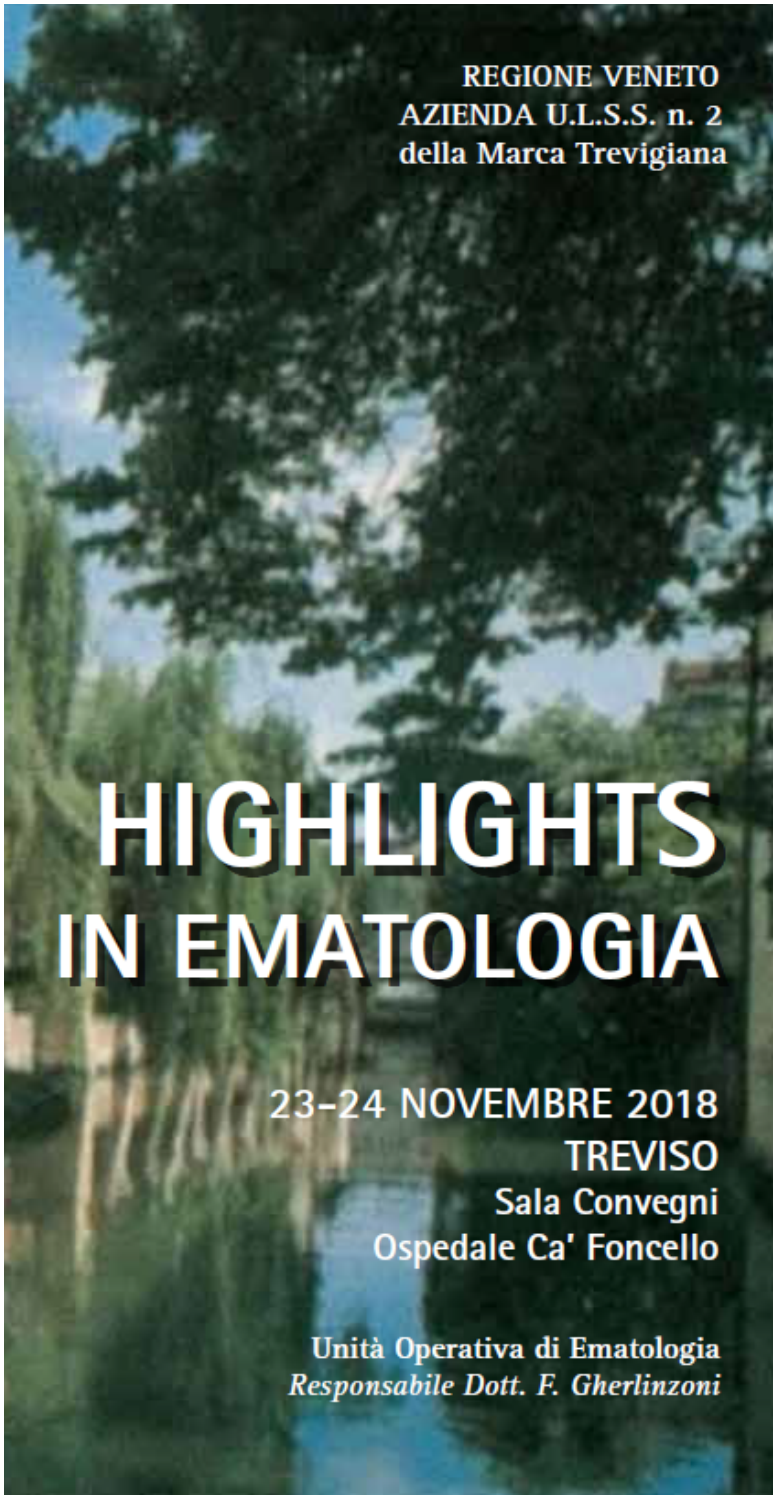


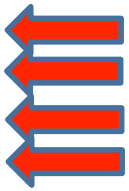
Tossicità cardiaca da chemioterapia

Michele Spina
Aviano

FONDAZIONE
ITALIANA
LINFOMI

Sede	N. di soggetti	
	Maschi	Femmine
Vie aero-digestive superiori*	7.100	2.200
Esofago	1.500	600
Stomaco	7.400	5.300
Colon-retto	29.500	22.900
Colon	20.700	16.400
Retto	8.800	6.500
Fegato	8.800	4.000
Colecisti e vie biliari	2.300	2.400
Pancreas	6.500	7.000
Polmone	27.800	13.500
Osso	400	300
Cute (melanomi)	7.200	6.600
Mesotelioma	1.500	400
Sarcoma di Kaposi	700	200
Tessuti molli	1.200	900
Mammella	500	50.200
Utero cervice	0	2.200
Utero corpo	0	8.200
Ovaio	0	5.200
Prostata	34.400	0
Testicolo	2.500	0
Rene, vie urinarie**	8.900	4.500
Parenchima	7.500	3.900
Pelvi e vie urinarie	1.400	600
Vescica***	21.400	5.200
Sistema nervoso centrale	3.300	2.700
Tiroide	4.300	11.000
Linfoma di Hodgkin	1.200	1000
Linfoma non-Hodgkin	8200	6.100
Mieloma	3.000	2.700
Leucemie	5.200	3.900
Tutti i tumori, esclusi carcinomi della cute	189.600	176.200

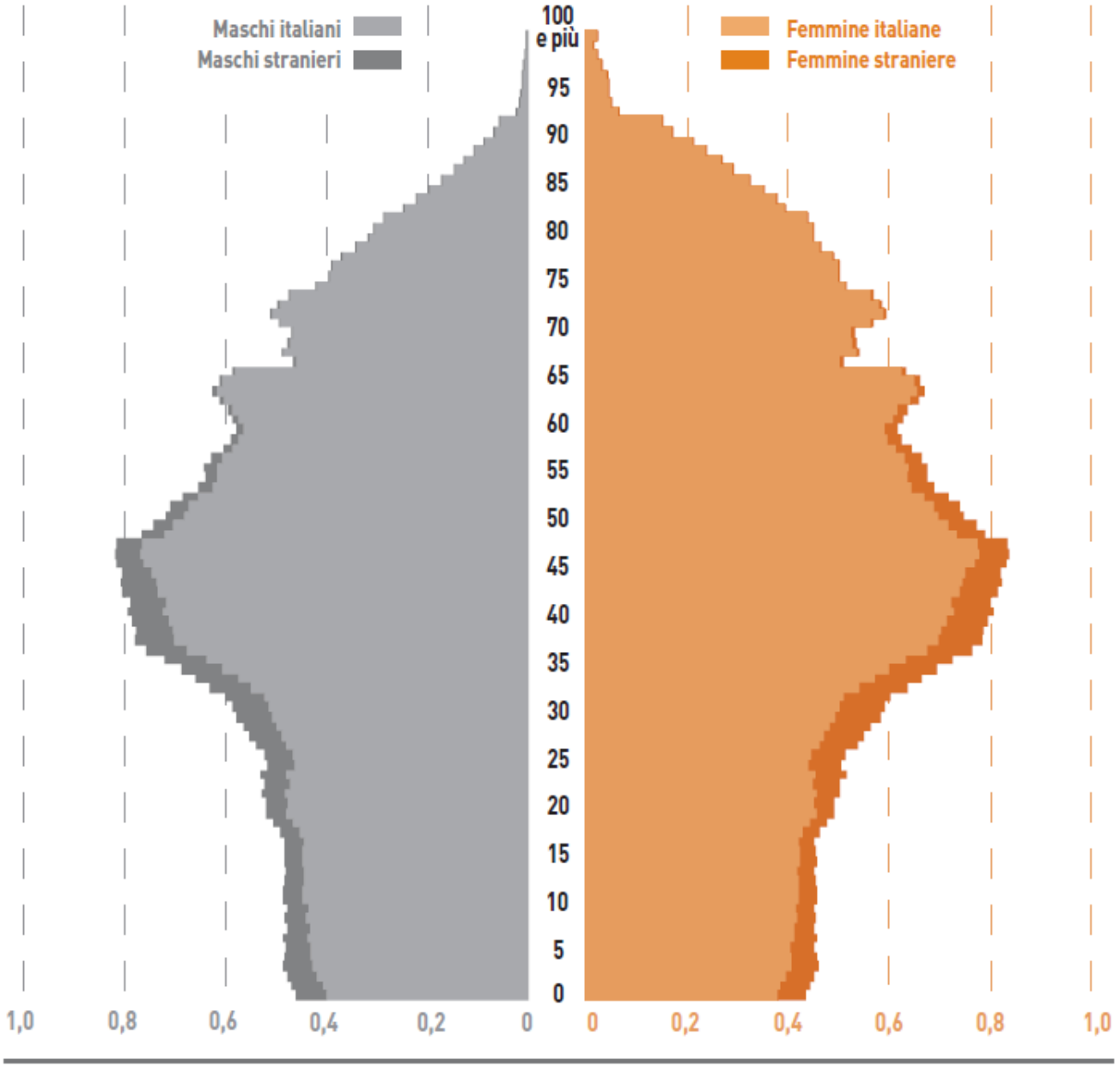
Nuovi casi di neoplasie ematologiche attese in ITALIA nel 2017



