes	0	0	0	0	1.00*
Hypercholesterolemia	1	4	0	0	1.00*
Current or past smokers	6	24	3	18	.71*
Family history of CAD	2	8	2	12	1.00*
LVEF before trastuzumab therapy	60 ± 4		61 ± 4		.43
LVEF at trastuzumab withdrawal	44 ± 6		37 ± 6		.001
TNI+ at baseline	0	0	7	41	.001*
TNI+ during trastuzumab treatment	9	36	17	100	<.001
ACEI + BB association	22	88	8	47	.004
Affected breast (left)	16	64	10	59	.73
Metastatic disease	15	60	13	76	.26
Chest wall radiotherapy (left)†	12	48	7	41	.66

MAJOR ADVERSE CARDIAC EVENTS IN PATIENTS WITH NORMAL OR ELEVATED TNI VALUE

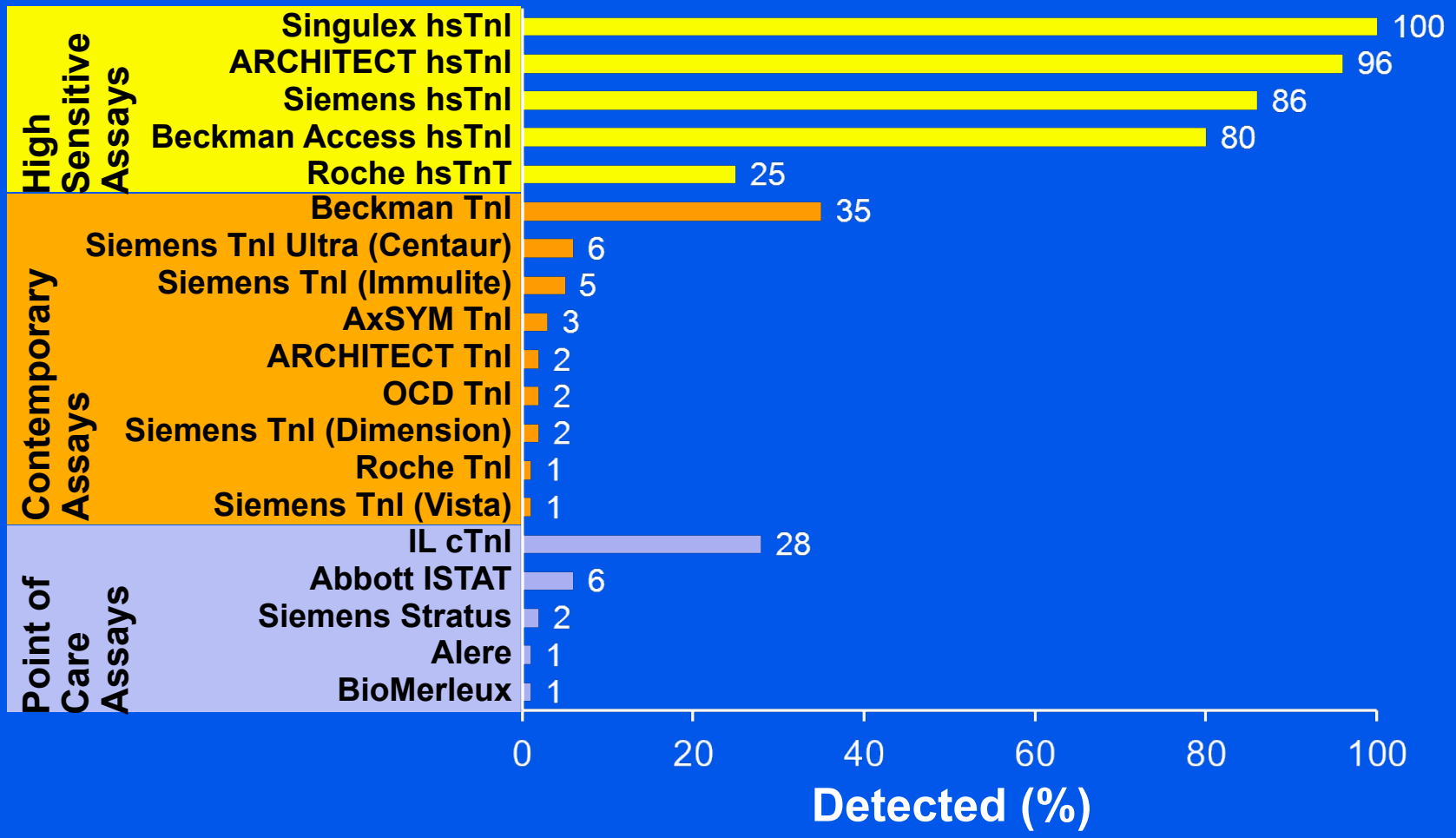
Event	Total (n = 251) No.	%	TNI+ (n = 36) No.	%	Normal TNI (n = 215) No.	%
Severe LVEF reduction (< 30%)	7	3	6	17	1	0.5
Cardiac death	0	0	0	0	0	0
Acute coronary syndrome	2	1	2	5	0	0
Acute pulmonary edema	1	0.5	1	3	0	0
Heart failure	7	3	7	19	0	0
Arrhythmias requiring treatment	5	2	2	8	3	1.4
Cumulative events	22	9	18	50	4	2*

Abbreviations: TNI, troponin I; TNI+, elevated TNI; LVEF, left ventricular ejection fraction.

*$P < .001$ *v* elevated troponin I (by Fisher's exact test).

Reference: J Clin Oncol 2010;28(25):3910 -3916.

Comparison of Normals Detected With Various Assays



Apple et al: Clin Chem 58(11):56, 2012

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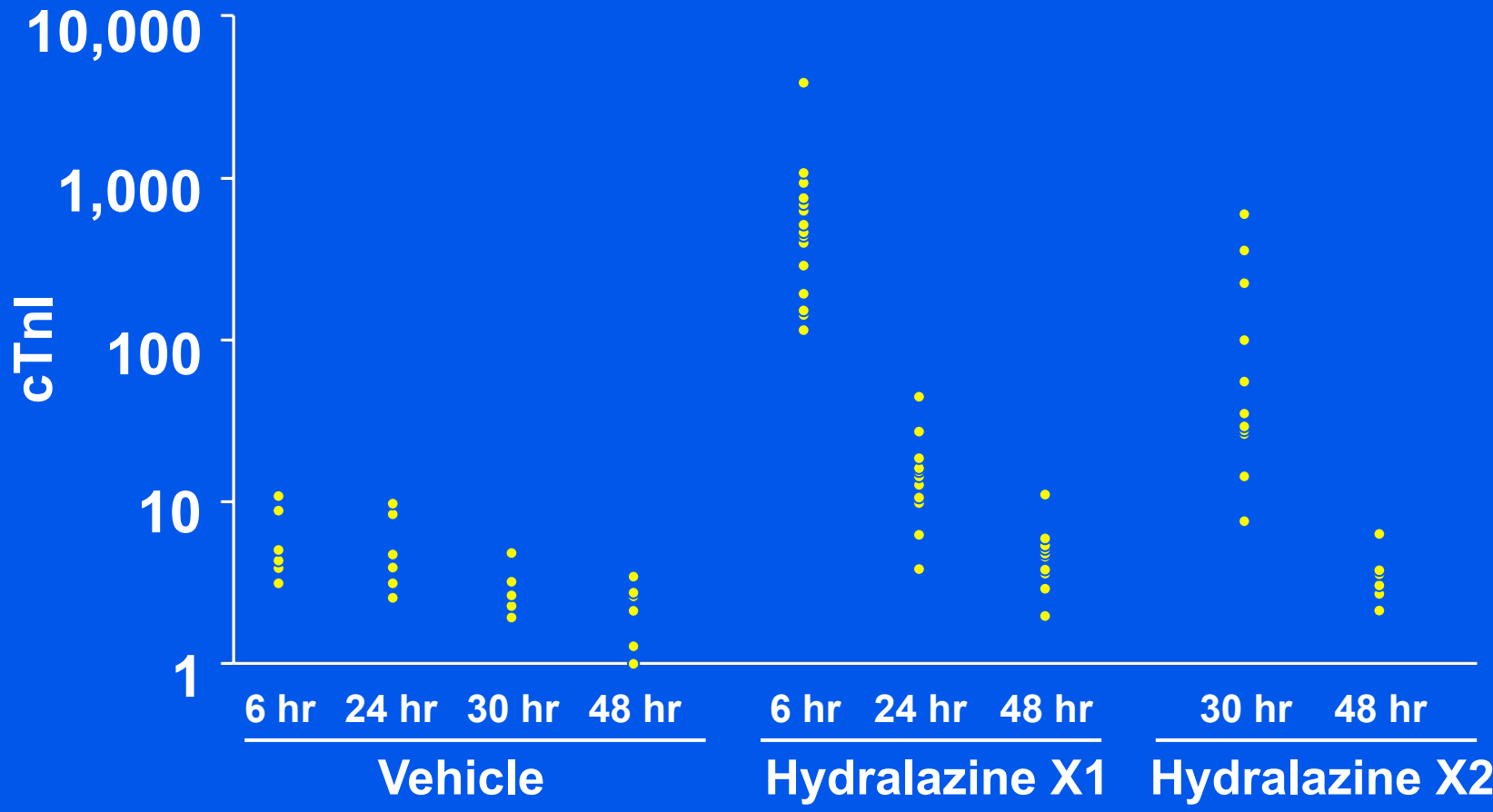
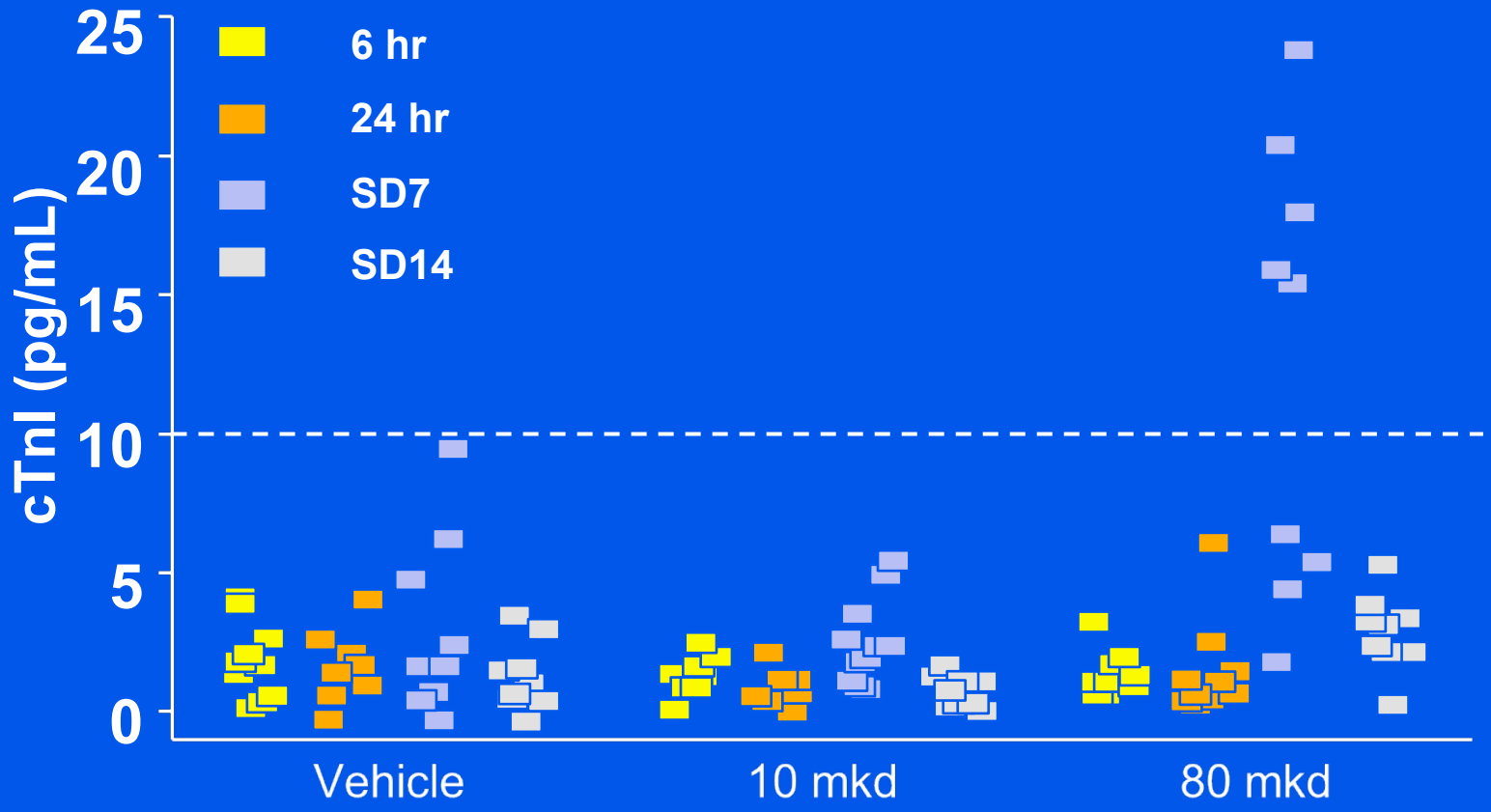
cTnI (Singulex) After Hydralazine in Rats
Dose of 25 mg/kg



