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Can point of care cardiac biomarker testing guide cardiac safety during oncology trials?

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Presenter Disclosure Information

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- I **will not** discuss off label use or investigational use in my presentation.
- I **have** financial relationships to disclose:
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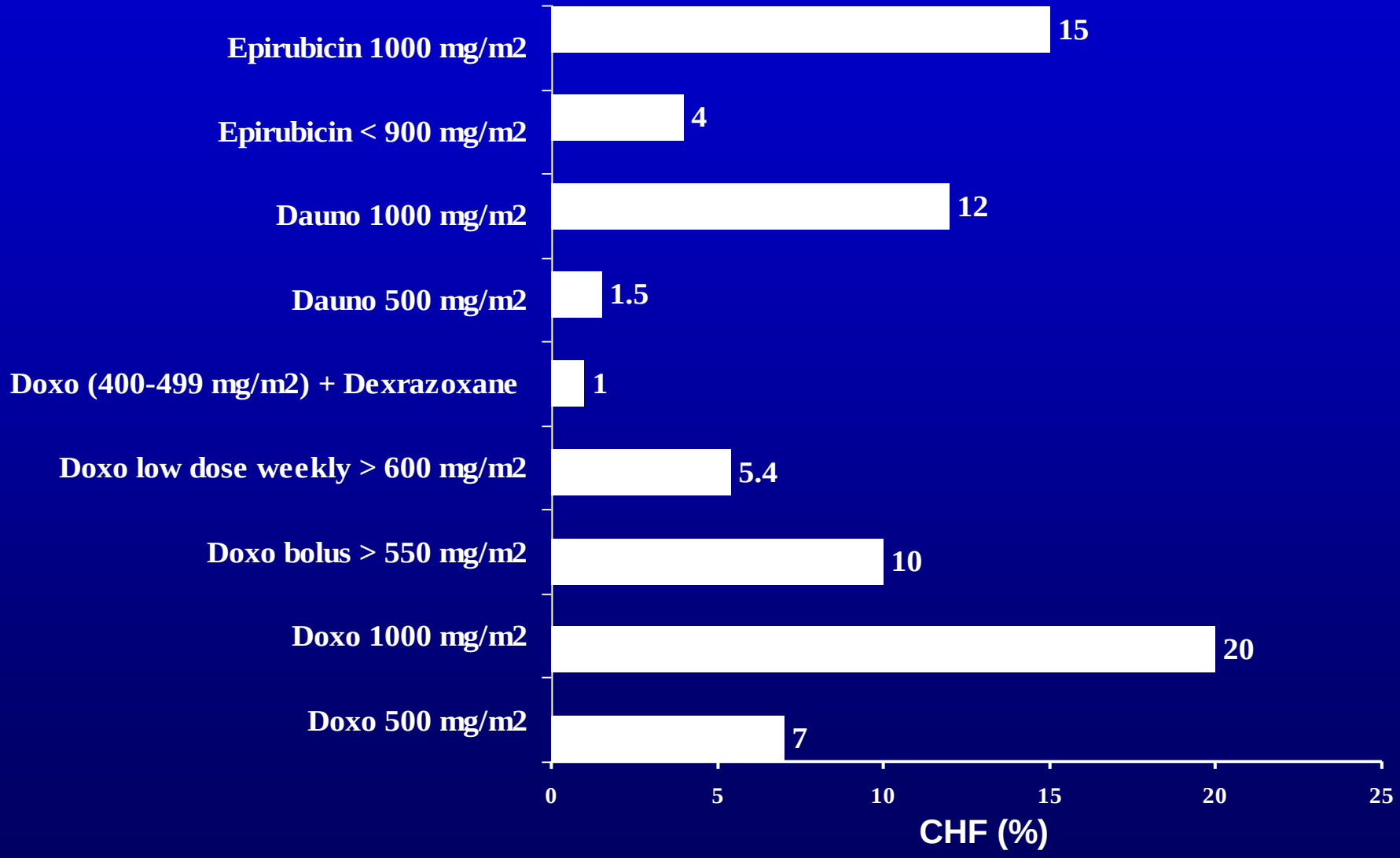
www.msnbc.msn.com. Aug 2005.

Anthracycline Cardiotoxicity : Effects of Different Drugs, Scheduling, and Cardiac Protection with Dexrazoxane



Hensley ML et al *J Clin Oncol* 1999; 17(10):3333-3355

How often is cardiac toxicity detected by Echo and MUGA After Four Cycles of AC Chemotherapy?

(NCI-CTC Version 2)

Method	Grade 1		Grade 2	
	No.	%	No.	%
MUGA/MUGA, n = 1,153	203	17.6	84	7.3
ECHO/ECHO, n = 305	40	13.1	12	3.9
MUGA/ECHO, n = 27	5	18.5	2	7.4
ECHO/MUGA, n = 53	10	18.9	3	5.7

Abbreviations: LVEF, left ventricular ejection fraction; NCI-CTC, National Cancer Institute Common Toxicity Criteria; AC, doxorubicin and cyclophosphamide; MUGA, multiple-gated aquisition; ECHO, echocardiogram.