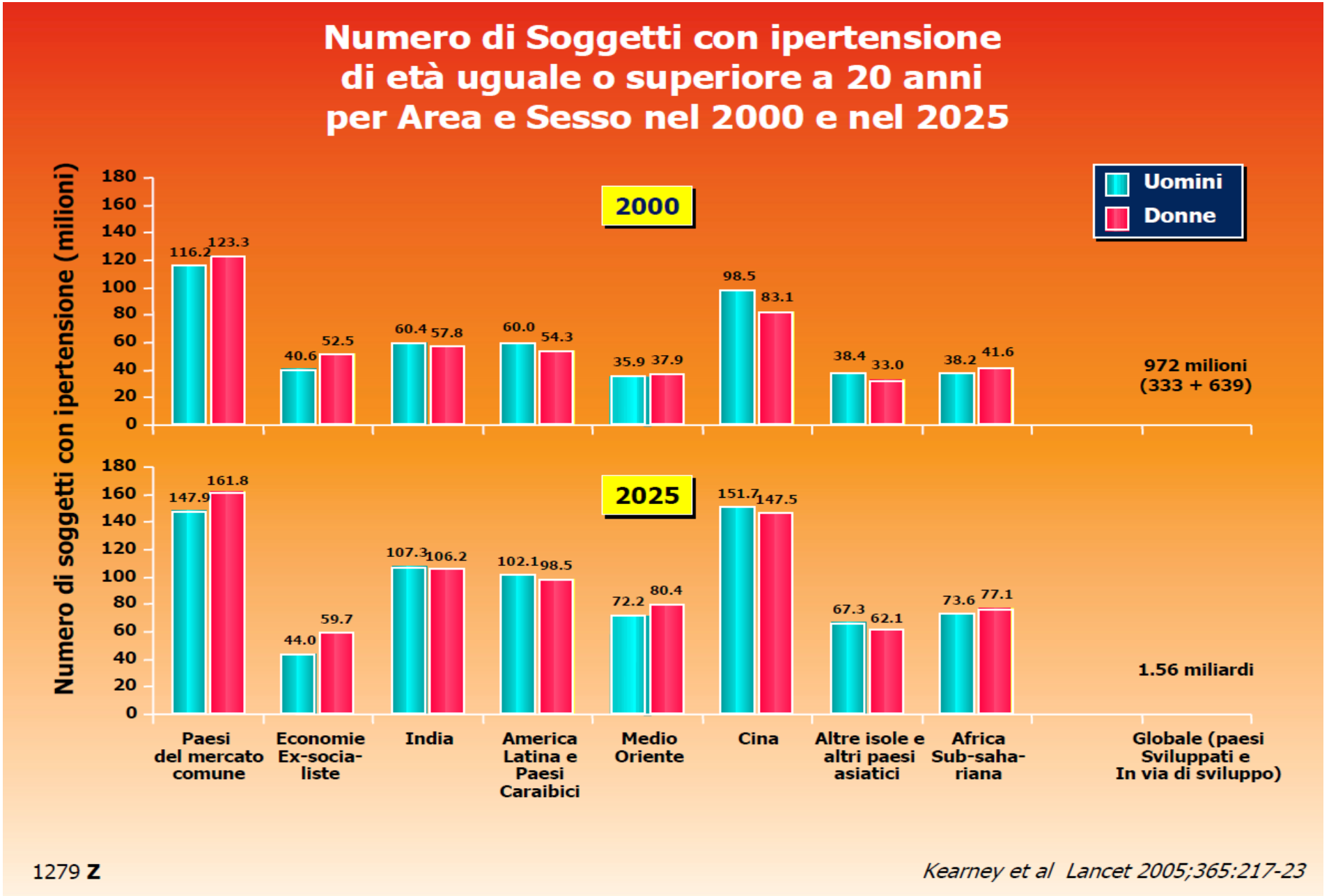
Circa 31.000 nuovi casi

PIRAMIDE DELLA POPOLAZIONE RESIDENTE PER SESSO E CITTADINANZA

Censimento 2011, valori percentuali



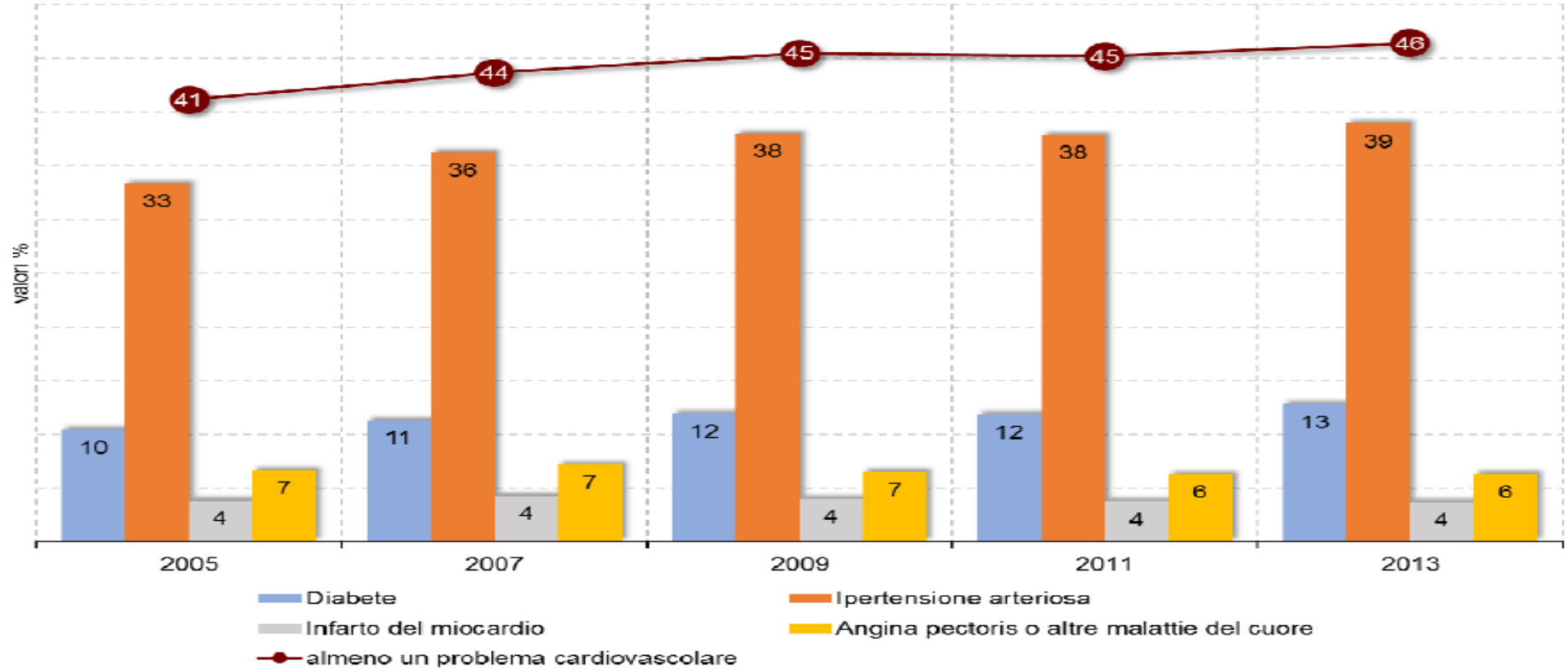
IL MONDO INVECCHIA……e non sempre bene



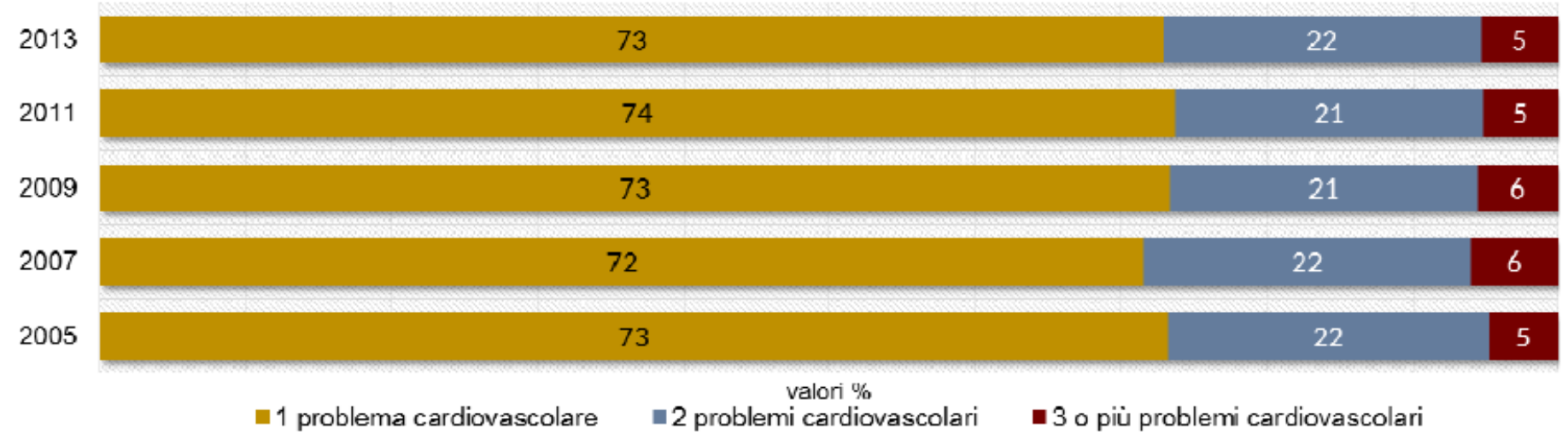
1279 **Z**

Kearney et al Lancet 2005;365:217-23

Popolazione di 50 anni e oltre per presenza di problemi cardiovascolari



Popolazione di 50 anni e oltre con problemi cardiovascolari per comorbidità



Principali comorbidità

Patologia	<60 anni	60-64 anni	65-74 anni	>75 anni
Ipertensione	8.7	34.3	43.5	53.9
Artrosi/Artrite	5.5	31.5	42	60
Osteoporosi	2.1	12.3	20.3	35.1
Diabete mellito	1.6	11.3	14.9	20.3
BPCO/Asma	1.1	7.8	11.3	20
Cardiopatie	0.6	4.8	8.8	17
Malattie Nervose	2.6	6.1	7	13.2
Allergie	12.1	9.2	9.4	9.1

Dati ISTAT 2012

The prevalence of multimorbidity, defined as the simultaneous existence of more than one pathologic condition in an individual, is increasing rapidly.

In USA, 64% of elderly people had two or more conditions and 24% had four or more conditions

A significant increase from 60 million in 2000 to 81 million in 2020

Oncologists can expect that more than half of the patients they see who are older than 65 years will have at least one other meaningful chronic condition that may affect their treatment

The FIL Experience: Pilot Study

Comprehensive geriatric assessment is an essential tool to support treatment decisions in elderly patients with diffuse large B-cell lymphoma: a prospective multicenter evaluation in 173 patients by the Lymphoma Italian Foundation (FIL)