Mikaelian et al, 2009

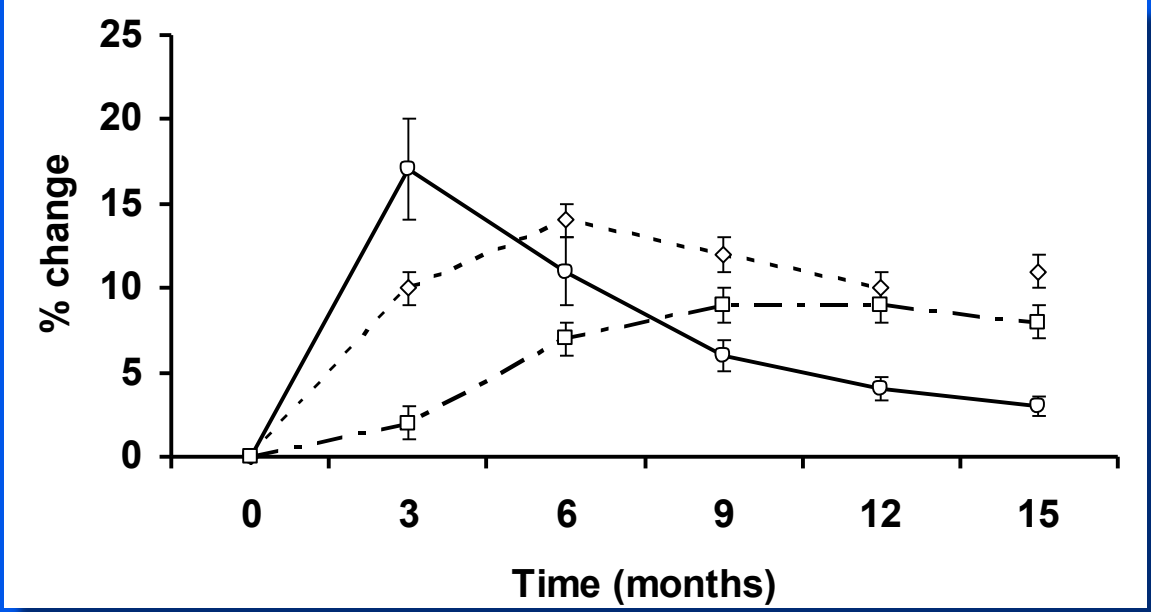
cTnI (Singulex) After Rosiglitazone in Rats



Hirkaler et al, 2010

Use of echo and hsTnI to predict cardiotoxicity following trastuzumab and anthracycline chemotherapy

Time course of mean change hsTnI (solid), longitudinal strain (dotted) and LVEF (dashed) following AC based chemotherapy



- 19% of patients had concentrations of hsTnI >45pg/mL immediately after treatment.
- Of these, 54% had cardiotoxicity during follow-up.
- Troponin I measured 3, 6 and 9 months was not predictive of later cardiotoxicity.

