



CARDIONCOLOGY:

a new medical issue

Daniela Cardinale, MD, PhD

Cardiology Unit
European Institute of Oncology
Milan - Italy

Background 1

- The number of patients presenting with oncologic and cardiologic co-morbidities are increasing, due to the ageing of the population and the increase of in prevalence of oncologic and cardiovascular disease.
- Patients with heart disease have a higher risk of cancer than the general population, because of overlapping risk factors, such as obesity, hormone replacement therapy and in particular, smoking.

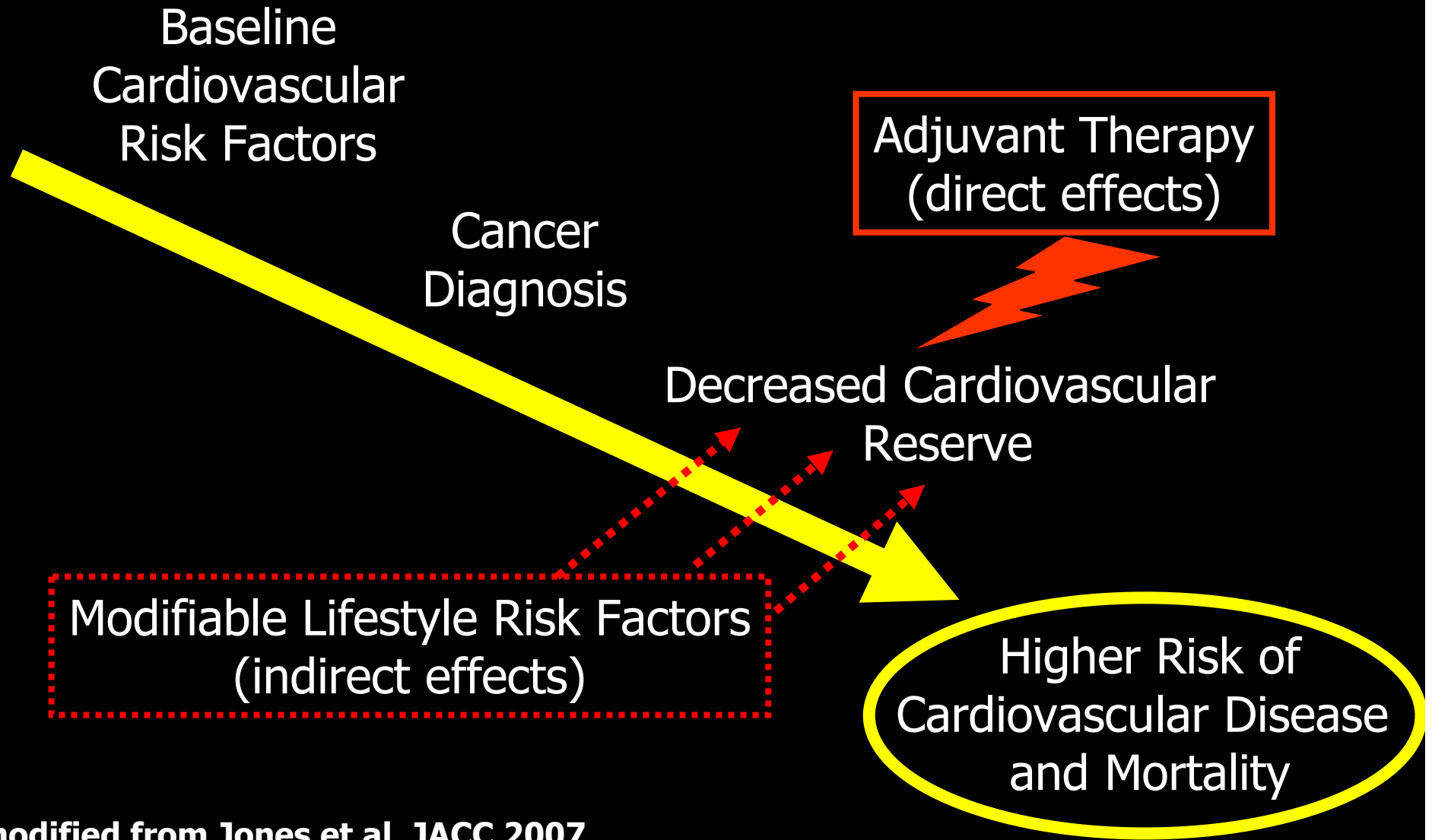
Background 2

- The survival rate of cancer pts has greatly increased over the 3 past decades because of:
 - improvement in pharmacologic treatment
 - improvement in surgery procedures
 - reduction and control of major risk factors
- At present, it has been estimated that more than 20 million cancer survivors, previously treated with chemotherapy and radiotherapy, exist in the USA and in Europe.