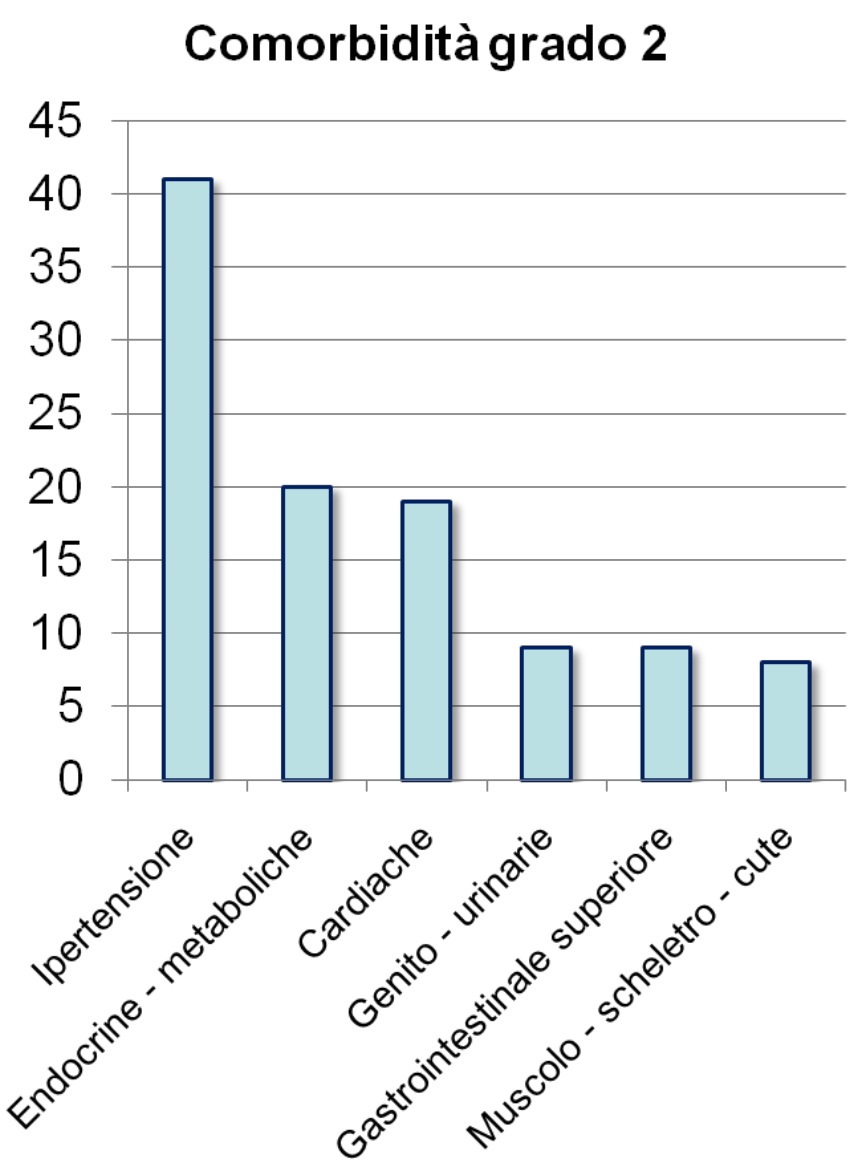
Tucci A. et al, Leuk Lymph, 2014

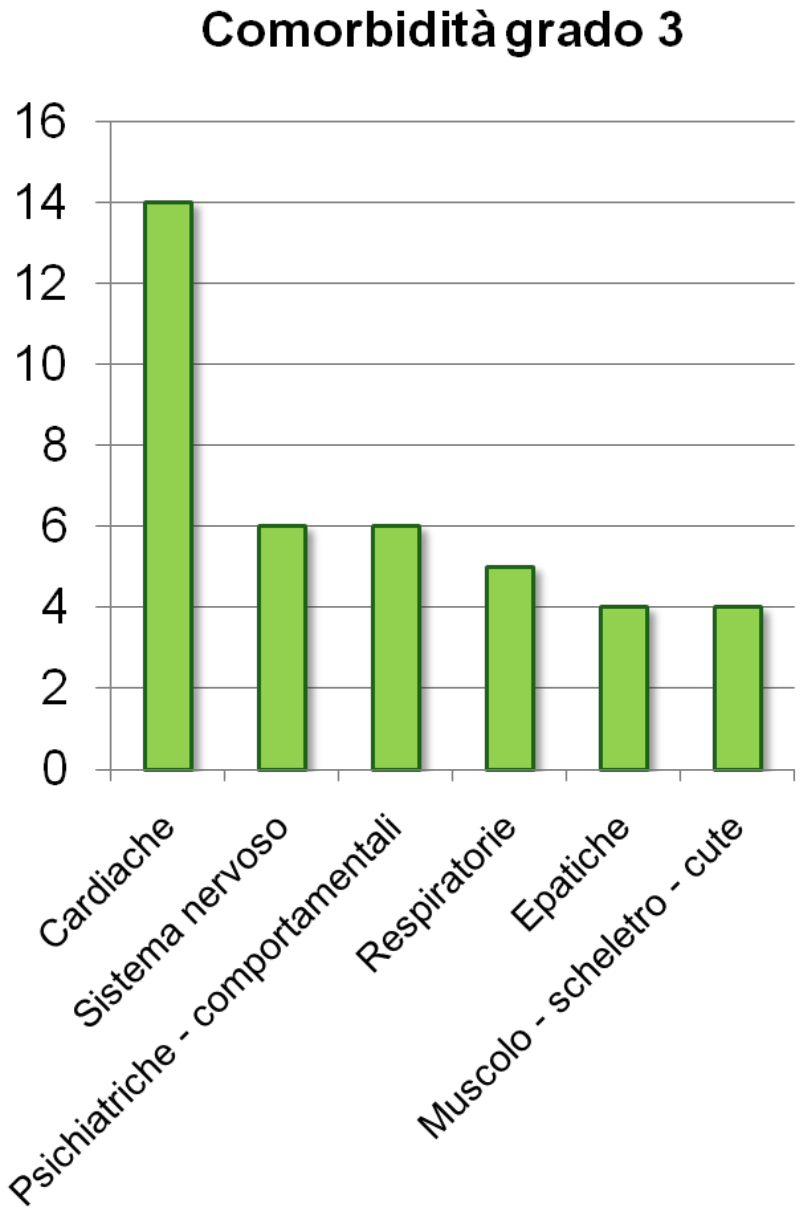
- Prospective multicenter observational study
  - Purpose: to evaluate the outcome of pts considering both the intensity of treatment received and the results of CGA