Sawaya, et al, Circ Imaging 2012;5:596–603

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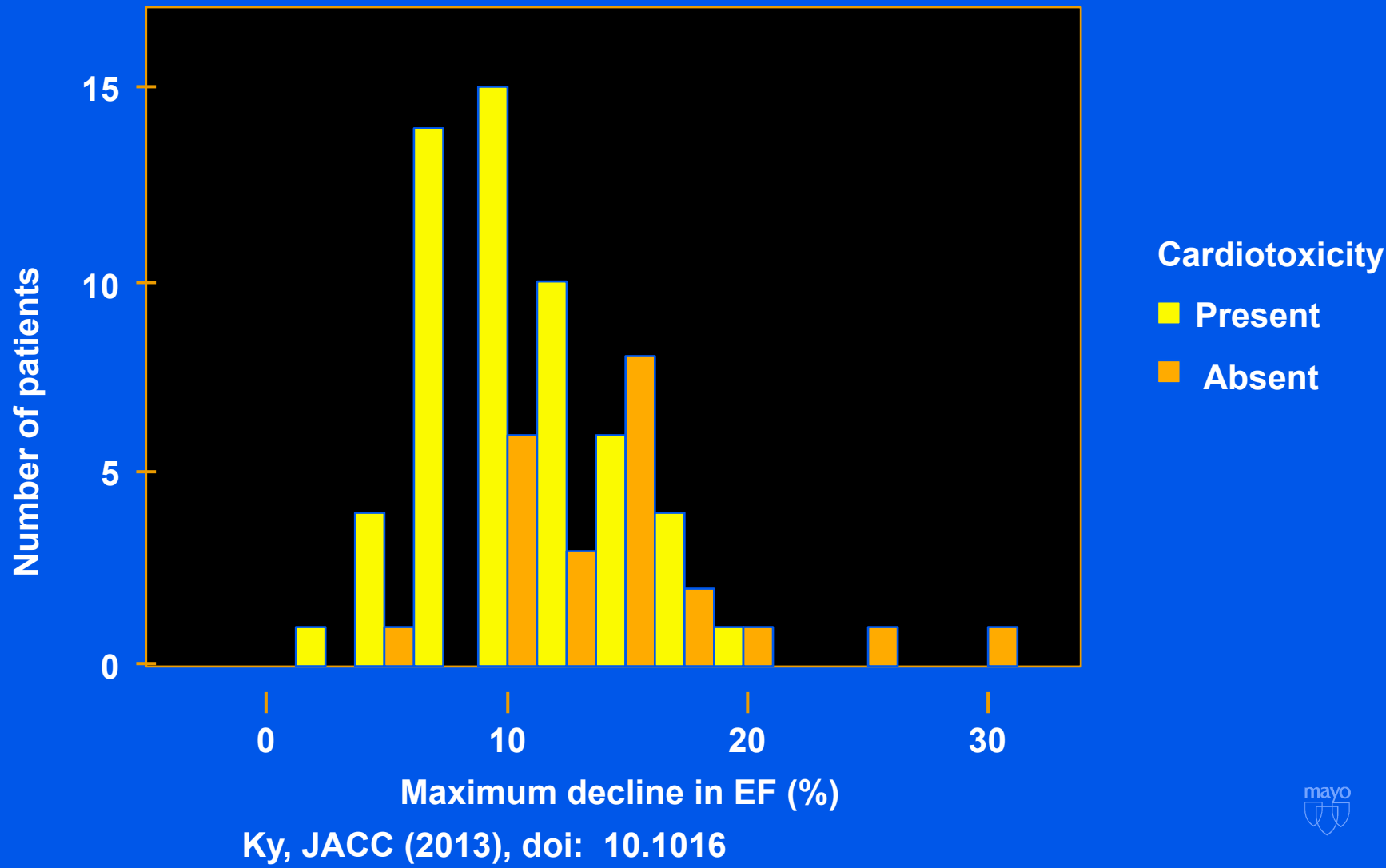
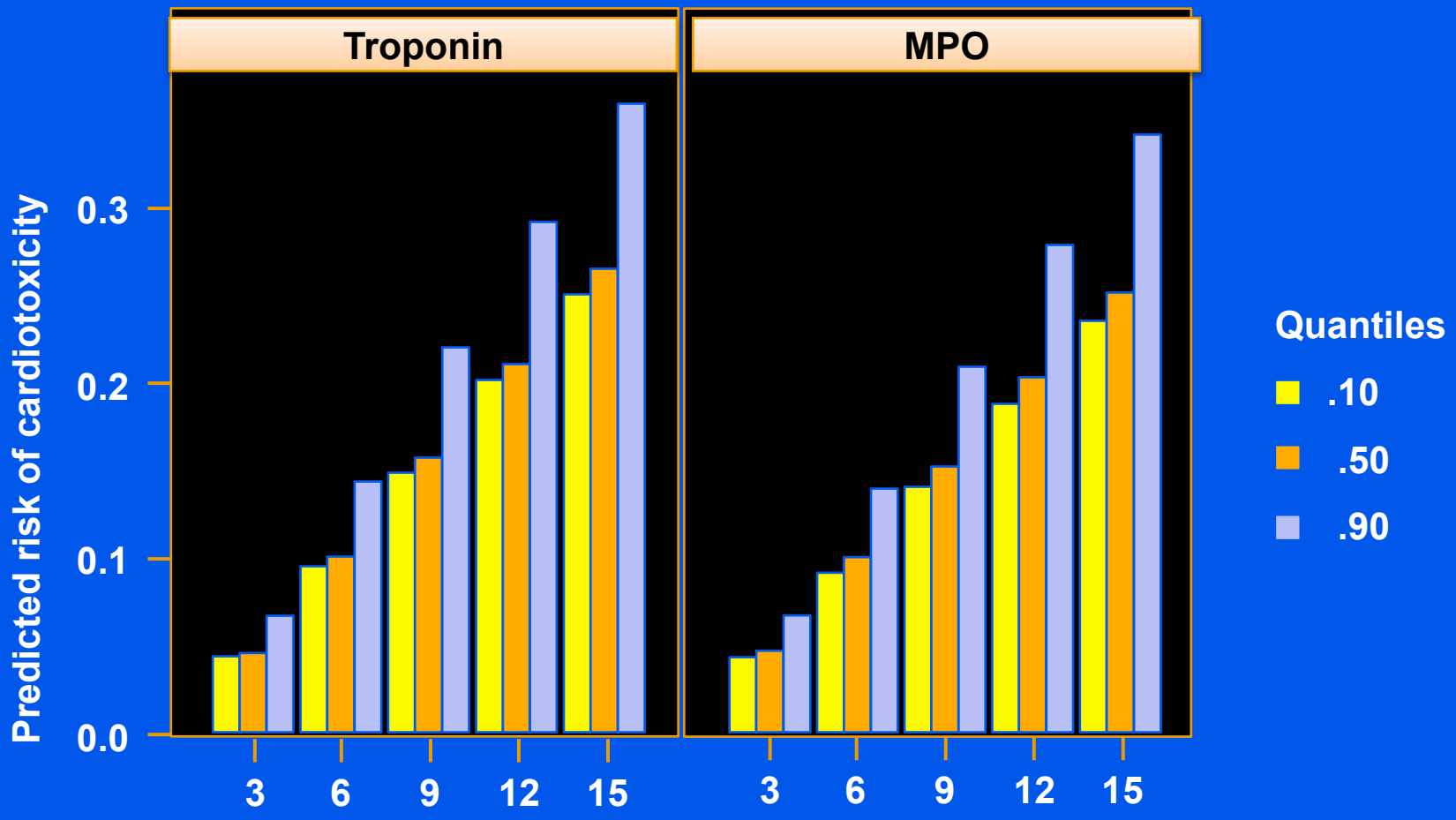
Decline in Ejection Fraction in Those with Cardiotoxicity



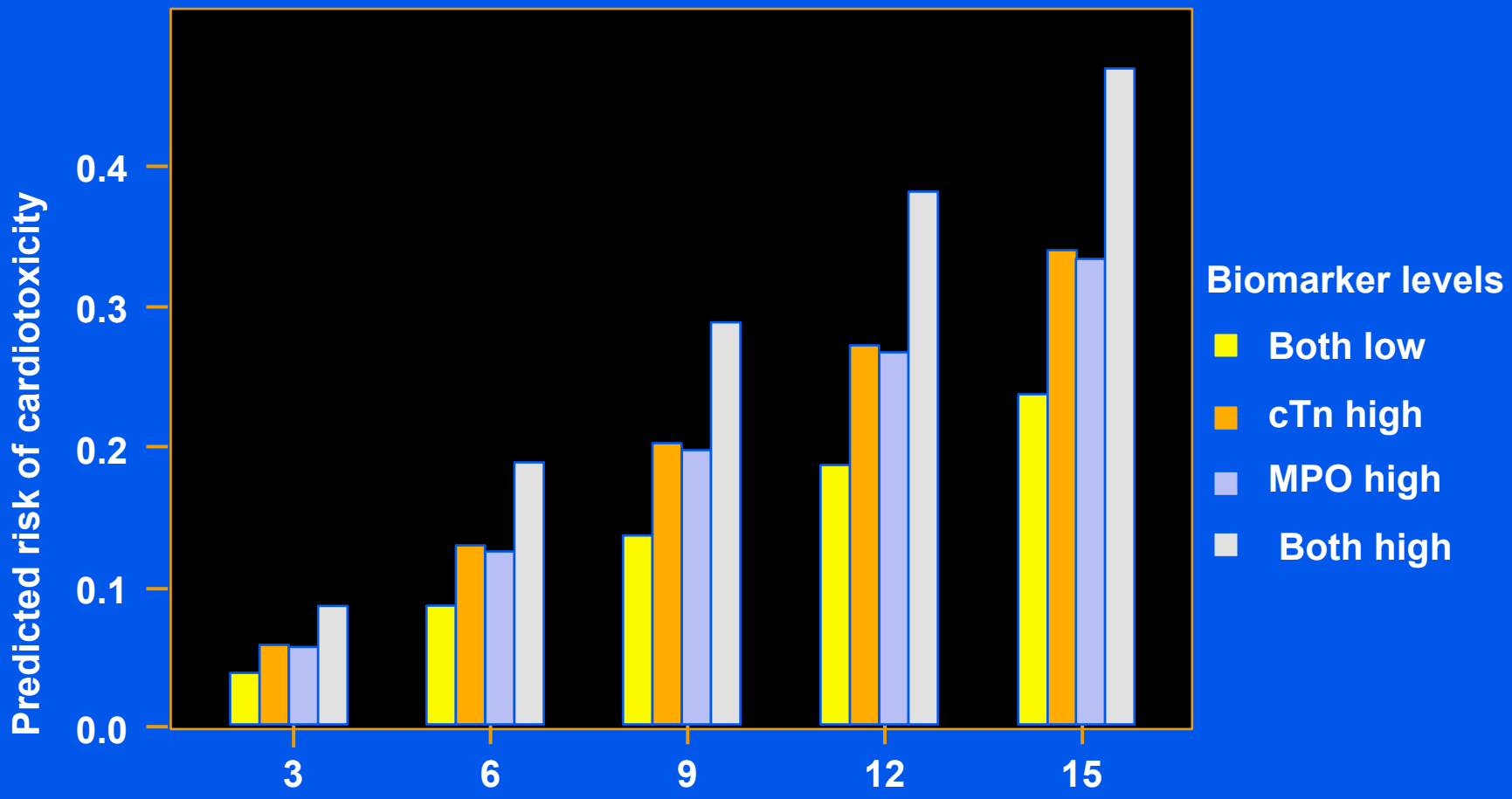
Ky, JACC (2013), doi: 10.1016

Prediction of Cardiotoxicity with hscTnI (Siemens) and MPO by Quartiles of Change from Baseline to Visit One