Cardiovascular problems in patients with cancer

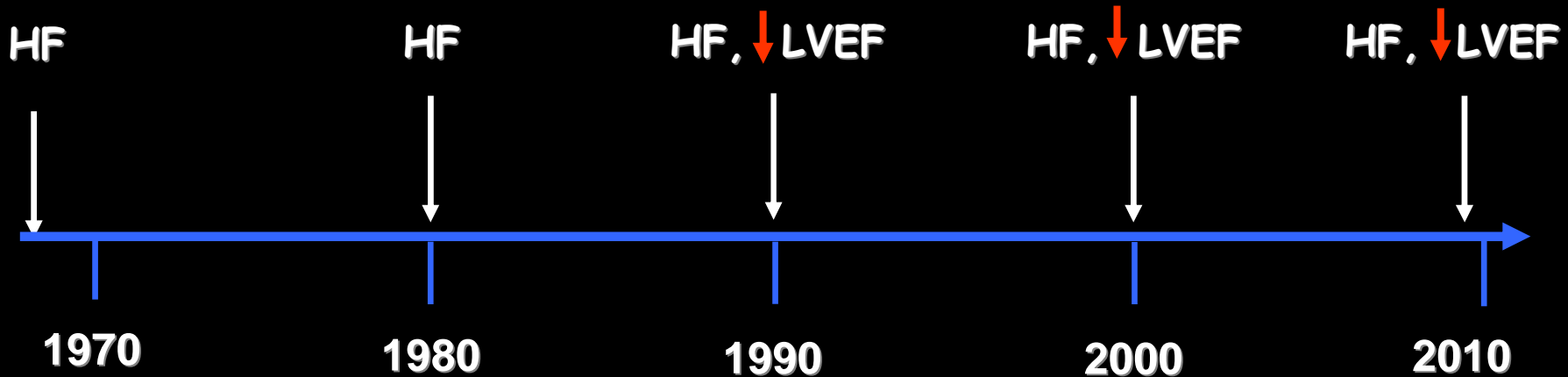
- Cardiac toxicity induced by chemotherapy (CT)
- Cardiovascular toxicity induced by radiotherapy
- Thromboembolic complications of cancer
- Treating CAD in cancer patients
- Treating cancer in patients with heart disease
- Cardiovascular disease in long-term cancer survivors
- Pericardial effusion
- Hypertension

The multiple-Hit Hypothesis



Diagnosis of cardiotoxicity

Tan 1967
Le Frak 1973
Von Hoff 1973
Bristow 1978
Cohen 1982
Haq 1985
Schwartz 1987
Steinherz 1992
Jensen 1996
Shan 1996
Sorensen 1997
CTCAE 1998
Ingal 1998
Pai 2000
Swain 2003
Youssef 2005
CTCAE 2006
Panjirath 2006
CTCAE 2007
CREC 2007
CTCAE 2008
CTCAE 2009



HF=heart failure LVEF=left ventricular ejection fraction

Case Report

- Mr. G. A. -

- **Age:** 36 years
- **Sex:** Male
- **Cardiovascular risk factors :** Ex-smoker
- **Oncologic diagnosis:** Large B-cell NHL
- **Oncologic therapy:** several CT schedules
- **Cumulative anthracycline dose:** 532 mg/mq

NHL=non-Hodgkin's lymphoma

Cardiac function monitoring during CT by LVEF

Date	CT schedule	LVEF
8/8/2003	ACOD	
8/29/2003	CHOP	
9/26/2003	CTX	61%
11/7/2003	VP16	
12/2/2003	Novantrone+Alkeran	67%
2/10/2004	R-ACOD X 4	
5/20/2004	Mabthera	59%
5/27/2004	Mabthera	
8/4/2004	ACOD X 2	57%
9/29/2004	ESHAP	
10/28/2004	ESHAP	
11/19/2004		51%
12/2/2004	BEAM	

Since November 2004, he hasn't had any echocardiographic checks.