- **Inclusion Criteria:**
  - DLBCL
  - Age > 69 years
  - CGA at diagnosis

- **Treatement based on physician's judgment**

Comorbidità





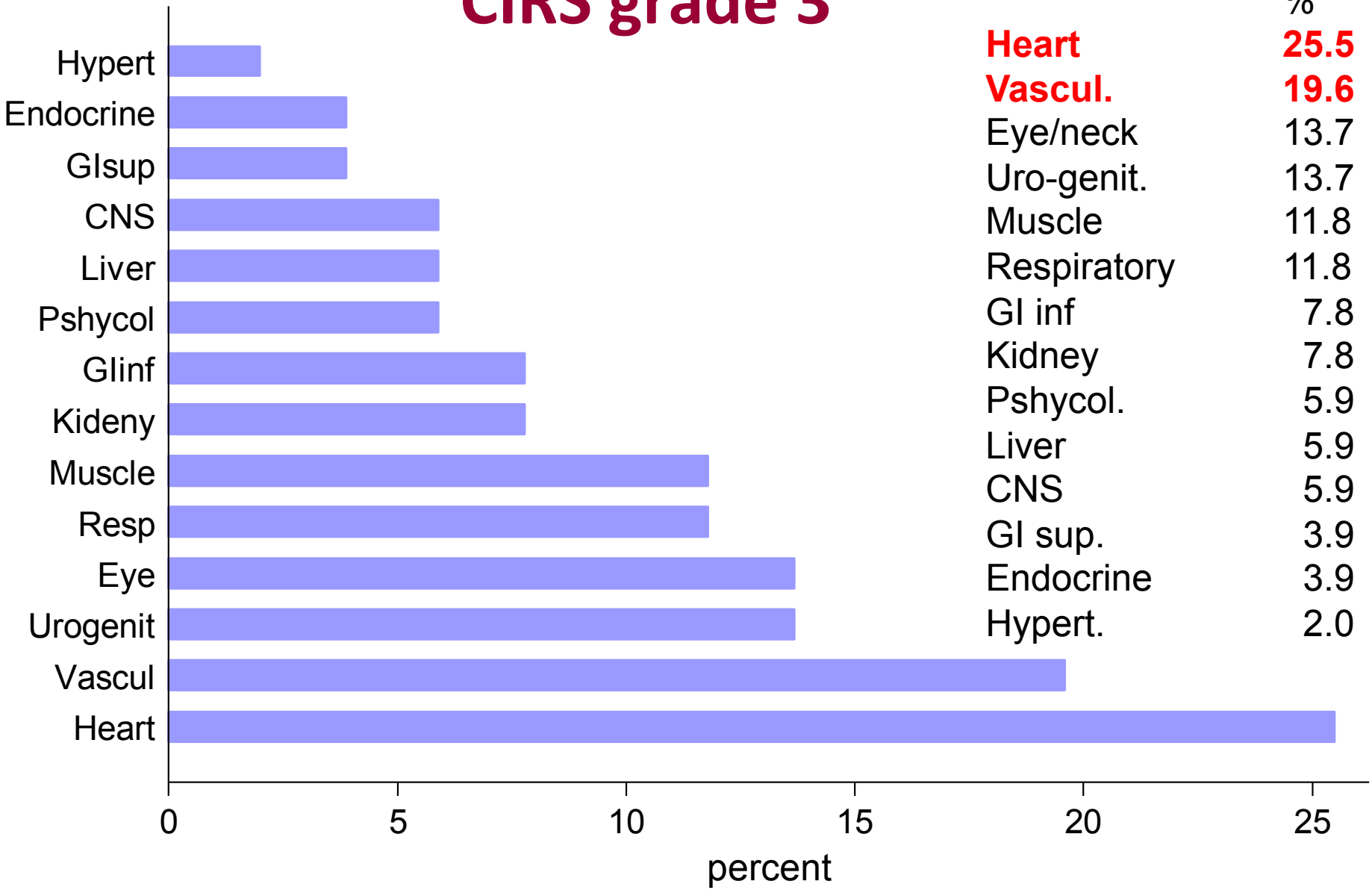
ELDERLY PROJECT

"Prospective Collection of Data of Elderly patients (≥ 65 years) with DLBCL undergoing a Multidimensional Geriatric Evaluation at diagnosis

FONDAZIONE ITALIANA LINFOMI

- Aims:
  - To provide clinicians with a **standardized tool** to assess CGA before treatment start;
  - To **validate CGA** results on a large series of consecutive patients.

Distribution of measured comorbidity with CIRS grade 3



	%
Heart	**25.5**
Vascul.	**19.6**
Eye/neck	13.7
Uro-genit.	13.7
Muscle	11.8
Respiratory	11.8
GI inf	7.8
Kidney	7.8
Pshycol.	5.9
Liver	5.9
CNS	5.9
GI sup.	3.9
Endocrine	3.9
Hypert.	2.0

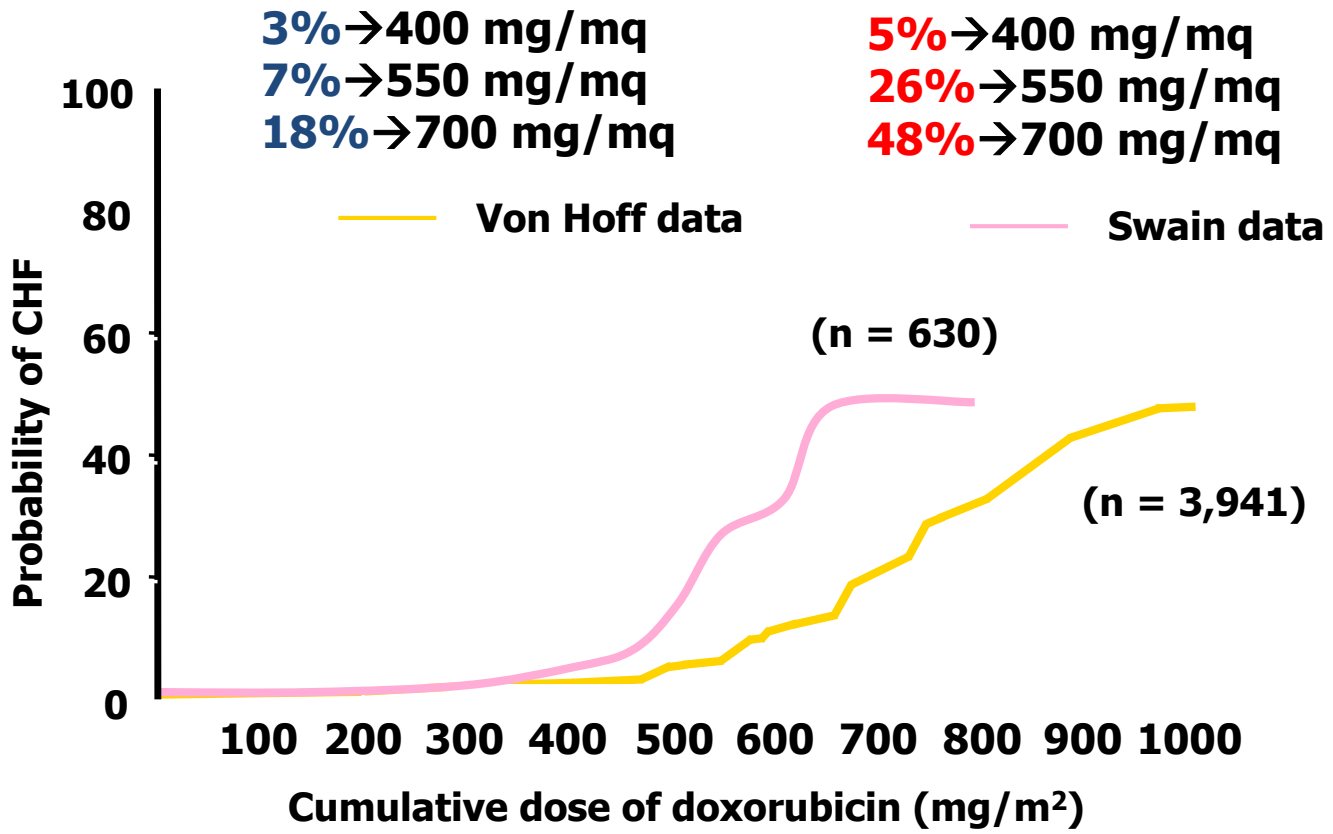
Nuovi e vecchi farmaci potenzialmente cardiotossici

Table 4 Cardiotoxicity of the main classes of cancer drugs used in clinical practice.

Class	Examples	Cancers treated	Cardiotoxicity	Mechanism of action
Anthracyclines	Doxorubicin, epirubicin, daunorubicin, idarubicin, mitoxantrone	Acute leukemias, Hodgkin's and non-Hodgkin's lymphomas, breast cancer	*Acute:* HF, arrhythmias, QT interval changes, ventricular repolarization abnormalities *Chronic (dose-dependent):* LV dysfunction (non-reversible)	Damage to cardiomyocytes: - Oxidative stress (ROS production) - Apoptosis
Alkylating agents	Cyclophosphamide	Bladder, endometrial, breast, ovarian, lung and blood cancers	Acute HF (usually reversible), pericardial effusion, arrhythmias	ROS production
	Cisplatin		Myocardial ischemia	–
Antimetabolites	5-Fluorouracil Capecitabine	Solid tumors, including lung, colon and breast	Myocardial ischemia, MI, arrhythmias	Coronary spasm, cardiomyocyte toxicity
Anti-microtubule agents	Paclitaxel	Breast and ovarian cancer, Kaposi's sarcoma, non-small-cell lung cancer	Bradycardia, syncope, LV dysfunction, ventricular arrhythmias, myocardial ischemia	Damage to cardiomyocytes
	Docetaxel	Breast cancer, non-small-cell lung cancer, head and neck cancers, prostate, bladder and ovarian cancer, gastric adenocarcinoma		
Vinca alkaloids	Vincristine, vinblastine and vinorelbine	Leukemias and lymphomas	Myocardial ischemia	–
Tyrosine kinase inhibiting antibodies	Trastuzumab	Breast cancer	LV dysfunction (reversible)	HER2 receptor inhibition
	Bevacizumab	Metastatic colorectal cancer, lung cancer	Systemic hypertension, venous thrombosis, LV dysfunction	VEGF inhibition
	Rituximab	Lymphomas, leukemias, transplant rejection, some autoimmune disorders	Orthostatic hypotension	Associated with allergies and angioedema
	Alemtuzumab	Chronic lymphocytic leukemia, cutaneous T-cell lymphoma, T-cell lymphoma	Hypotension, myocardial ischemia, LV dysfunction	–