Ky, JACC (2013), doi: 10.1016

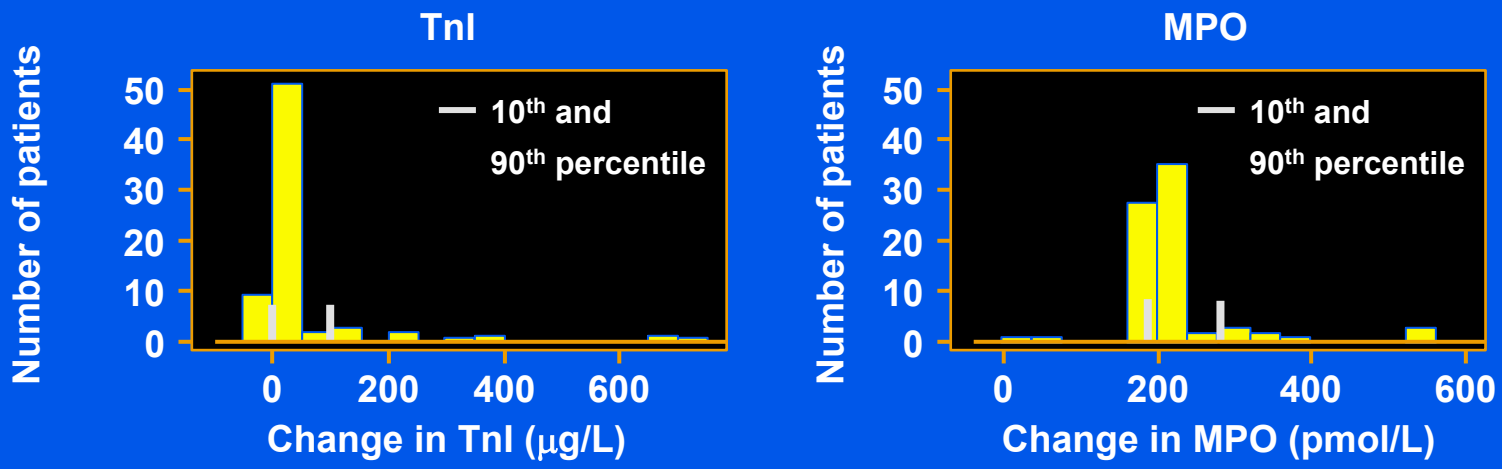
Predication of Cardiotoxicity With hs-cTnI (Siemens) and MPO by Quartiles of Change for Each



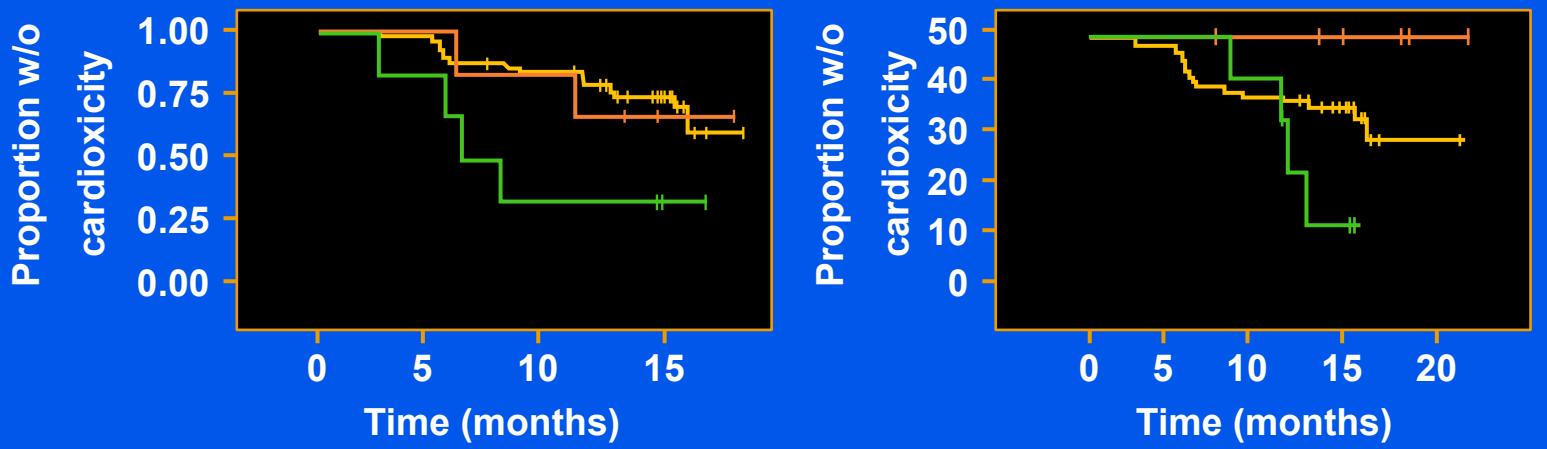
Ky, JACC (2013), doi: 10.1016

Change in cTnI and MPO

Decline in Ejection Fraction in Those with Cardiotoxicity



Changes in cTnI and MPO



Ky, JACC (2013), doi: 10.1016

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Longitudinal Association Between Increases in Biomarkers Relative to Baseline and Cardiotoxicity

	Risk of cardiotoxicity at the same visit				Risk of cardiotoxicity at the subsequent visit			
	Univariable		Multivariable		Univariable		Multivariable	
Biomarker	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
GDF-15	1.80 (1.20-2.69)	0.007	2.16 (1.49-3.13)	<0.001	1.59 (1.06-2.40)	0.02	1.62 (1.07-2.44)	0.01
MPO	1.37 (1.11-1.69)	0.02	1.31 (1.08-1.60)	0.004	1.32 (1.11-1.58)	0.003	1.30 (1.06-1.58)	0.006
PlGF	3.77 (1.43-9.89)	0.04	3.09 (1.24-7.72)	0.008	2.61 (0.95-7.19)	0.08	3.27 (1.19-8.94)	0.01
hsCRP	1.18 (0.97-1.44)	0.07			1.12 (0.88-1.42)	0.19		
hsTnI	1.04 (0.91-1.20)	0.30			1.08 (0.96-1.20)	0.14		
Gal-3	1.31 (0.86-1.99)	0.14			1.60 (1.12-2.28)	0.04		
NT-proBNP	1.13 (0.86-1.49)	0.19			1.07 (0.83-1.38)	0.31		
sFlt-1	1.08 (0.54-2.16)	0.41			0.86 (0.49-1.50)	0.31		

Putt et al: Clinical Chemistry 61:9, 2015

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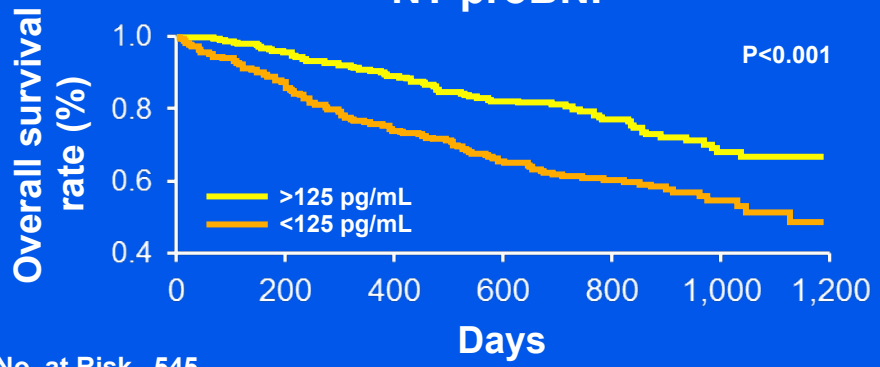
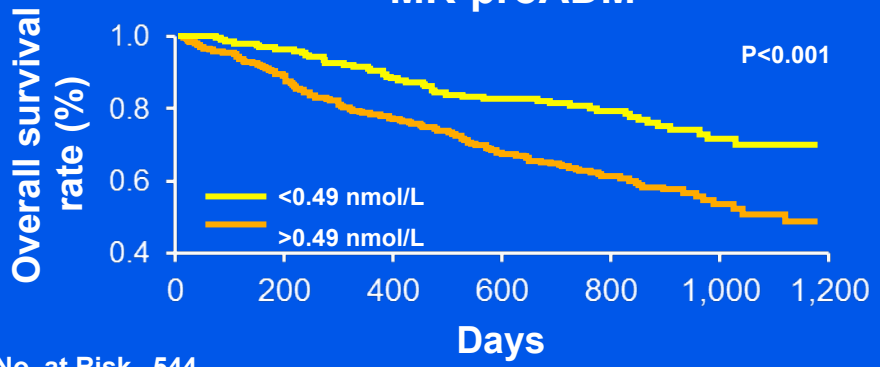
Impact of Biomarkers at Baseline in Cancer Patients

NT-proBNP



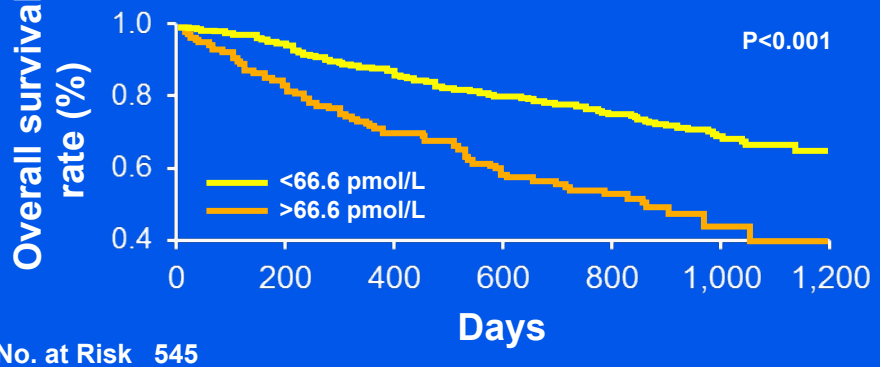
No. at Risk	545						
<125pg/mL	268	257	239	185	141	62	67%
>125pg/mL	277	241	205	153	112	43	49%