Follow-up data

10.4.2005

Onset of low effort threshold dyspnea.
Hospitalization for congestive HF.
Hypokinetic cardiomyopathy with LVEF = 21%
Start of heart failure therapy:

ACEI + Digoxin + Diuretics

9.10.2005

STOP ACEI because hypotension.

1.2.2006

Re-hospitalization for congestive HF
LVEF = 25%

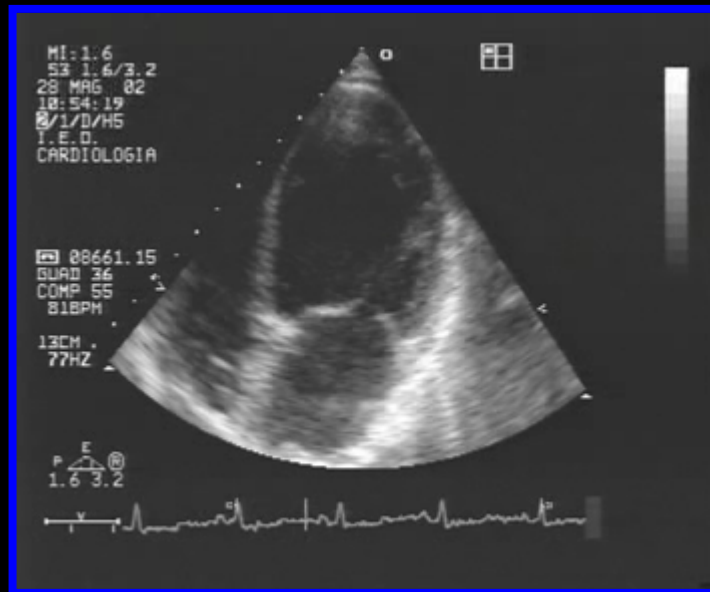
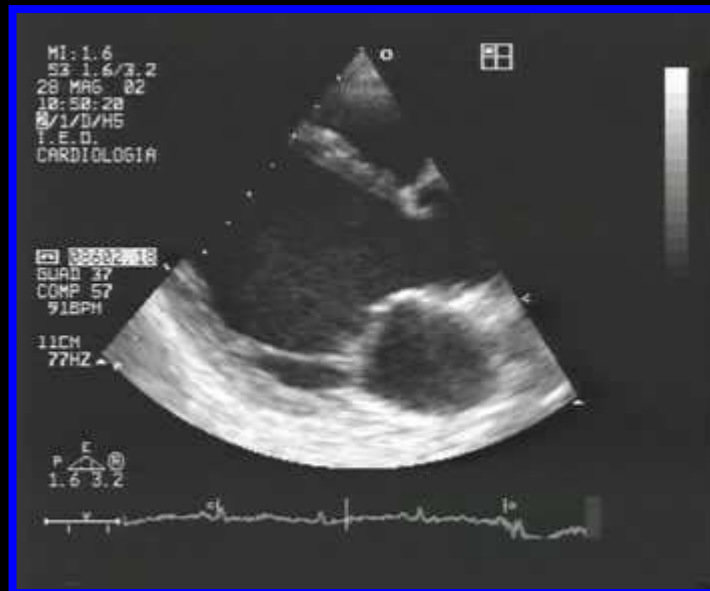
1.2.2006

Cardiologic therapy:

ACEI + Beta Blockers + Diuretics

Current condition (2010):