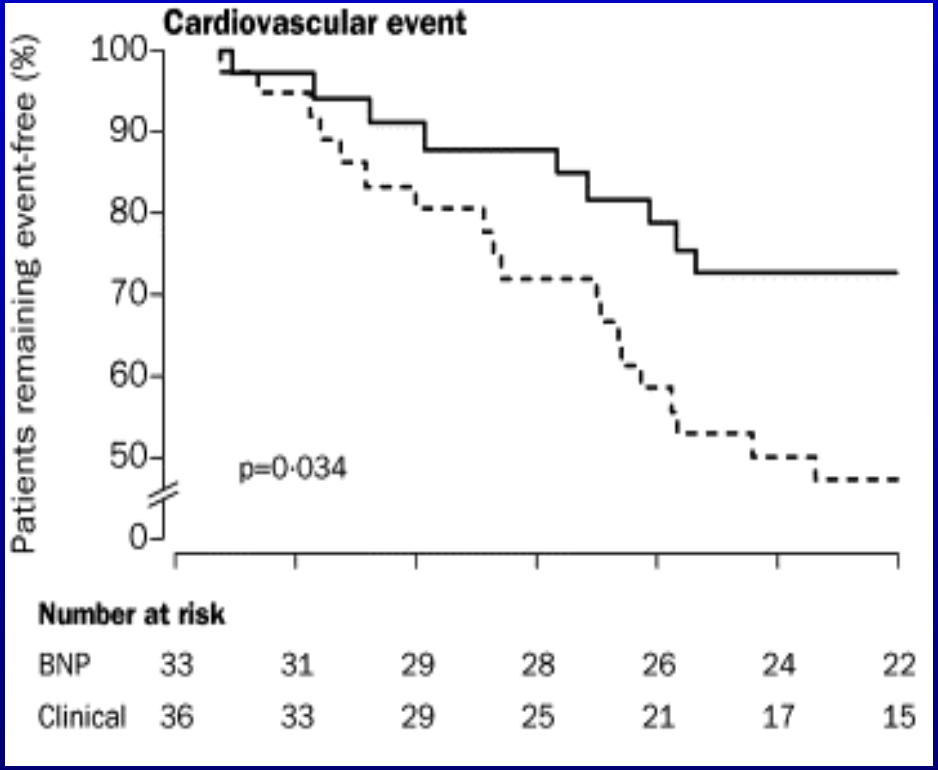
Perez EA et al. J Clin Onco. 2004:22, 3700-3704

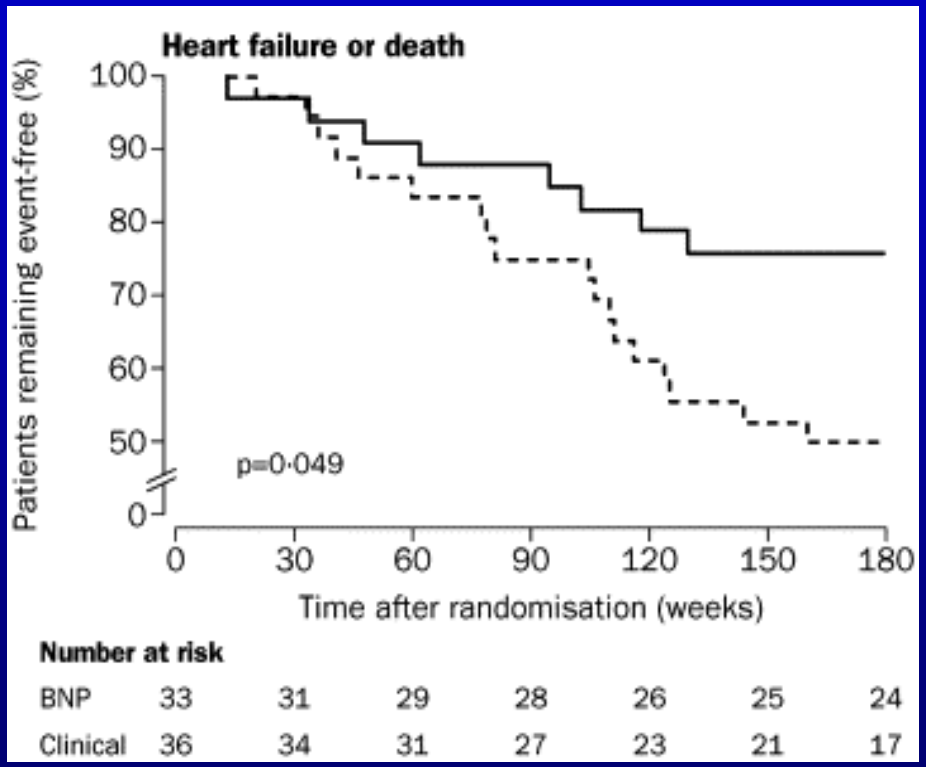
Detecting Cardiotoxicity
Summary of current methods

- The guidelines* at present suggest a baseline EF measurement and a repeat study at some time interval (keep in mind that more than 1/3 of patients with heart failure have a normal EF and their prognosis is similar to those with systolic dysfunction)
- Symptoms are the mainstay of the diagnosis of heart failure (and the utility of that is in question)
- No recommendation for biomarker testing or preventive therapy

*AHA,ACC,HFSA, and ASCO websites

BNP guided therapy for cardiac disease (eg. HF) is very useful and appears to change the outcome….





Kaplan-Meier curves examining time to first event of the primary clinical endpoint showed a clear divergence between the groups by 6 months (p=0·034) and remained significant when reanalysed to include only heart-failure events or death (p=0·049).