MR-proADM



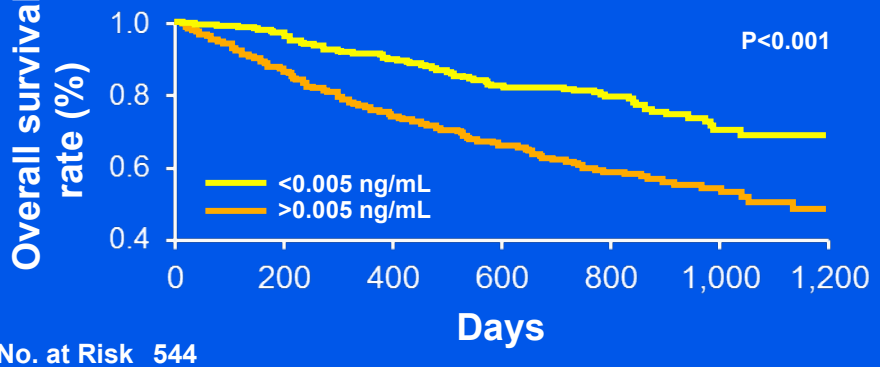
No. at Risk	544						
<0.49 nmol/L	192	185	170	142	109	57	71%
>0.49 nmol/L	352	312	273	196	144	49	50%

CT-proET-1



No. at Risk	545						
<125pg/mL	395	374	340	271	204	95	65%
>125pg/mL	150	124	104	67	49	11	38%

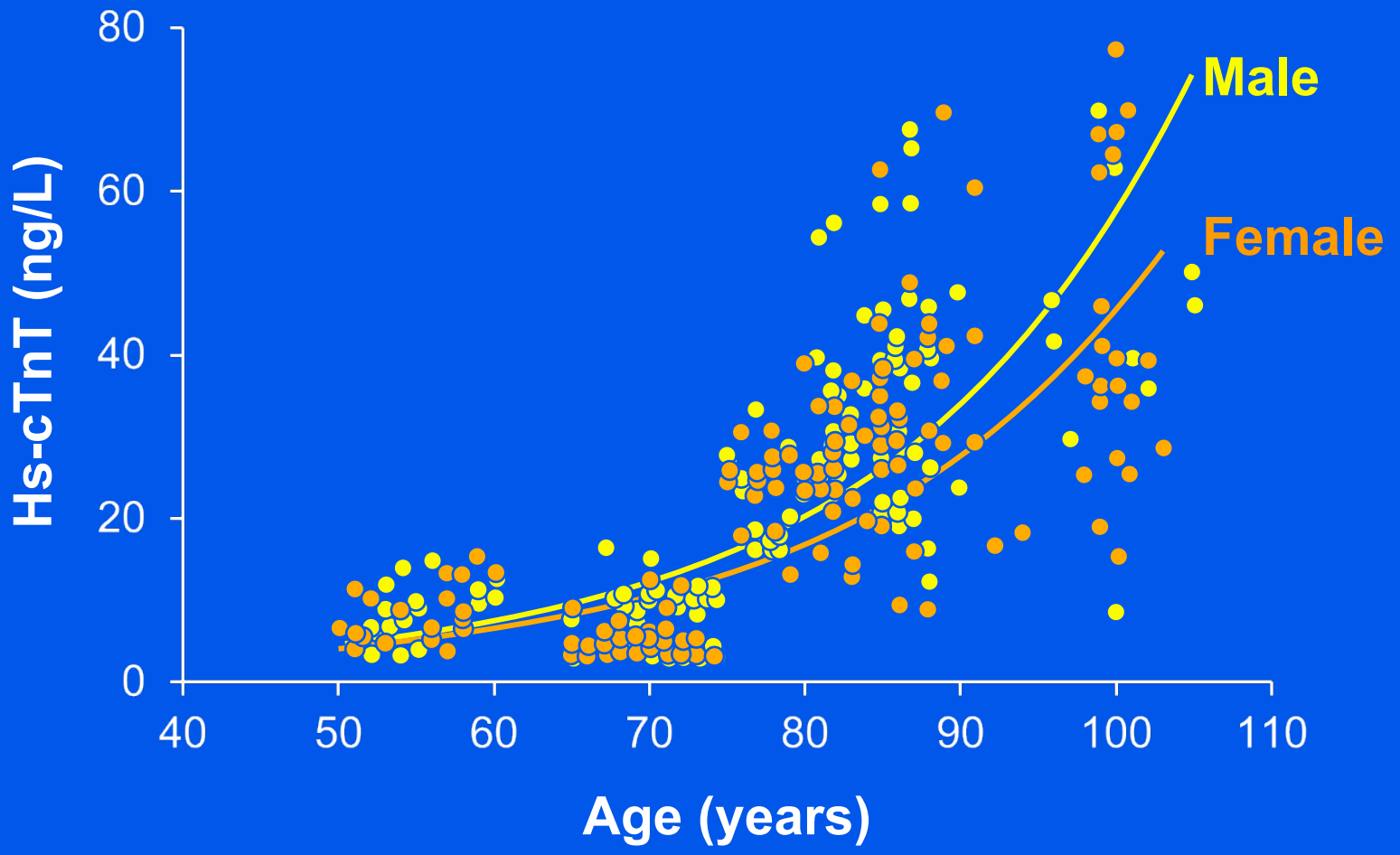
hsTnT



No. at Risk	544						
<0.005 ng/mL	271	262	243	198	150	59	69%
>0.005 ng/mL	273	236	201	140	104	47	48%

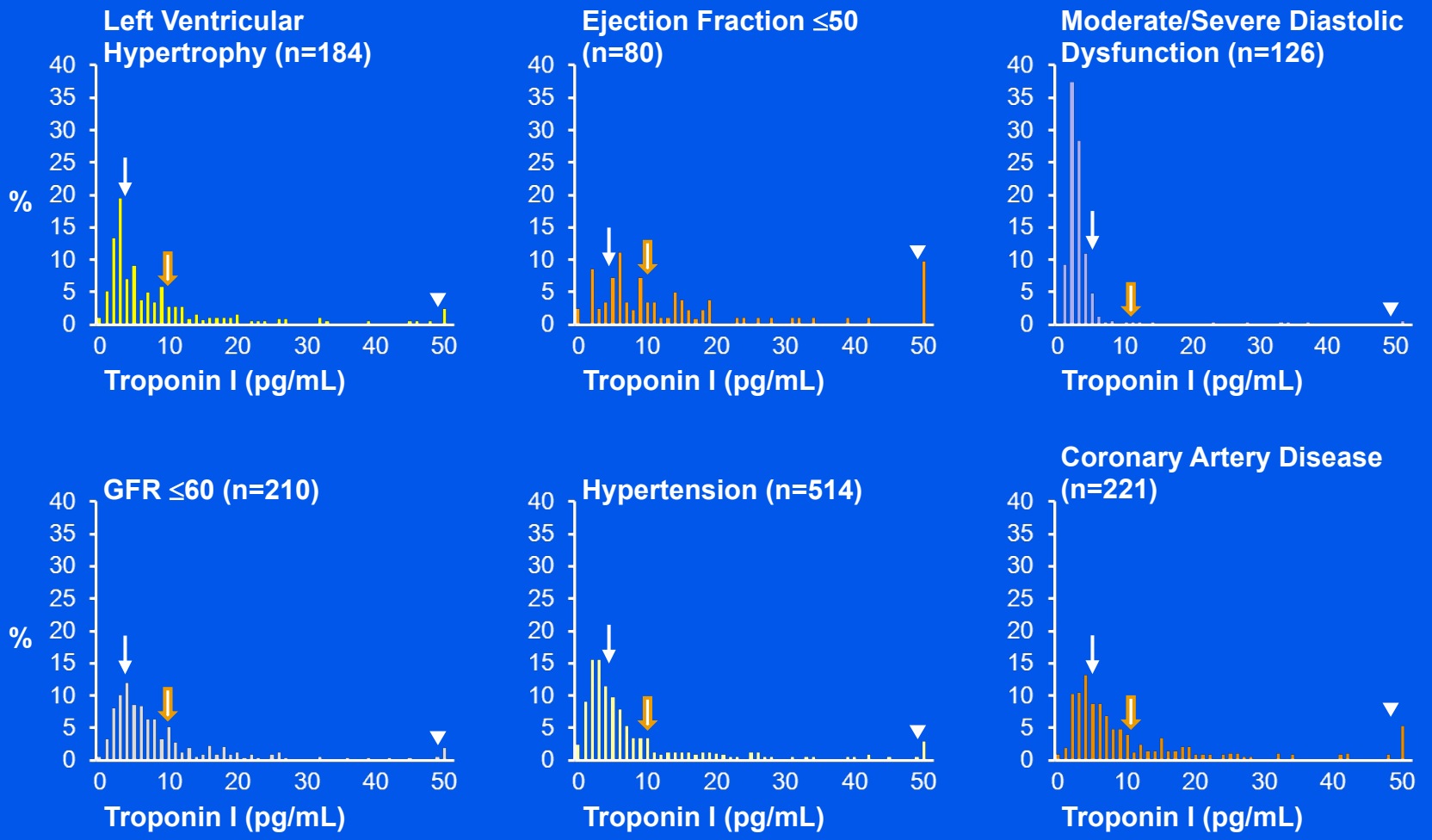
Pavo et al: Heart 0:1-7, doi:10.1136; **2015**