R. Adão et al. Cardiotoxicity associated with cancer therapy: Pathophysiology and prevention strategies

Relationship between doxorubicin cumulative dose and probability of developing CHF



CHOP in LNH = 20% cardiac events within 1y (CHF 10%)
(cum doses >200 mg/mq)
[Limat S. et al: Ann Oncol, 14:277-281,2003]

Von Hoff *et al, Ann Intern Med* 1979; 91:710
Swain *et al, Cancer* 2003; 97:2869

FONDAZIONE ITALIANA LINFOMI

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Table 2 Factors associated with risk of cardiotoxicity following treatment with anthracyclines[a]

Risk factors
• Cumulative dose • Female sex • Age - >65 years old - Paediatric population (<18 years) • Renal failure • Concomitant or previous radiation therapy involving the heart • Concomitant chemotherapy - alkylating or antimicrotubule agents - immuno- and targeted therapies • Pre-existing conditions - Cardiac diseases associating increased wall stress - Arterial hypertension - Genetic factors

[a]Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin) or anthracenedione (mitoxantrone).

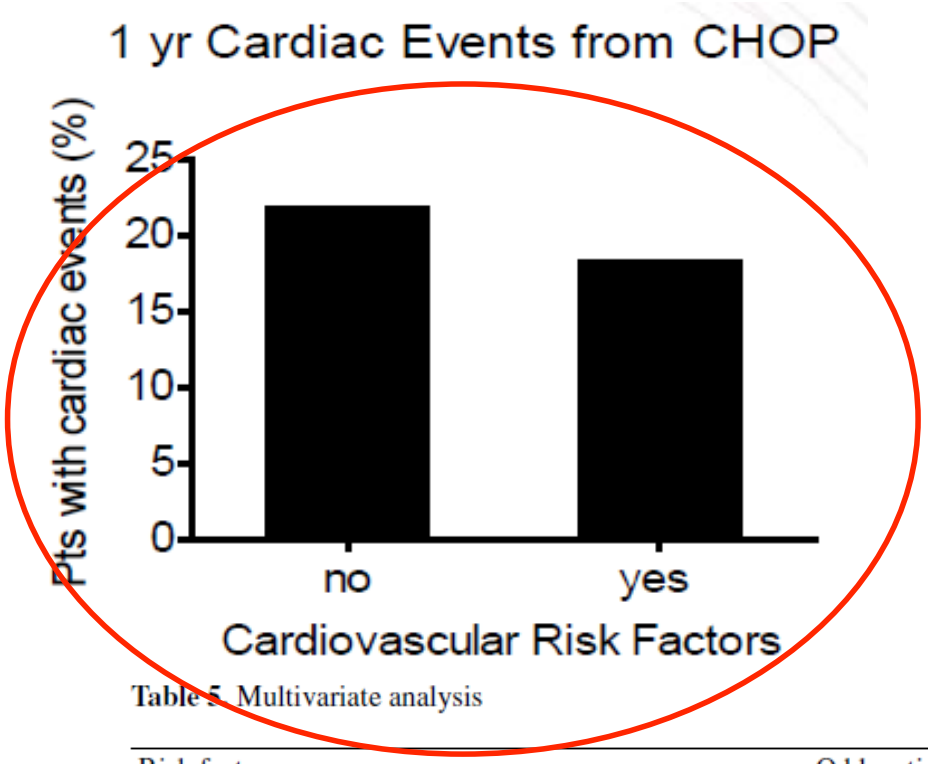
IL RISCHIO CARDIONCOLOGICO NON COINCIDE CON IL RISCHIO CARDIOLOGICO DEL PAZIENTE

Eur Heart Journal 2016

FONDAZIONE ITALIANA LINFOMI

Early cardiotoxicity of the CHOP regimen in aggressive non-Hodgkin's lymphoma

S. Limat[1], K. Demesmay[1], L. Voillat[2], Y. Bernard[3], E. Deconinck[2], A. Brion[2], A. Sabbah[4], M. C. Woronoff-Lemsi[1] & J. Y. Cahn[2]*



La tossicità a un anno sembra essere indipendente dai fattori di rischio cardiovascolare

Table 5. Multivariate analysis

Risk factors	Odds ratio	95% CI	*P* value
Cumulative dose of doxorubicin >200 mg/m^2	4.2	1.3–13.5	0.005
Age >50 years	2.9	1–8.5	0.03

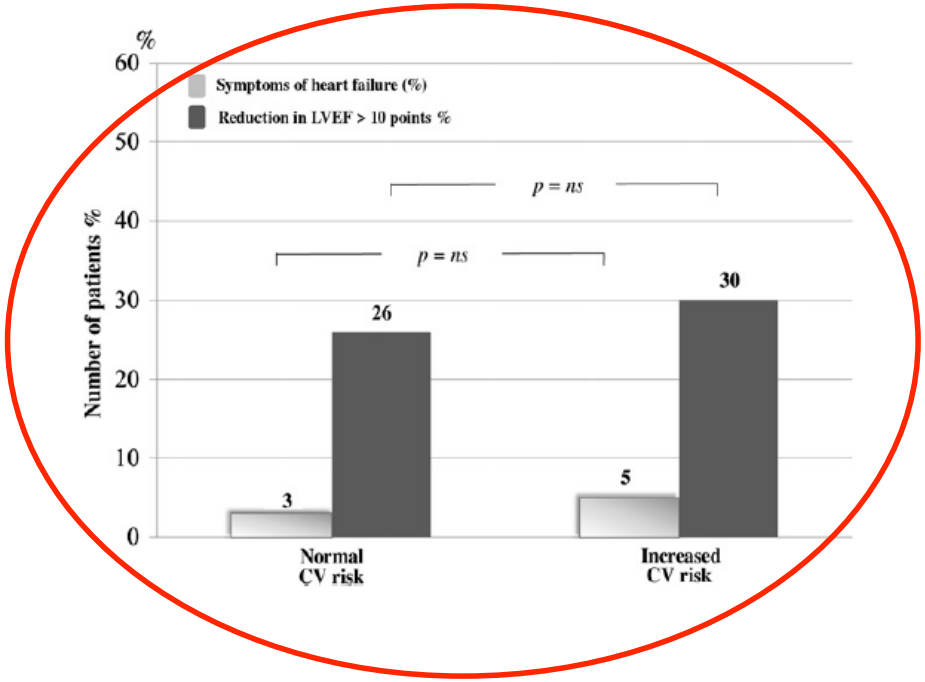
CI, confidence interval.

Limat S. et al – Annals of Oncol 2003

FONDAZIONE ITALIANA LINFOMI

Trastuzumab Adjuvant Chemotherapy and Cardiotoxicity in Real-World Women With Breast Cancer

LUIGI TARANTINI, MD,[1] GIOVANNI CIOFFI, MD,[2] STEFANIA GORI, MD,[3] FAUSTO TUCCIA, MD,[1] LIDIA BOCCARDI, MD,[4] DANIELLA BOVELLI, MD,[5] CHIARA LESTUZZI, MD,[6] NICOLA MAUREA, MD,[7] STEFANO OLIVA, MD,[8] GIULIA RUSSO, MD,[9] AND POMPILIO FAGGIANO, MD,[10] ON BEHALF OF THE ITALIAN CARDIO-ONCOLOGIC NETWORK*



La tossicità a un anno sembra essere indipendente dai fattori di rischio cardiovascolare

Stesse evidenze nel ca mammario!!