Troughton et al. Lancet. 2000: 355, 1126-30

Troponin I is valuable in detecting Cardiotoxicity

TABLE 3. Cardiac Events In the Study Groups

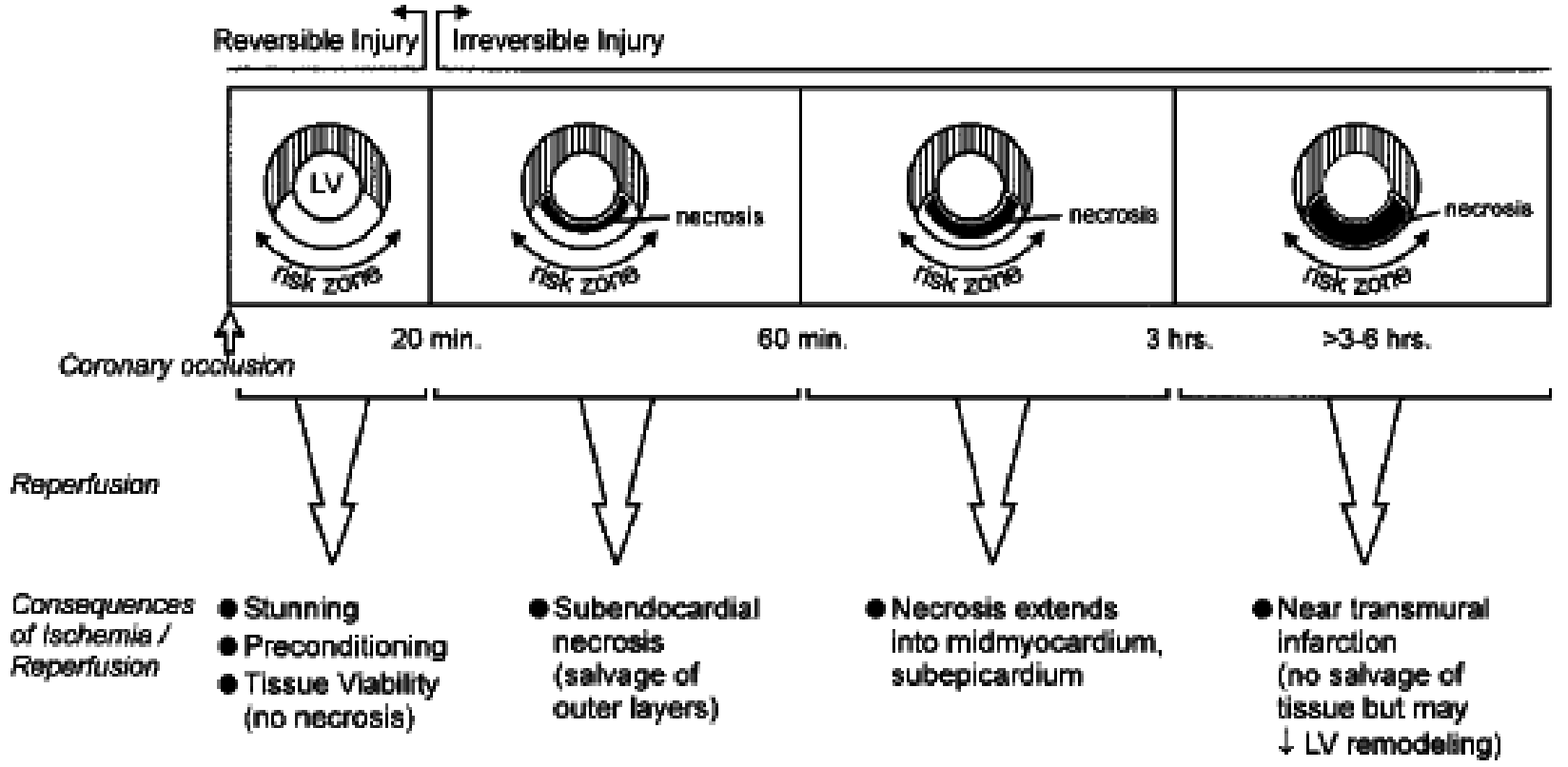
	Total (n=703)	$TnI^{-/-}$ (n=495)	$TnI^{+/-}$ (n=145)	$TnI^{+/+}$ (n=63)
Sudden death	3 (0.4)	0 (0)	0 (0)	3 (5)
Cardiac death	2 (0.3)	0 (0)	0 (0)	2 (3)
Acute pulmonary edema	3 (0.4)	0 (0)	1 (0.7)	2 (3)
Heart failure	47 (7)	1 (0.2)	18 (12)	28 (44)
Asymptomatic left ventricular dysfunction	37 (5)	2 (0.4)	24 (17)	11 (17)
Life-threatening arrhythmias	17 (2)	2 (0.4)	10 (7)	5 (8)
Conduction disturbances requiring pacemaker implantation	2 (0.3)	0 (0)	0 (0)	2 (3)
Cumulative events	111 (16)	5 (1)	53 (37)*	53(84)*†

Values are given as n (%).

*$P<0.001$ vs $TnI^{-/-}$ group; †$P<0.001$ vs $TnI^{+/-}$ group.