Hs-cTnT Reference Values According to Age and Gender



Mechanisms of Aging and Development 2013

Change in hscTnI Values with Comorbidities
Siemens hscTnI Assay



McKie, Jaffe, Clin Chem 59:7, 2013

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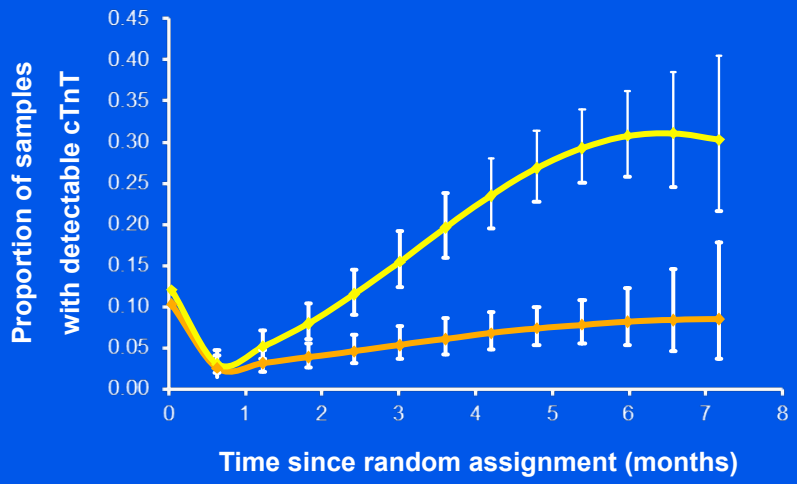
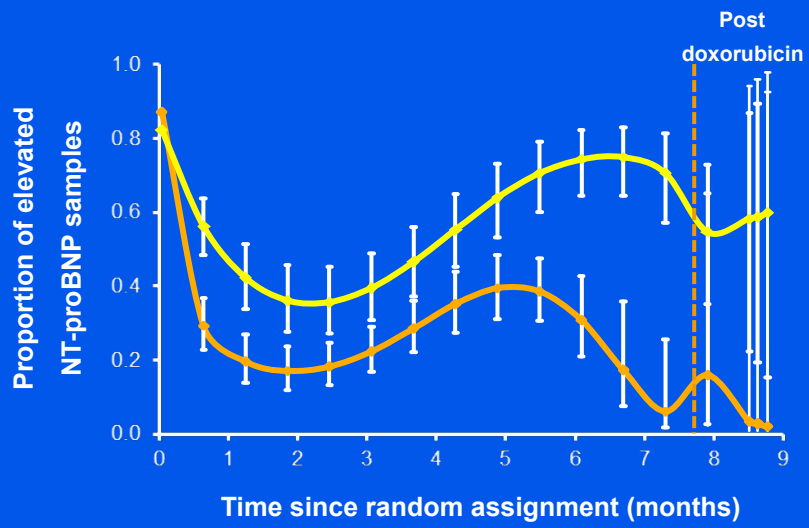
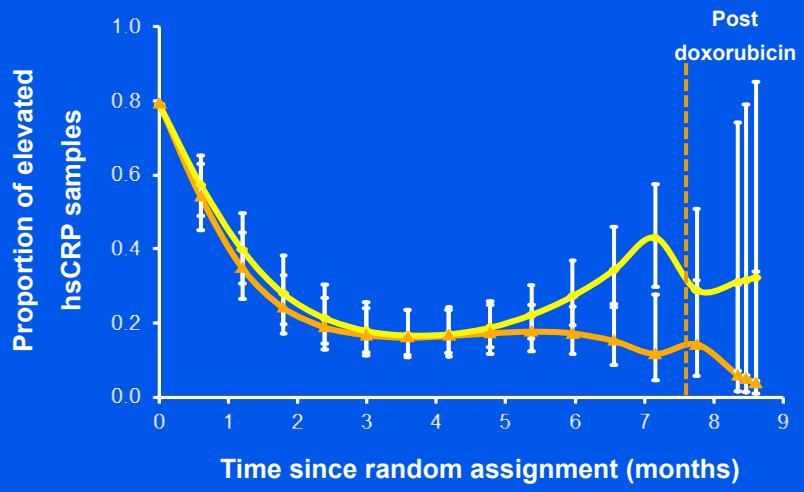
Frequency of Elevated Biomarkers Over Time







Lipshultz et al: J Clin Oncol 30:1042, 2012

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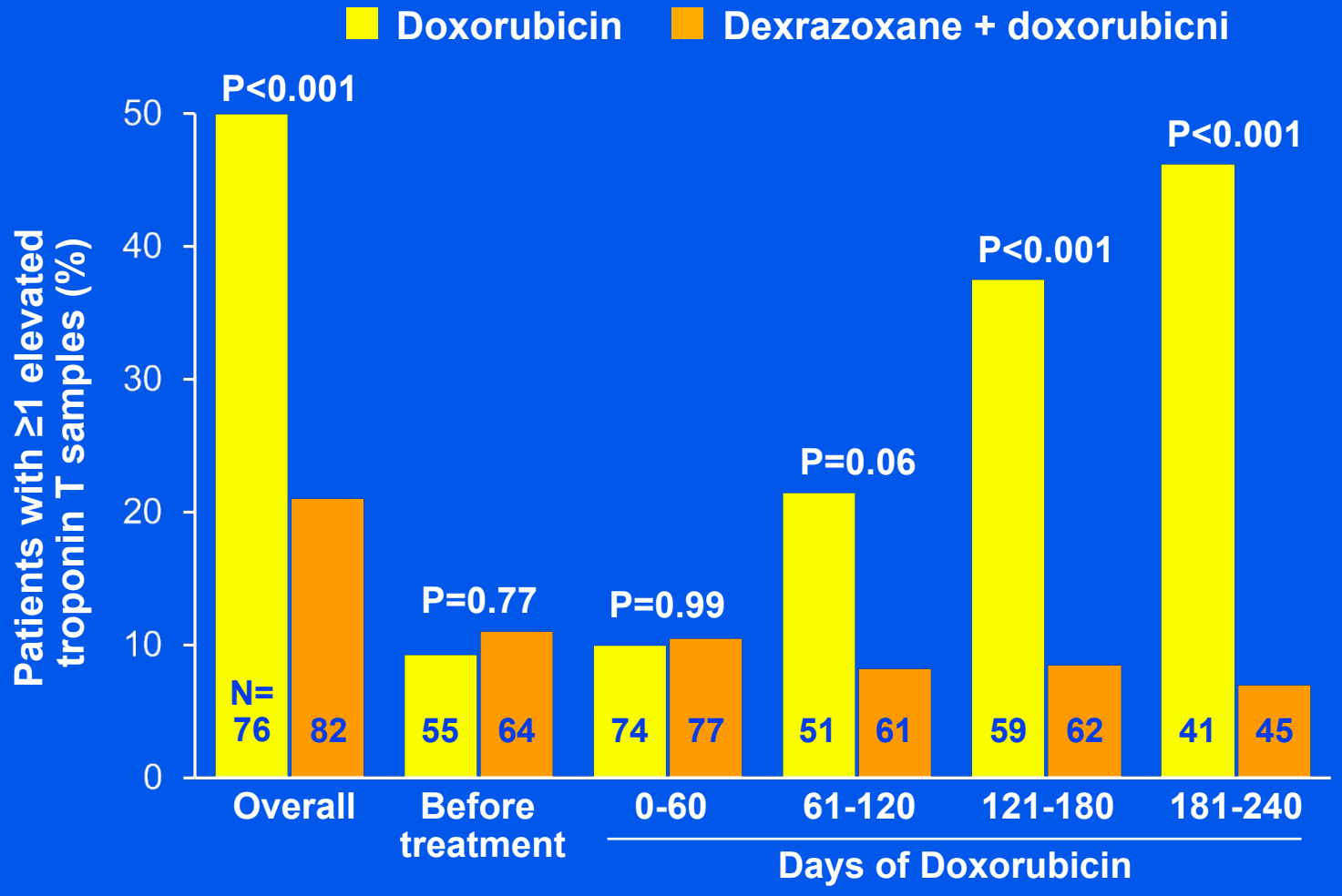
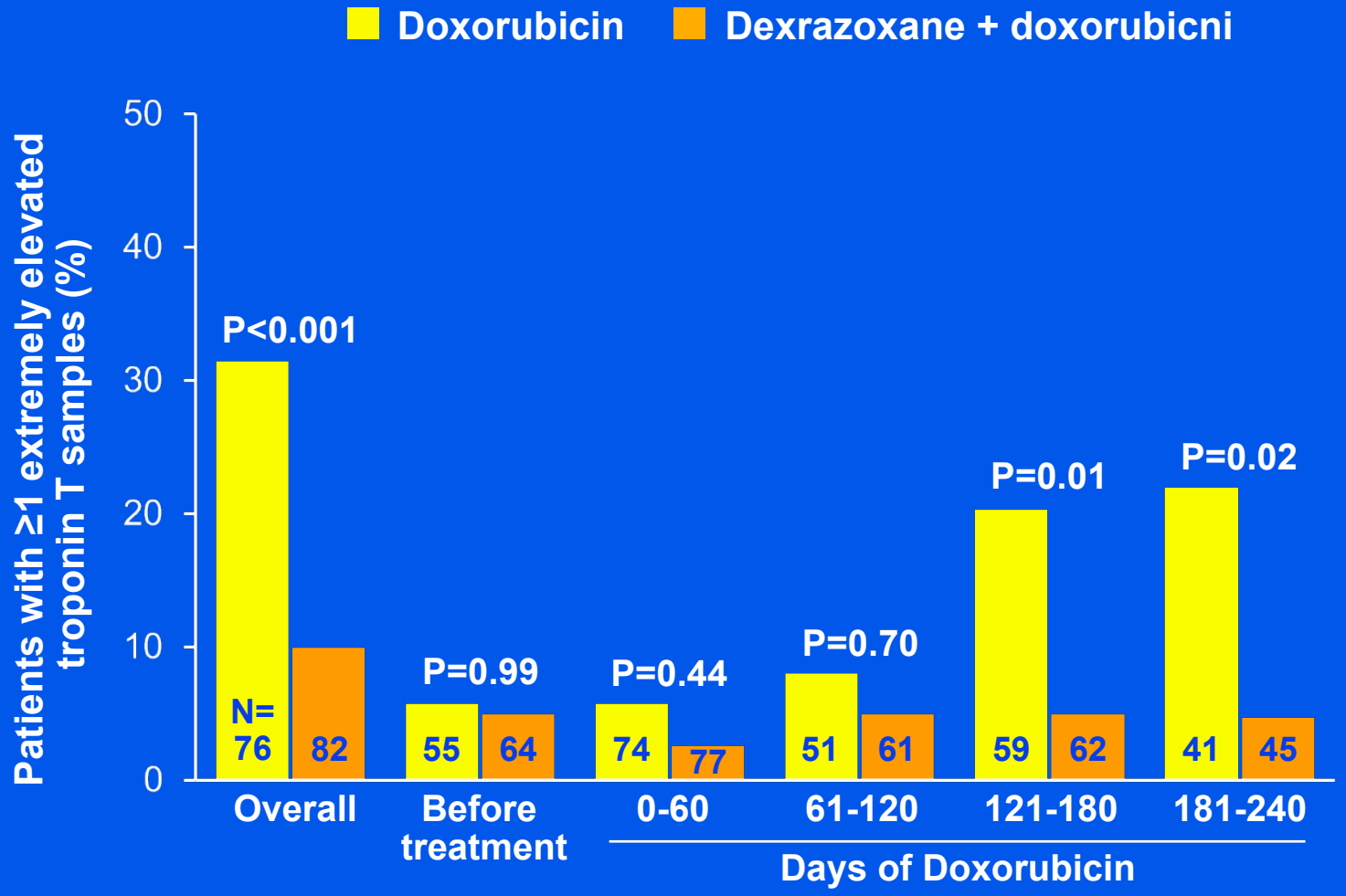
Effect of Dexrazoxane on cTnT Values