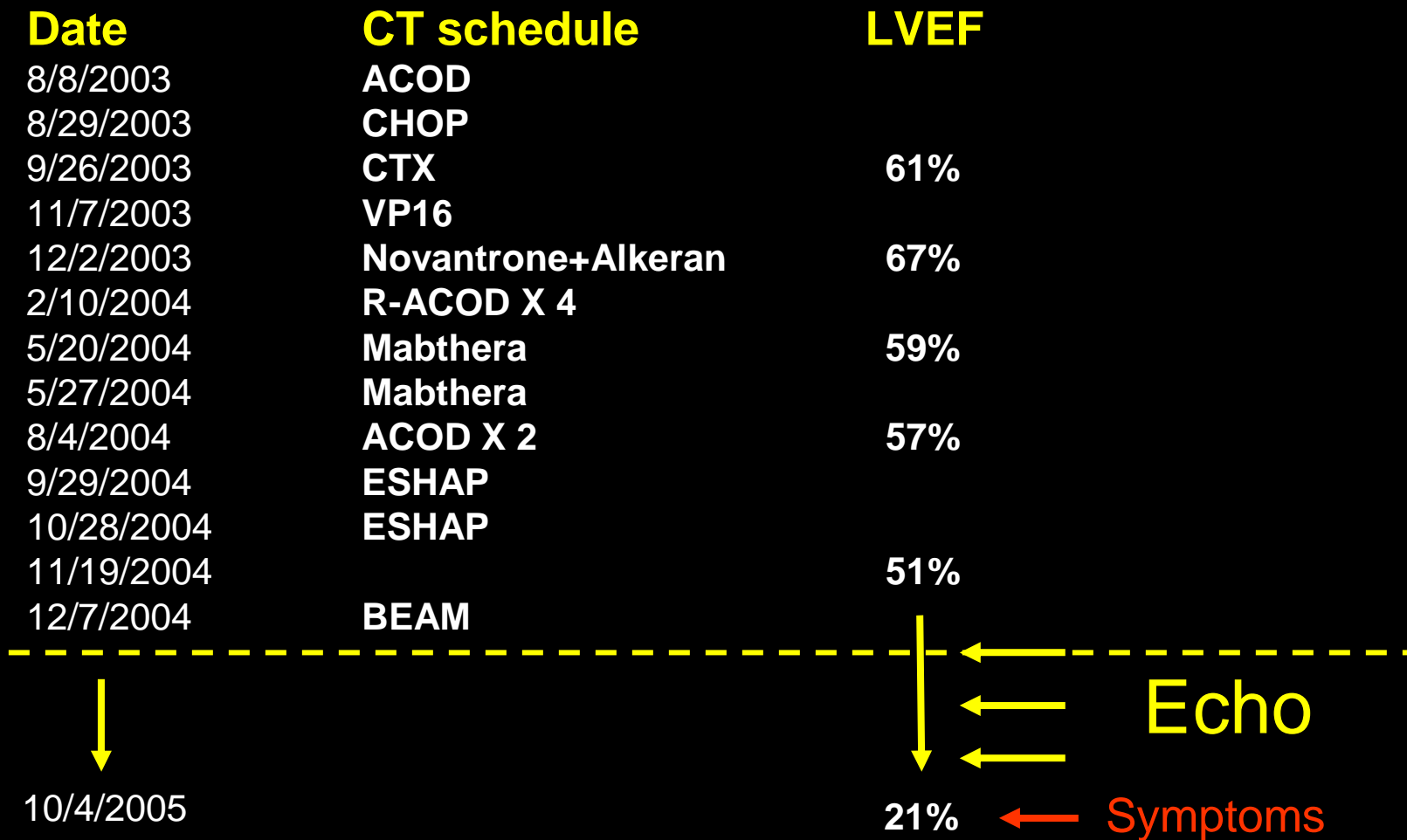
- NYHA class III
- LVEF 21%



QUESTION 1

- Which cardiologic strategy would have been helpful for early detection of chemotherapy-induced cardiomyopathy?
 - 1) Monitoring symptoms
 - 2) Monitoring LVEF
 - 3) Serial ECG evaluations

Monitoring Cardiac Function also after completion of CT



QUESTION 1

Correct answer: 2

- Current guidelines suggest that monitoring cardiac function should continue after the end of chemotherapy. It is well known that cardiac dysfunction can develop even months after the completion of antineoplastic treatments. The key is to detect a decrease in LVEF in a very early phase.
- In this patient, for example, periodic evaluations of LVEF, also after the completion of oncologic treatments, would probably have helped to identify a ventricular dysfunction even before the onset of congestive heart failure symptoms, allowing cardiologists to start a preventive therapy.