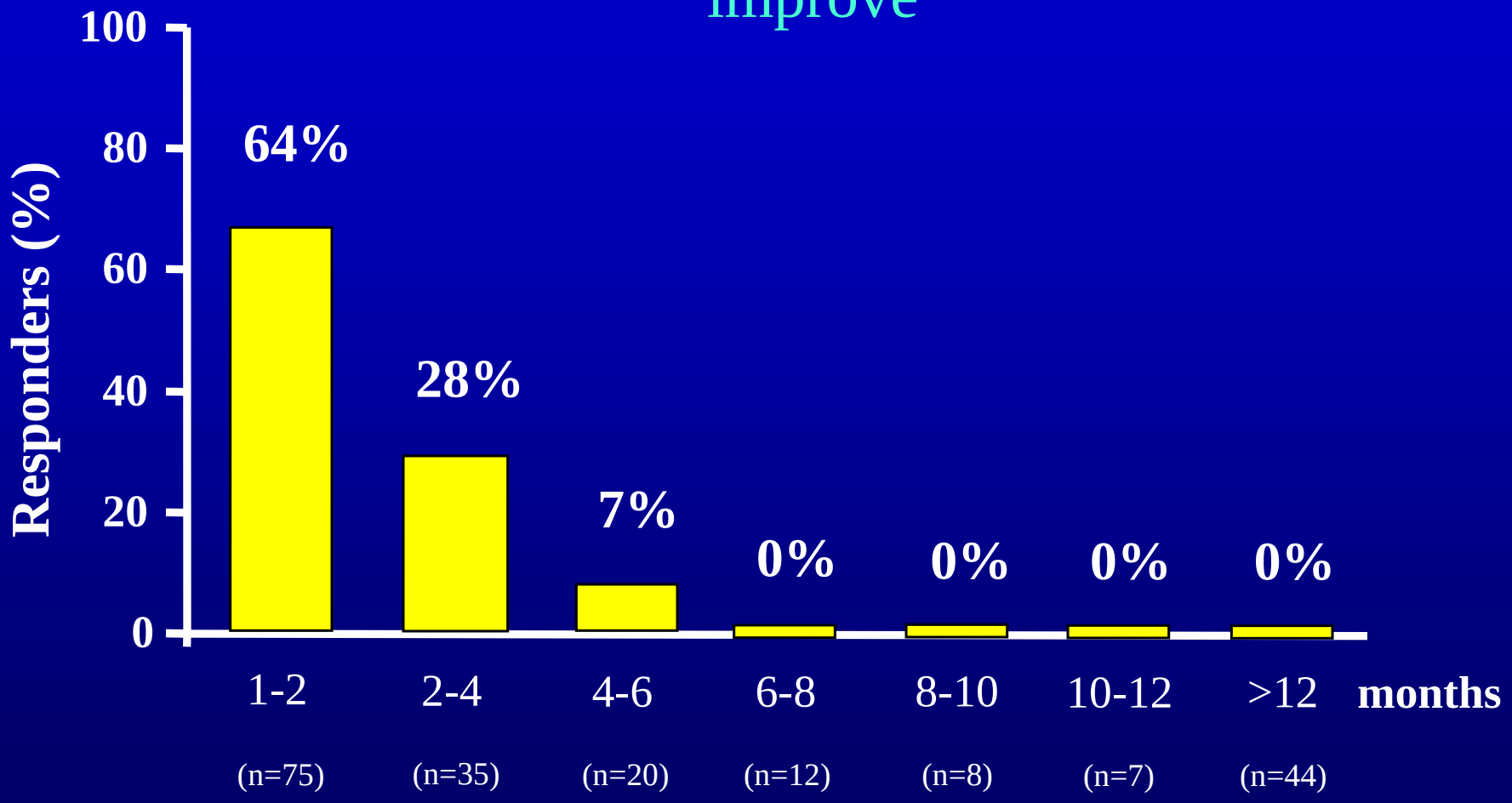
Cardinale et al. Circ. 2004;109:2749-2754