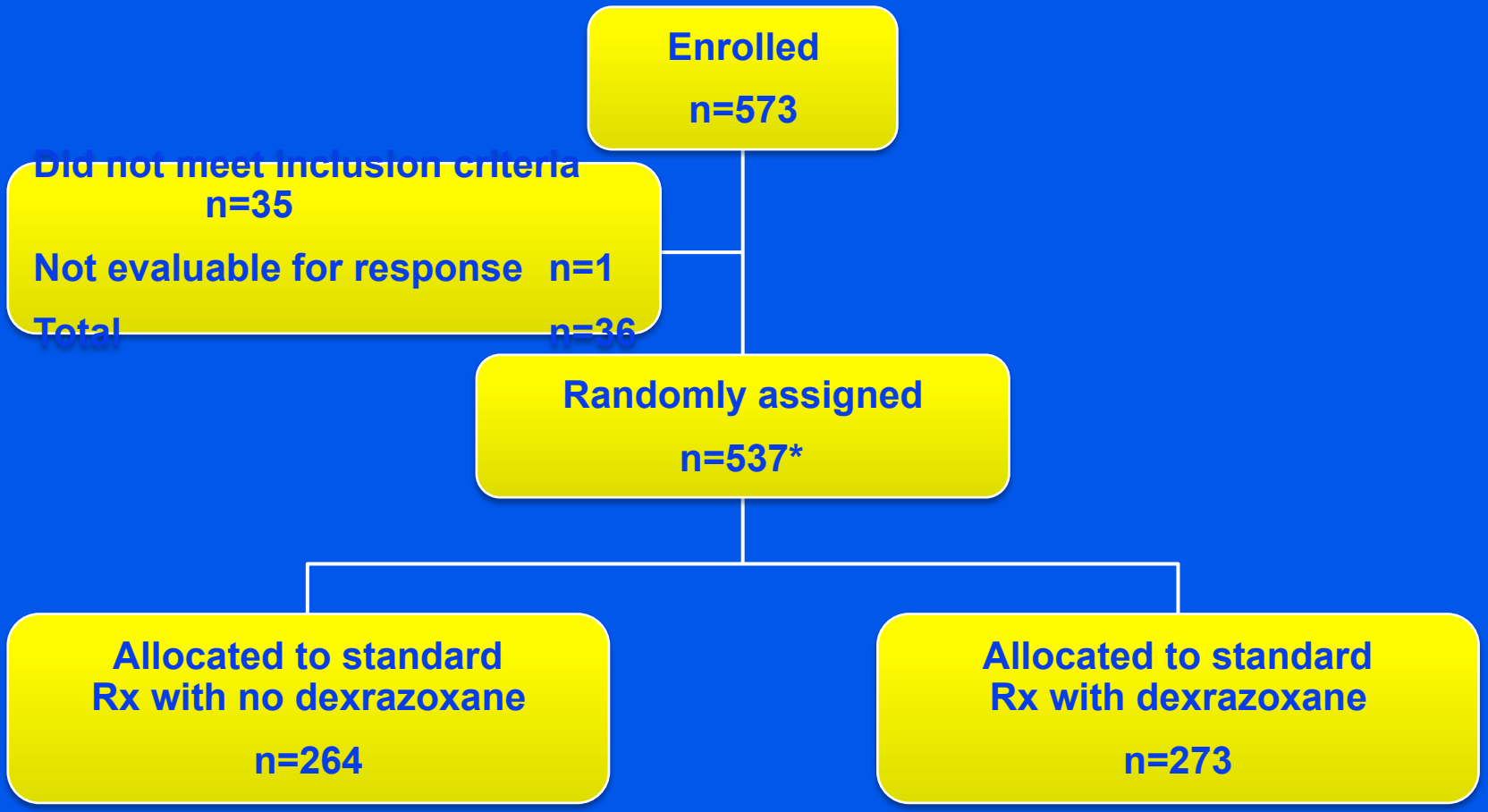
Lipshulz et al: NEJM 351:145, 2004

Effect of Dexrazoxane on cTnT Values



Lipshulz et al: NEJM 351:145, 2004

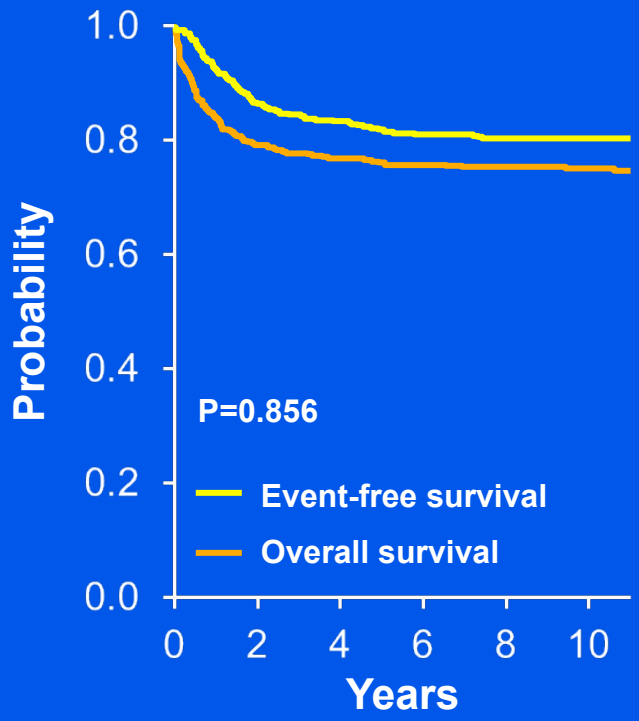
Randomization Schema



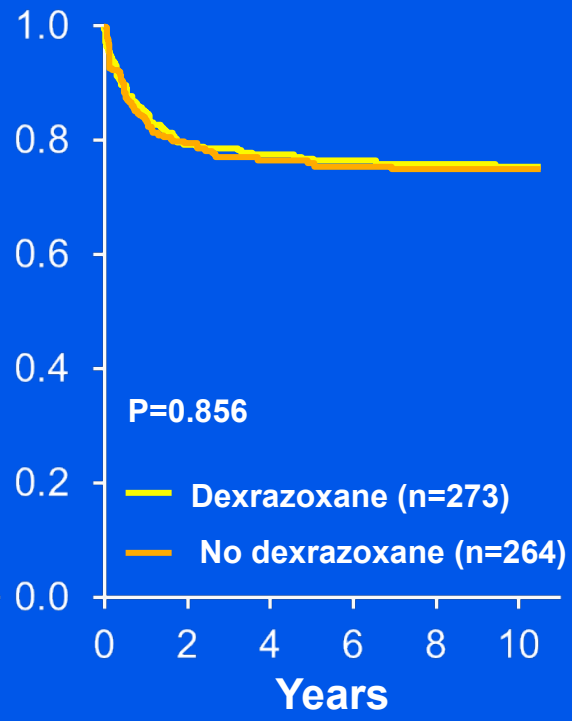
Asselin et al: J Clin Oncol 34:854, 2015; *Sept 2000, based on interim analysis for efficacy, Data Safety Monitoring Committee closed methotrexate randomization