Tarantini L. et al – J Card Fail 2012

FONDAZIONE ITALIANA LINFOMI

Doxorubicin, Cardiac Risk Factors, and Cardiac Toxicity in Elderly Patients With Diffuse B-Cell Non-Hodgkin's Lymphoma

Dawn L. Hershman, Russell B. McBride, Andrew Eisenberger, Wei Yann Tsai, Victor R. Grann, and Judith S. Jacobson

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

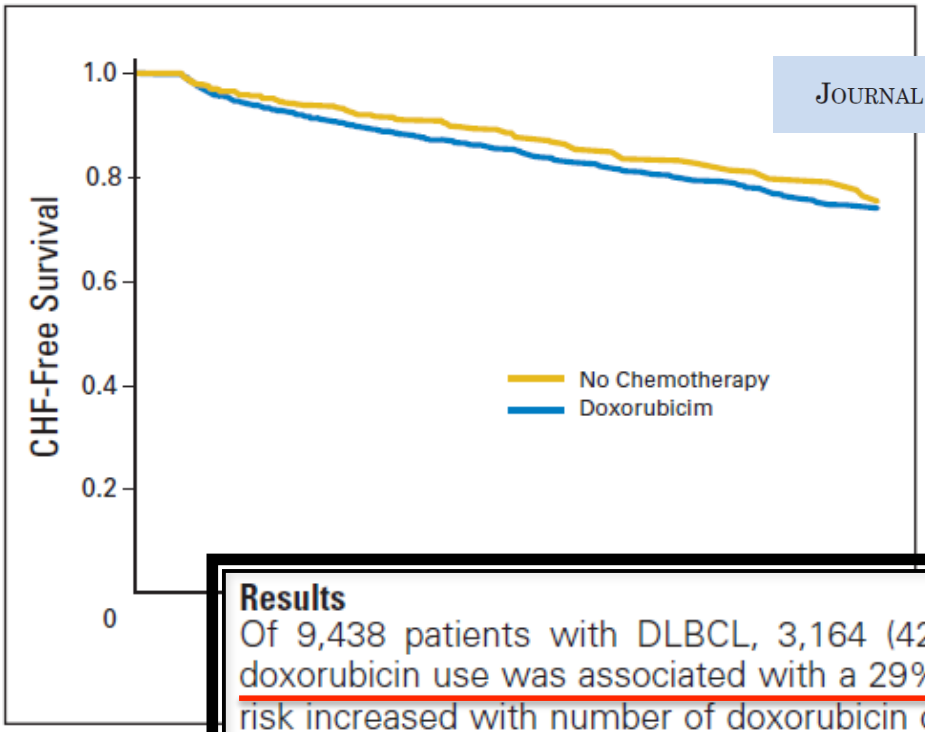


Fig 1. Weighted survival in patients chemotherapy (*P*

Results

Of 9,438 patients with DLBCL, 3,164 (42%) received doxorubicin-based chemotherapy. Any doxorubicin use was associated with a 29% increase in risk of CHF (95% CI, 1.02 to 1.62); CHF risk increased with number of doxorubicin claims, increasing age, prior heart disease, comorbidities, diabetes, and hypertension; hypertension intensified the effect of doxorubicin on risk of CHF (hazard ratio = 1.8; $P < .01$). In the 8 years after diagnosis, the adjusted CHF-free survival rate was 74% in doxorubicin-treated patients versus 79% in patients not treated with doxorubicin.

Hershman D.L. et al – JCO 2008

FONDAZIONE ITALIANA LINFOMI

Preexisting Cardiovascular Risk and Subsequent Heart Failure Among Non-Hodgkin Lymphoma Survivors

Talya Salz, Emily C. Zabor, Peter de Nully Brown, Susanne Oksberg Dalton, Nirupa J. Raghunathan, Matthew J. Matasar, Richard Steingart, Andrew J. Vickers, Peter Svenssen Munksgaard, Kevin C. Oeffinger, and Christoffer Johansen

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Results

- Among 2,508 survivors of NHL and 7,399 controls, **there was a 42% increased risk of HF among survivors** compared with general population controls;
- The cardiovascular risk factors determine the survivorship

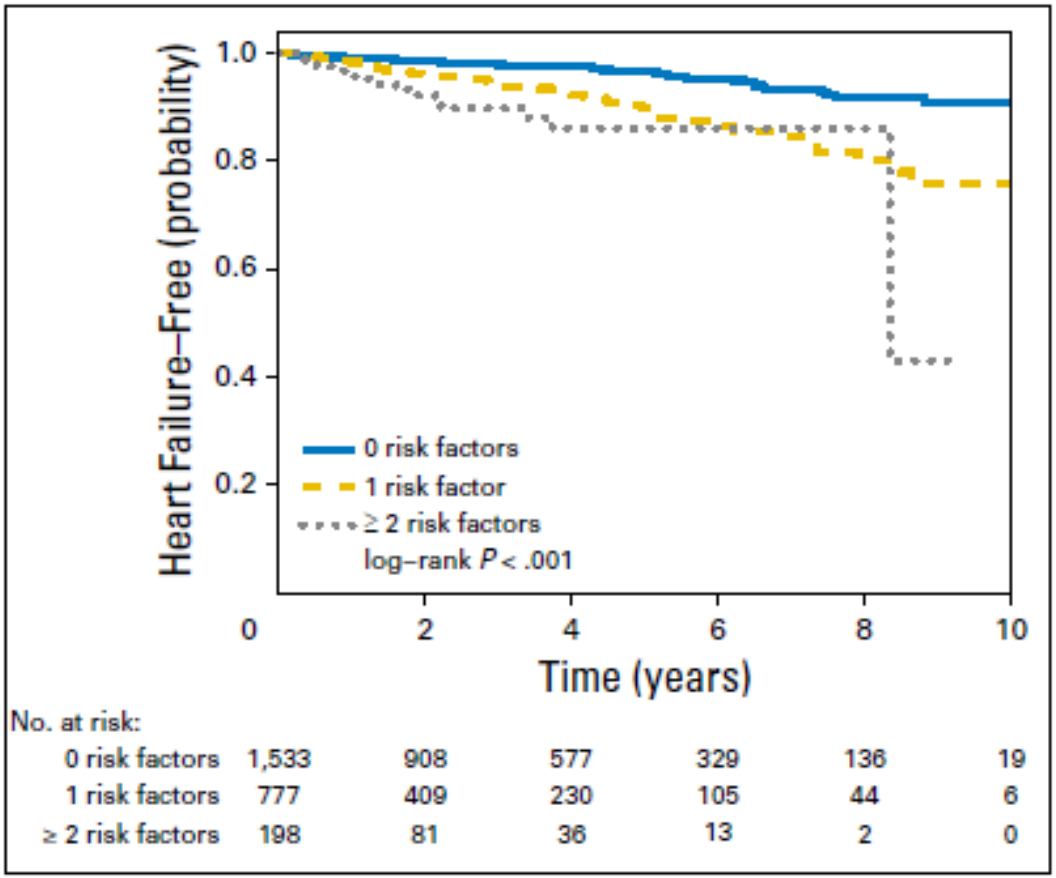


Fig 2. Kaplan-Meier estimates of remaining free of heart failure among lymphoma survivors with 0, 1, or ≥ 2 risk factors.