In regards to *Ischemic* insults, we have a paradigm



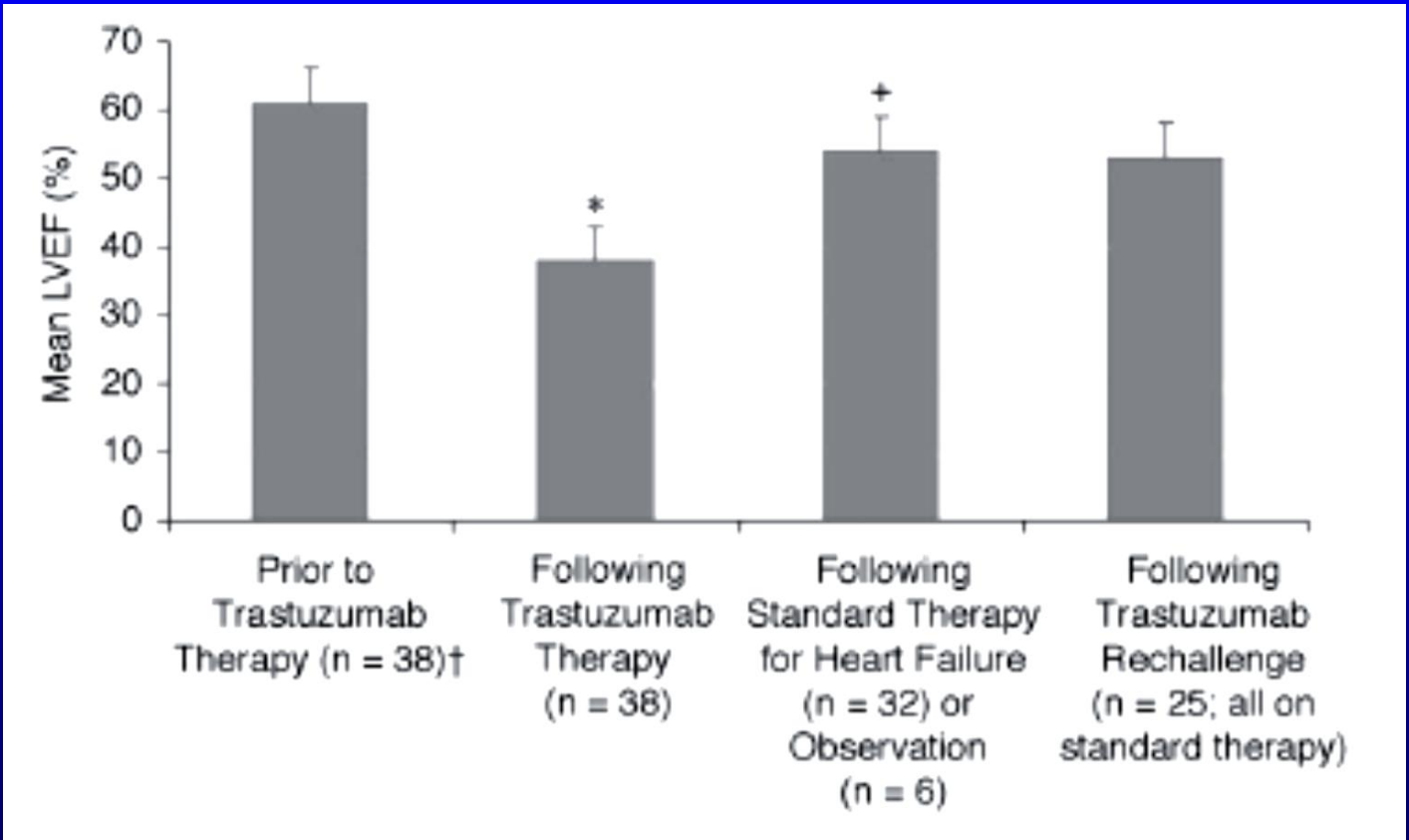
Kloner et al, Circ 2001; p2981

The effect of time for initiation of HF therapy and the percent of patients who improve



D Cardinale, et al. JACC 2010, jan 26.

There is significant reversibility of LV dysfunction with trastuzumab-related cardiac toxicity



Ewer, et al Journ of Clinical Oncology 2005,23;p 7820-6.

Rationale

- Anthracycline-induced cardiotoxicity is well known and frequently limits treatment.
- The severity of myocardial damage is dependent on several factors.
- Current monitoring techniques, such as MUGA or Echo, have major limitations and only detect LV dysfunction when there is a substantial decrease

Pilot Study

Cycle		1	2	3	4	5	6		
Weeks (approximate)	0	3	6	9	12	15	18	24	
BNP	x	x	x	x	x	x	x	x	
TROPONIN	x	x	x	x	x	x	x	x	
EF (by Echo)	x						x	x[+]	
Physical Exam	x	x	x	x	x	x	x	x	
ECG	x						x	x[+]	
MDASI	x			x			x	x	
	Baseline							End	

[+]if clinically indicated

Pilot Study Data

TABLE 1. BASELINE DEMOGRAPHICS

	%
Number of patients=109	
Gender (Male/Female)	48 / 52
Age (years std dev)	56 14
Cancer Diagnosis	
Breast	10
Sarcoma	55
Lymphoma	32
Other	3
Cardiac Diagnosis	
Coronary Artery Disease	10
Prior Myocardial Infarction	4
Risk Factors	
Diabetes	14
Family History of Early Heart Disease	20
Hypertension	50
Hyperlipidemia	32
Obesity	35
Smoking	11
Cardiac Medications	
Beta Blocker	22
Ace Inhibitor	17
ARB	13
Statins	23
Aspirin	10
Antiplatelets	6

Elevated pre-chemo BNP predicted toxicity in patients receiving anthracyclines

Patient	BNP Value	Time to Event*	Event
1	215	244	Decreased LVEF/ Symptomatic arrhythmias
2	322	2	ACS
3	279	13	Symptomatic arrhythmia
4	303	215	Symptomatic HF
5	306	25	Symptomatic arrhythmia
6	986	0	Symptomatic HF
7	273	19	ACS
8	353	33	Symptomatic HF
9	241	305	Symptomatic HF
10	155	0	Symptomatic Arrhythmia
11	264	3	Symptomatic HF

*Number of days from first BNP > 150 pg/ml, LVEF = left ventricular ejection fraction, ACS = acute coronary syndrome, HF = heart failure

Lenihan, et al: JCO 08, abstract 18S

BNP use for the detection of cardiac toxicity with anthracycline based chemotherapy

- The only factors significantly associated with cardiac toxicity included older age, history of MI and elevated BNP

Lenihan, et al: JCO 08, abstract 18S

Factors associated with having a cardiac event during the study period

Table 1. Univariate logistic regression modeling the probability of having a cardiac event

Variable	Value	Cardiac Event				Total	Relative Risk	
		No	(%)	Yes	(%)		RR	(95% CI)
2 BNP > 100	Yes	20	69	9	31	29	12.41	(2.85, 54.10)
	No	78	98	2	3	80		
2 BNP > 150	Yes	7	50	7	50	14	11.88	(3.98, 35.42)
	No	91	96	4	4	95		
1 BNP > 200	Yes	10	50	10	50	20	44.50	(6.04, 328.02)
	No	88	99	1	1	89		
*EF suggests cardiotoxicity	Yes	15	83	3	17	18	2.00	(0.57, 7.00)
	No	77	92	7	8	84		

*Completion CF was unavailable for 7 study participants.