Overall Results

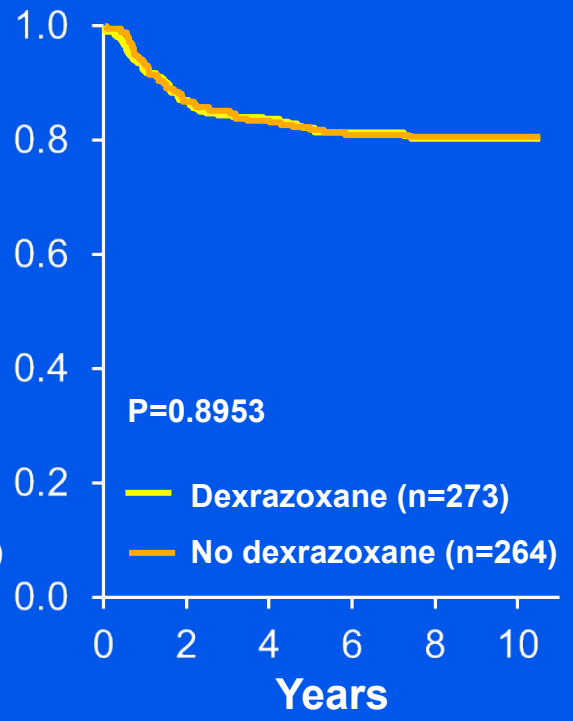
All Eligible, Evaluable Patients Enrolled



Event-Free Survival by Treatment Group



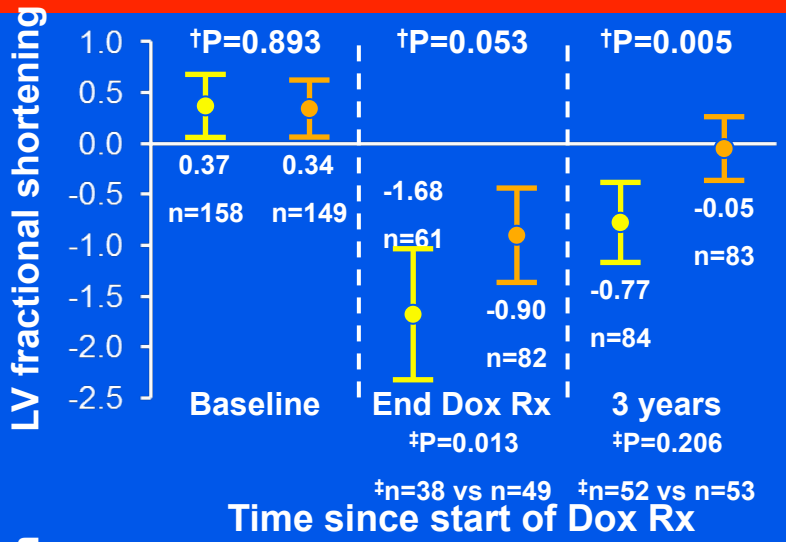
Overall Survival by Treatment Group

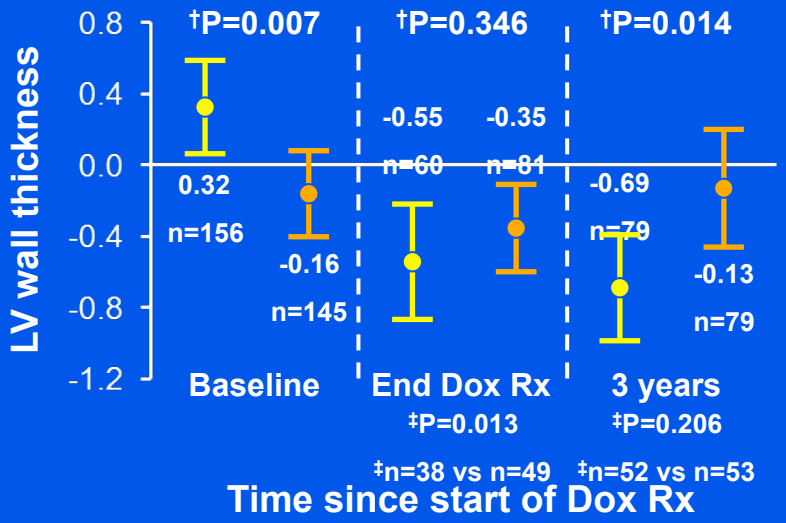


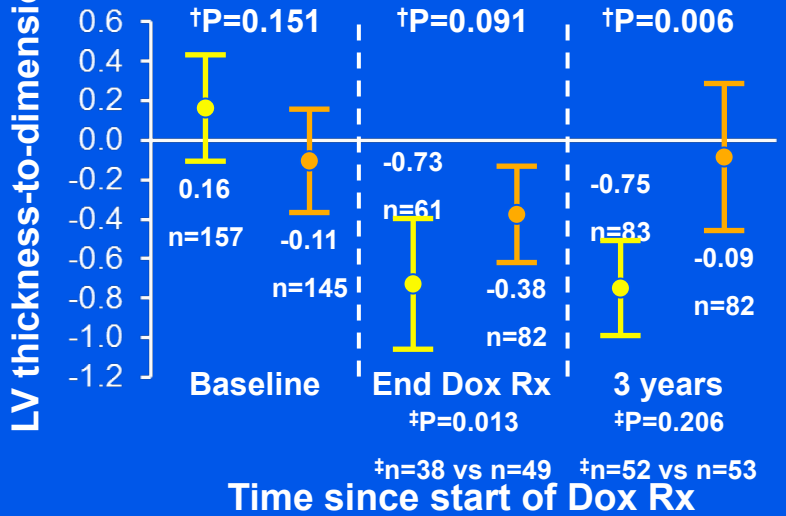
At risk	273	216	202	176	153	113	273	236	218	189	159	115
Event	0	56	5	3	1	1	0	36	8	6	2	0
At risk	264	208	194	176	142	94	264	277	211	189	152	102
Event	0	54	8	2	1	0	0	35	9	5	1	0

Asselin et al: J Clin Oncol 34:854, 2015

Echocardiographic Results
Z Score





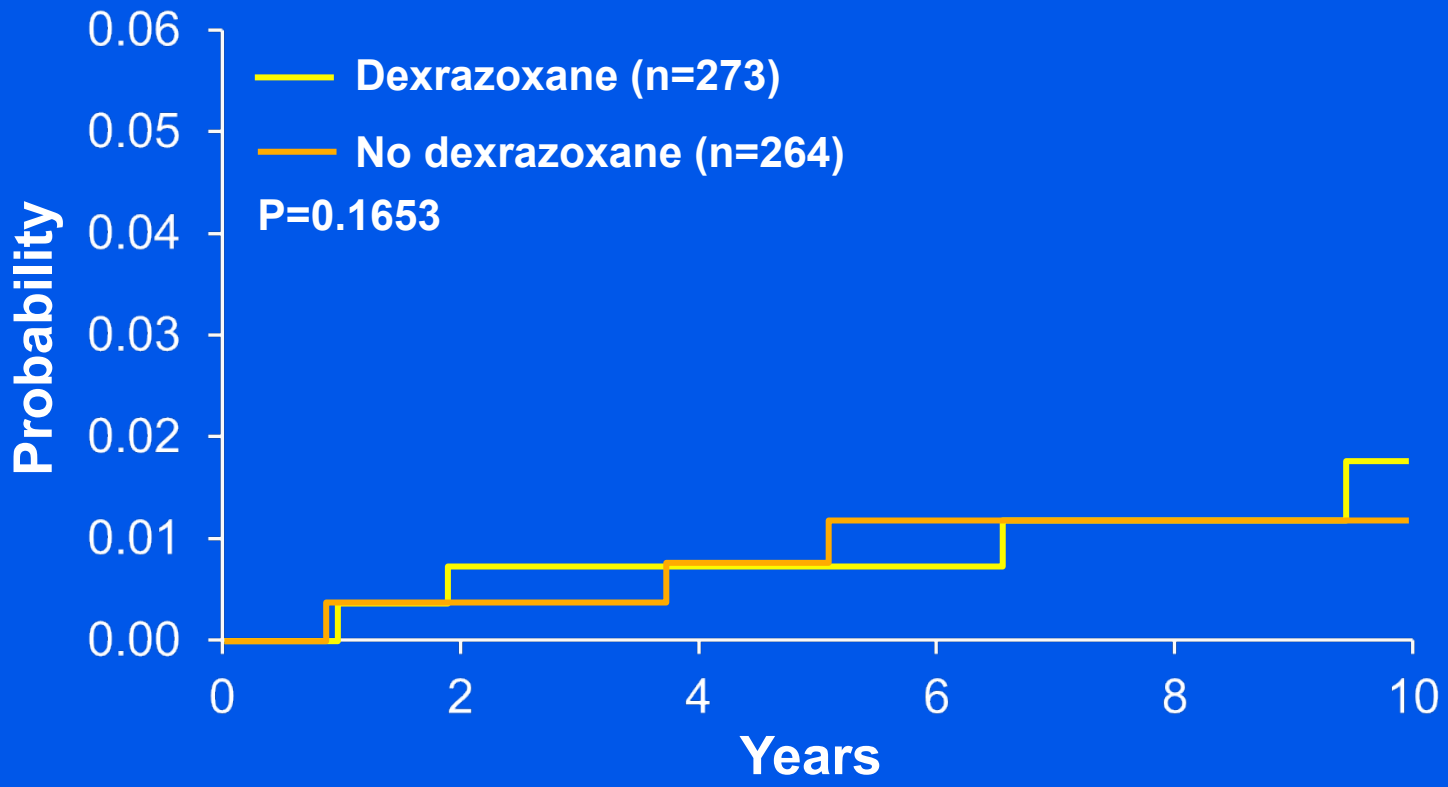


Standard Rx only

Dex + standard Rx

Asselin et al: J Clin Oncol 34:854, 2015; †P comparing 2 groups at each time point;
‡P for differences in change in mean z scores since BL in Dox vs Dox + Drz-treated pt

Frequency of Second Malignancies



At risk	273	216	202	176	153	113
Event	0	2	0	0	1	1
At risk	264	208	194	176	142	94
Event	0	1	1	1	0	0

Asselin et al: J Clin Oncol 34:854, 2015

THE FUTURE IS NOW