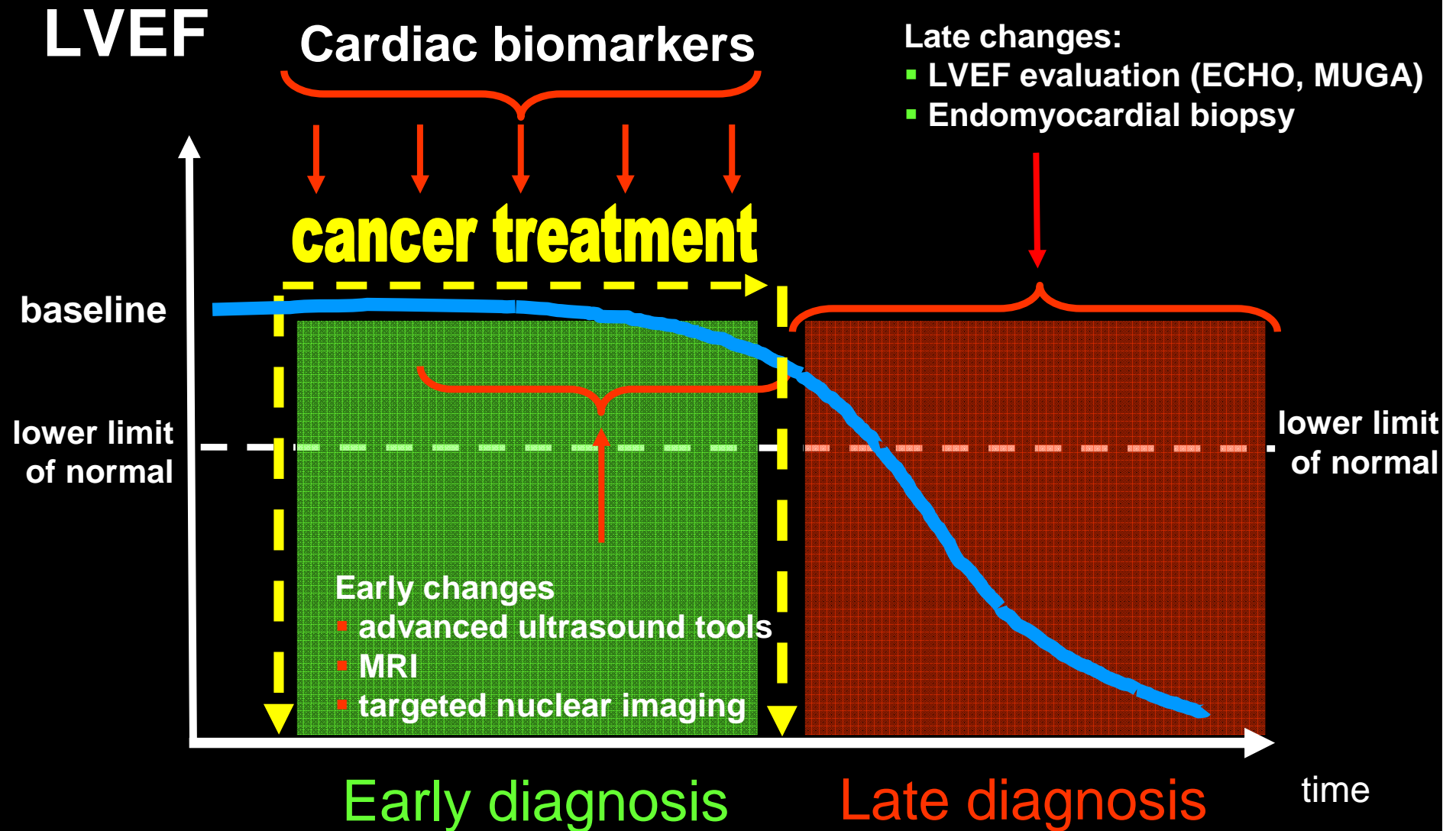
QUESTION 2

- Which is the most useful parameter to monitor during chemotherapy in order to predict cardiotoxicity?
 - 1) Left Ventricular Ejection Fraction
 - 2) Cumulative dose of anthracyclines
 - 3) Troponin I

Monitoring Myocardial Damage by Troponin I (TNI; n.v <0.07 ng/ml)

Date	CT schedule	LVEF	TNI
8/8/2003	ACOD		
8/29/2003	CHOP		
9/26/2003	CTX	61%	0.01
11/7/2003	VP16		0.00
12/2/2003	Novantrone+Alkeran	67%	0.00
2/10/2004	R-ACOD X 4		
5/20/2004	Mabthera	59% ←.....	0.07 ←
5/27/2004	Mabthera		←
8/4/2004	ACOD X 2	57% ←.....	0.10 ←
9/29/2004	ESHAP	←.....	0.16 ←
10/28/2004	ESHAP	←.....	0.14 ←
11/19/2004		51%	←
12/7/2004	BEAM	←.....	0.10 ←
		↓	
10/4/2005		21% ←	Symptoms