Normal BNP < 100 pg/ml

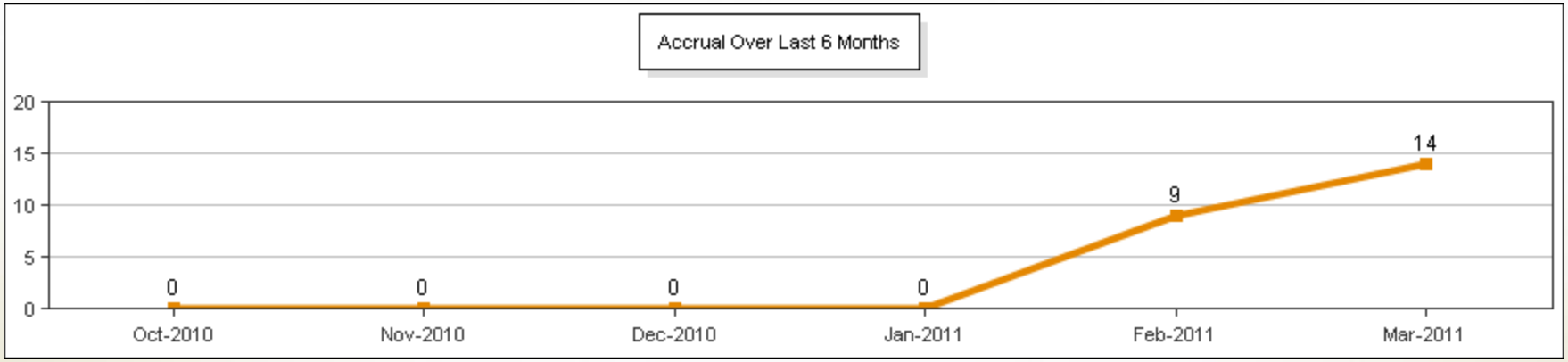
Accuracy of each test for predicting cardiac events

Table 2: Factors Associated with a Cardiac Event

test	n	Sensitivity	Specificity	Positive predictive Value	Negative predictive value
1 BNP > 100	109	100 (72, 100)	59 (49, 69)	22 (11,35)	100 (94,100)
1 BNP > 150	109	100 (72, 100)	81 (71, 88)	37 (20, 56)	100 (95, 100)
1 BNP > 200	109	91 (59, 100)	90 (82, 95)	50 (27, 73)	99 (94, 100)
EF<50 or change>15%	102	30 (7, 65)	84 (75, 91)	17 (4, 41)	92 (84, 97)

All data expressed as percent (95% Confidence Interval)

PREDICT Study:
A multicenter study in Patients undergoing anthRacycline-based chemotherapy to assess the Effectiveness of using biomarkers to Detect and Identify Cardiotoxicity and describe Treatment



Inclusion Criteria

- Patient age 18-85 years
- Starting a new course of chemotherapy that includes an anthracycline (does not have to be first-line therapy and previous anthracycline use is allowed)
- Has a life expectancy greater than 12 months

Exclusion Criteria

- Unstable angina or MI within 3 months of registration
- LVEF less than 50%
- Patients receiving concurrent dexrazoxane
- Decompensated HF in the last 3 months prior to registration
- Pre-existing or prior symptomatic arrhythmia (within 3 months)
- Severe pulmonary disease (FEV </= 1.0 liters), and/or pulmonary hypertension (mean pulmonary artery pressure >/=60mm Hg), and/or dependent use of oxygen
- BNP >/= 200 pg/ml or troponin >/= 0.4 ng/ml at baseline

Cardiac Event

- Any new symptomatic cardiac arrhythmia
- Acute coronary syndrome
- Symptomatic heart failure (HF)
- Development of asymptomatic left ventricular dysfunction (defined as LVEF reduction of 10% to less than 50% or a decrease of greater than 15% from baseline)
- Sudden cardiac death (defined as rapid and unexpected death from cardiac causes with or without known underlying heart disease)

PREDICT Study

8.0 Study Calendar of Events

	Study Timeline											
Visit	1	2	3	4	5	6	7	8	9	10[2, 3]	11[4]	12
Cycles	1	2	3	4	5	6	7	8				
Weeks (approximate)	0/1	3	6	9	12	15	18	21	26			52
BNP	x	x	x	x	x	x	x	x	x	x	x	x
TROPONIN	x	x	x	x	x	x	x	x	x	x	x	x
CHEM 8+/CBC[1]	x								x			x
EF (by ECHO)[1]	x								x			x
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x
EKG[1]	x								x			x
MDASI-HF[1]	x		x			x			x	x[3]	x	x
	Baseline									End		

[1] may be performed at any time if clinically indicated (i.e. patient has symptoms suggestive of cardiac event)

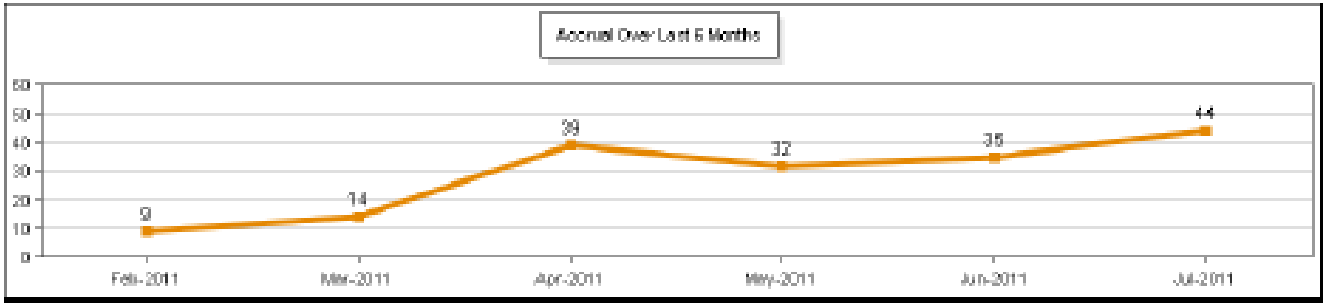
[2] additional chemotherapy cycles (labeled visit 10) performed beyond 8 cycles should have biomarker assessments and physical exam performed at least every 4 weeks.

[3] additional chemotherapy cycles (labeled visit 10) performed beyond 8 cycles should continue to have the MDASI-HF completed every 3rd cycle (e.g. 9, 12, 15, 18……)

[4] unscheduled visits (labeled visit 11) will be completed at any time there is suspicion of a cardiac event, particularly between labeled visit 9 (the six month visit) and labeled visit 12 (the 12 month visit).

A multicenter study in Patients undergoing anthRacycline-based chemotherapy to assess the Effectiveness of using biomarkers to Detect and Identify Cardiotoxicity and describe Treatment (PREDICT)

NCI Number	Active Sites	Open Date	Annual Exp. Date	Term. Date	Monthly Accrual	Accrual-to-Date	Credits-to-Date
IL147	Central Illinois CCOP	09/09/2010	09/10/2011		0	2	2
IL103	Central Illinois Hematology Oncology Center	09/09/2010	09/08/2011		0	0	0
LA067	Christus St. Frances Cabrini Hospital	09/28/2010	12/21/2011		3	7	7
MI021	Grand Rapids Clinical Oncology Program	11/09/2010	11/08/2011		2	16	16
SC036	Greenville CCOP	10/25/2010	11/17/2011		0	1	1
MI147	Kalamazoo CCOP	12/22/2010	12/21/2011		1	3	3
LA017	LSU Health Sciences Center - Shreveport	03/14/2011	03/13/2012		0	1	1
TX035	MD Anderson Cancer Center	06/04/2008	11/09/2011		3	7	7
FL020	MD Anderson Cancer Center-Orlando	11/29/2010	11/28/2011		1	7	7
NY076	Maimonides Medical Center	03/24/2011	03/26/2012		0	5	5
PA163	Main Line Health CCOP	03/02/2011	03/01/2012		0	2	2
TN037	Meharry Medical College MBCCOP	02/11/2011	02/10/2012		1	2	2
MN043	Metro-Minnesota CCOP	03/09/2011	03/08/2012		9	34	34
MI086	Michigan Cancer Research Consortium CCOP	11/18/2010	11/17/2011		1	5	5
AR012	Saint Edward Mercy Medical Center	10/07/2010	10/06/2011		0	2	2
TX027	Scott and White Memorial Hospital	01/10/2011	01/09/2012		4	10	10
IL015	Sherman Hospital	09/09/2010	09/08/2011		0	2	2
MD020	Sinai Hospital of Baltimore	03/09/2011	03/08/2012		4	4	4
SC024	Spartanburg Regional Medical Center	01/20/2011	01/19/2012		0	0	0
TN008	Vanderbilt University	01/20/2011	01/19/2012		5	17	17
MO011	Washington University School of Medicine	01/20/2011	01/19/2012		3	11	11
KS017	Wichita CCOP	12/10/2010	12/09/2011		7	30	30
MI005	William Beaumont Hospital	05/10/2011	05/09/2012		0	4	4
	Terminated/Other Institutions				0	1	1
				Total Accrual	44	178	178



Total Accrual To date:

275 pts (67 in Sept)

Recent cases in PREDICT
At VUMC (Cardiac events)

- 19 y/o F, with leukemia and treatment with adriamycin 6 cycles previously, received 2 cycles of mitoxantrone then became hypoxic (TI 0.09, BNP 1169, EF 52, Pulmonary edema on CXR and exam)
- 63 y/o F, with leukemia treated with 6 cycles of adriamycin based chemo previously, developed shortness of breath then atrial fibrillation and hypotension, EF 48 (previous 56) (TI 0.05, BNP 371, pulmonary edema on CXR and exam)
- 61 y/o M, known CAD s/p CABG developed lymphoma, received 6 cycles of adria based chemo. On final visit after 6 months, was fatigued but not PND or orthopnea. EF45 (prev 59), BNP 157, TI 0.2
- 52 y/o M, no previous history, developed PMML was treated with adria for one cycle. Developed neutropenia, then fatigue and shortness of breath. EF now 47, prev 54. BNP 1300, TI 0.08