EARLY DETECTION OF CARDIOTOXICITY



QUESTION 2

Correct answer: 3

- Decrease in LVEF usually occurs late and it does not permit a preventive treatment.
- Even though there is a clear relationship between cumulative dose of anthracyclines and cardiotoxicity risk, individual susceptibility to drugs does not allow us to detect a standard threshold for toxicity. Conversely, Troponin I is able to early identify patients at higher risk of developing late cardiac dysfunction.

QUESTION 3

- Which strategy has proved to be the most effective in preventing chemotherapy-induced cardiomyopathy?
 - 1) Use of less cardiotoxic drugs
 - 2) Stopping CT soon after the detection of a decrease in LVEF ($>10\%$)
 - 3) Starting enalapril in patients with increased risk (Troponin I > 0.06 ng/ml)

Preventing Cardiotoxicity by Enalapril in High Risk Patients Identified by Increased Troponin I

Date	LVEF	TNI	
8/8/2003			
29/8/2003			
26/9/2003	61%	0.01	
7/11/2003		0.00	
2/12/2003	67%	0.00	
10/2/2004			
20/5/2004	59%	0.07	←.....
27/5/2004			
4/8/2004	57%	0.10	←.....
29/9/2004		0.16	←.....
28/10/2004		0.14	←.....
19/11/2004	51%		
7/12/2004		0.10	←.....
			} Enalapril
3/3/2010	21%		← Symptoms

Preventing Cardiotoxicity by Enalapril in High Risk Patients Identified by Increased Troponin I

Date	LVEF	TNI	
8/8/2003			
29/8/2003			
26/9/2003	61%	0.01	
7/11/2003		0.00	
2/12/2003	67%	0.00	
10/2/2004			
20/5/2004	59%	0.07	←..... ←..... ←..... ←..... ←..... } Enalapril
27/5/2004			
4/8/2004			
29/9/2004			
28/10/2004		<0.07	
19/11/2004			
7/12/2004		<0.07	
3/3/2010	59%		

QUESTION 3

Correct answer: 3

- The first two strategies could compromise the effectiveness of antineoplastic therapies.
- Conversely, a prophylactic treatment with enalapril, in patients with increased risk (high Troponin I) is able to prevent the development of cardiotoxicity.