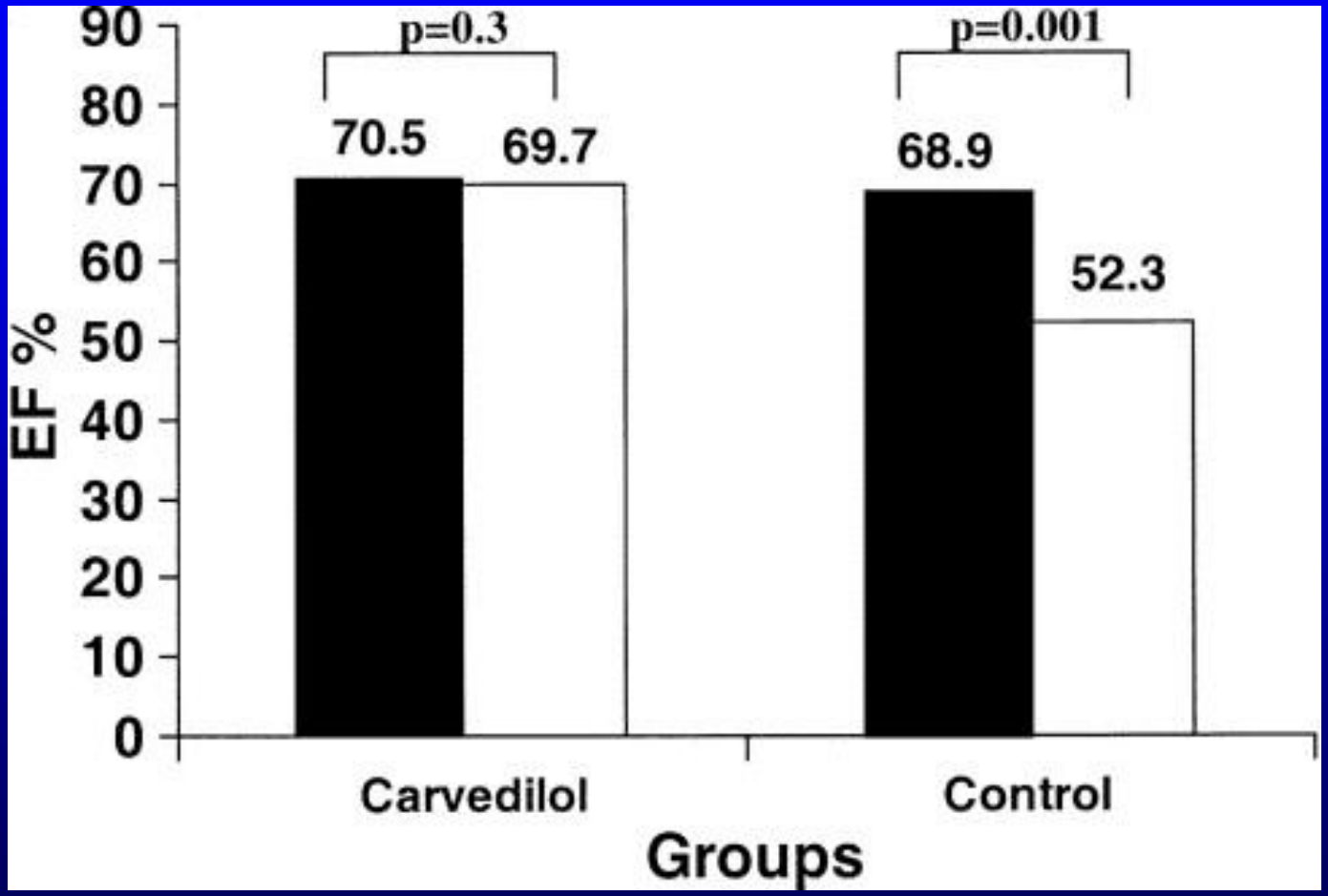
ACE Inhibition appears quite important in preventing heart failure

	Total (n=114), n (%)	ACEI Group (n=56), n (%)	Control Subjects (n=58), n (%)	*P*
Sudden death	0 (0)	0 (0)	0 (0)	1.0*
Cardiac death	2 (2)	0 (0)	2 (3)	0.49*
Acute pulmonary edema	4 (3)	0 (0)	4 (7)	0.07*
Heart failure	14 (12)	0 (0)	14 (24)	<0.001
Arrhythmias requiring treatment	11 (10)	1 (2)	10 (17)	0.01
Cumulative events	31	1	30	<0.001

*Fisher exact test.

Cardinale D et al. Circulation. 2006;114:2474-2481

Carvedilol appears protective during adriamycin based chemotherapy



Data expressed as mean values.

Kalay et al. JACC. Dec 2006. 48:2258-62

Point of Care testing for Cardiotoxicity

- Cardiac biomarkers are critical for detecting cardiotoxicity
- Point of care testing prior to chemotherapy can be done and stratify high risk patients
- Echo imaging is important but may not detect small changes and not frequently feasible due to expense of repeat testing
- Future strategies can expect to identify high risk patients to direct preventive therapy