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

JACC 2000

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

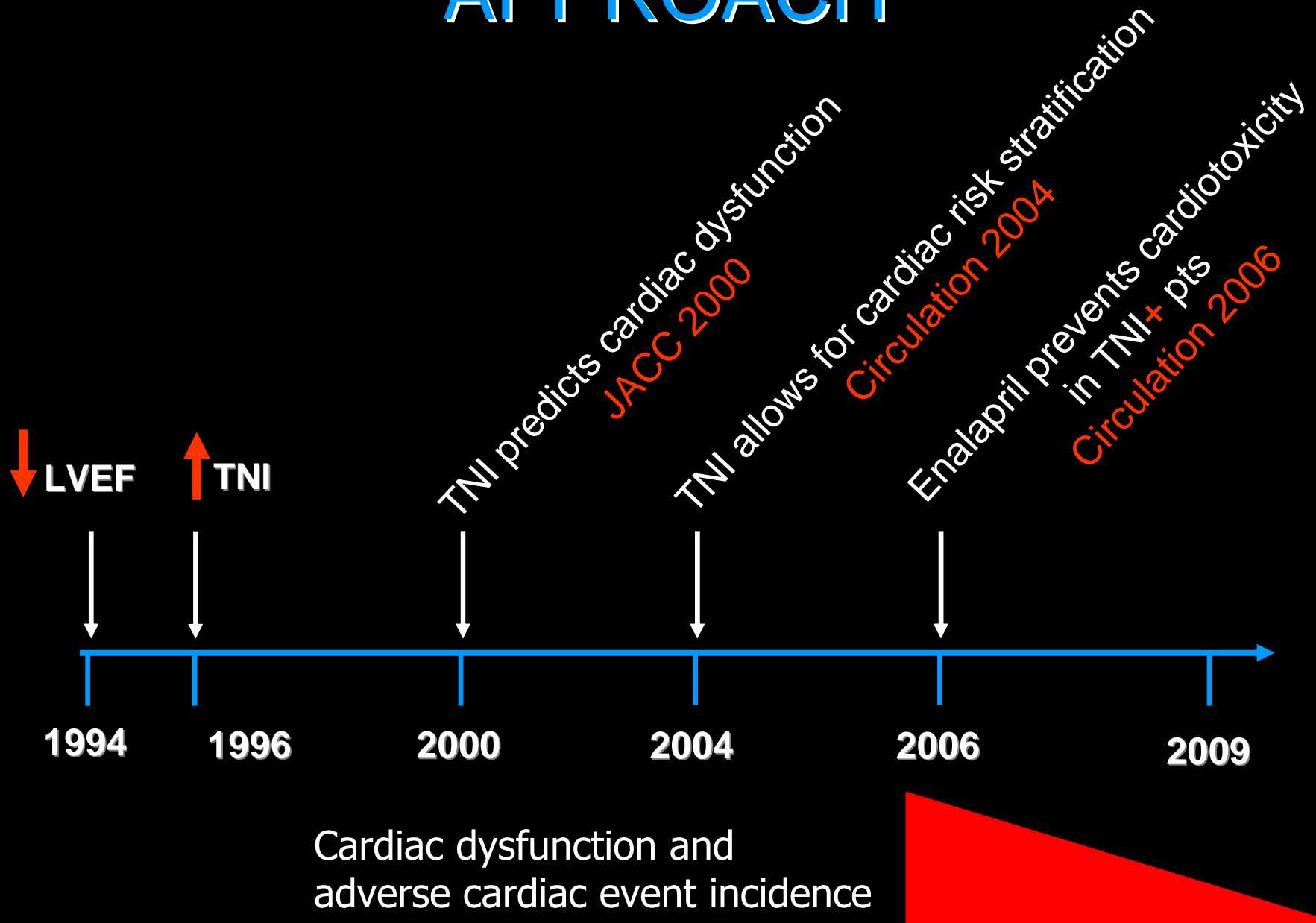
Circulation 2004

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

Circulation 2006

APPROACH



Conclusions¹

**Cardiotoxicity and increased CV risk
are potentially serious complication
occurring after chemotherapy.**

Conclusions²

Evaluation of TNI after CT allows for:

prediction of cardiotoxicity and associated cardiac events

early stratification of cardiac risk

comparison of cardiotoxic effect of old and novel antitumoral agents

identification of high-risk patients in whom a prophylactic pharmacologic treatment may prevent cardiac dysfunction and associated cardiac events.

THE ASSOCIATION

- » CONSTITUTION
- » FOUNDERS
- » MEMBERS

CARDIONCOLOGY

- » RESEARCH
- » ACTIVITY
- » BACKGROUND ARTICLES
- » SPOTLIGHT
- » ASK THE EXPERT
- » REGISTER CARDIOTOXICITY

SCIENTIFIC PROTOCOLS

- » ONGOING STUDIES

LEGALE

- » ASK THE LAWYER



CARDIONCOLOGY 2009 MILANO 25 - 26 SEPTEMBER 2009



FOTOS

MINUTES

In heart we trust!

TEMPORARY BOARD OF DIRECTORS

Dan Lenihan	Nashville	Honorary President
Carlo Cipolla	Milan	President
Daniela Cardinale	Milan	VicePresident
Maria Teresa Sanori	Milan	VicePresident
Giuseppe Curigliano	Milan	Scientific Secretary
Tommaso De Pas	Milan	Chief of Scientific Committee
Franco Del Curto	Milan/Orlavenna	Legal Assistance
Flavio Pirota	Milan	Treasurer
Anna Eggertz	Como/Stockholm	Website
Natalia Pozzi	Milan	Fund Raising

REGISTER CARDIOTOXICITY

CONSULT THE REGISTER

ADD PATIENT FORM

MEMBERSHIP FORM

CARDIONCOLOGY

Daniela Cardinale MD, PhD
 Cardiology Unit, IEO, Cardioncology

ASK THE EXPERT

ONCOLOGY

Giuseppe Curigliano MD, PhD
 Oncology Unit, IEO

SPOTLIGHT: News and views from literature

LEGAL

Franco Del Curto
 Lawyer

ASK THE LAWYER