Salz T. et al – JCO 2017

FONDAZIONE ITALIANA LINFOMI

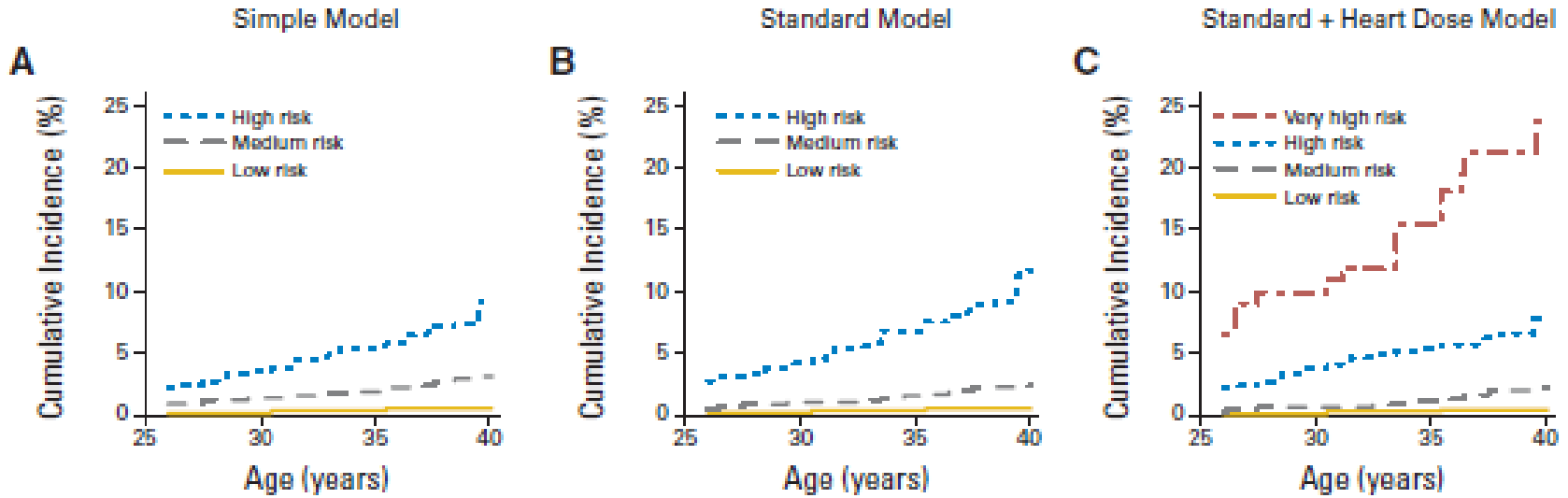
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Individual Prediction of Heart Failure Among Childhood Cancer Survivors

Eric J. Chow, Yan Chen, Leontien C. Kremer, Norman E. Breslow, Melissa M. Hudson, Gregory T. Armstrong, William L. Border, Elizabeth A.M. Feijen, Daniel M. Green, Lillian R. Meacham, Kathleen A. Meeske, Daniel A. Mulrooney, Kirsten K. Ness, Kevin C. Oeffinger, Charles A. Sklar, Marilyn Stovall, Helena J. van der Pal, Rita E. Weathers, Leslie L. Robison, and Yutaka Yasui

Results

Heart failure occurred in 285 CCSS participants. Risk scores based on selected exposures (sex, age at cancer diagnosis, and anthracycline and chest radiotherapy doses) achieved an area under the curve of 0.74 and concordance statistic of 0.76 at or through age 40 years. Validation cohort estimates ranged from 0.68 to 0.82. Risk scores were collapsed to form statistically distinct low-, moderate-, and high-risk groups, corresponding to cumulative incidences of heart failure at age 40 years of 0.5% (95% CI, 0.2% to 0.8%), 2.4% (95% CI, 1.8% to 3.0%), and 11.7% (95% CI, 8.8% to 14.5%), respectively. In comparison, siblings had a cumulative incidence of 0.3% (95% CI, 0.1% to 0.5%).

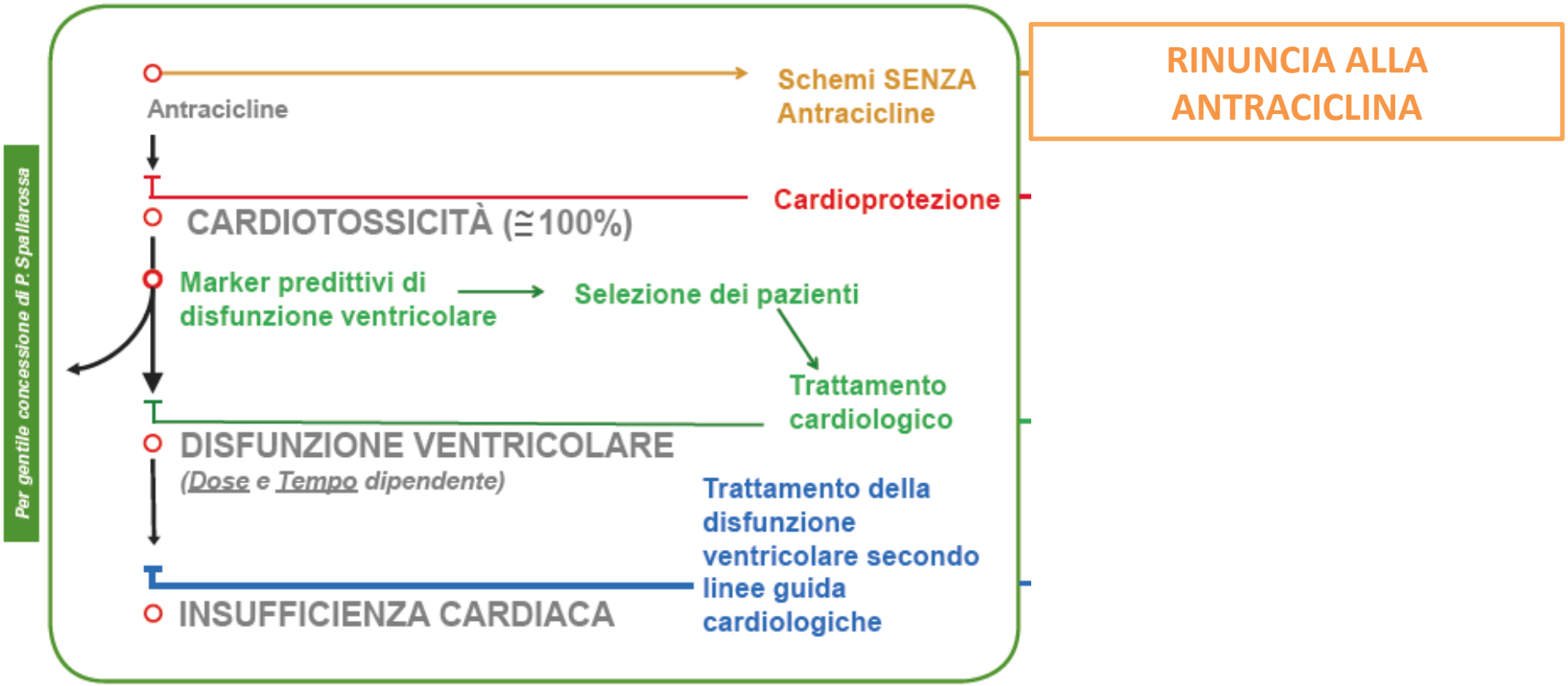


JCO 2015

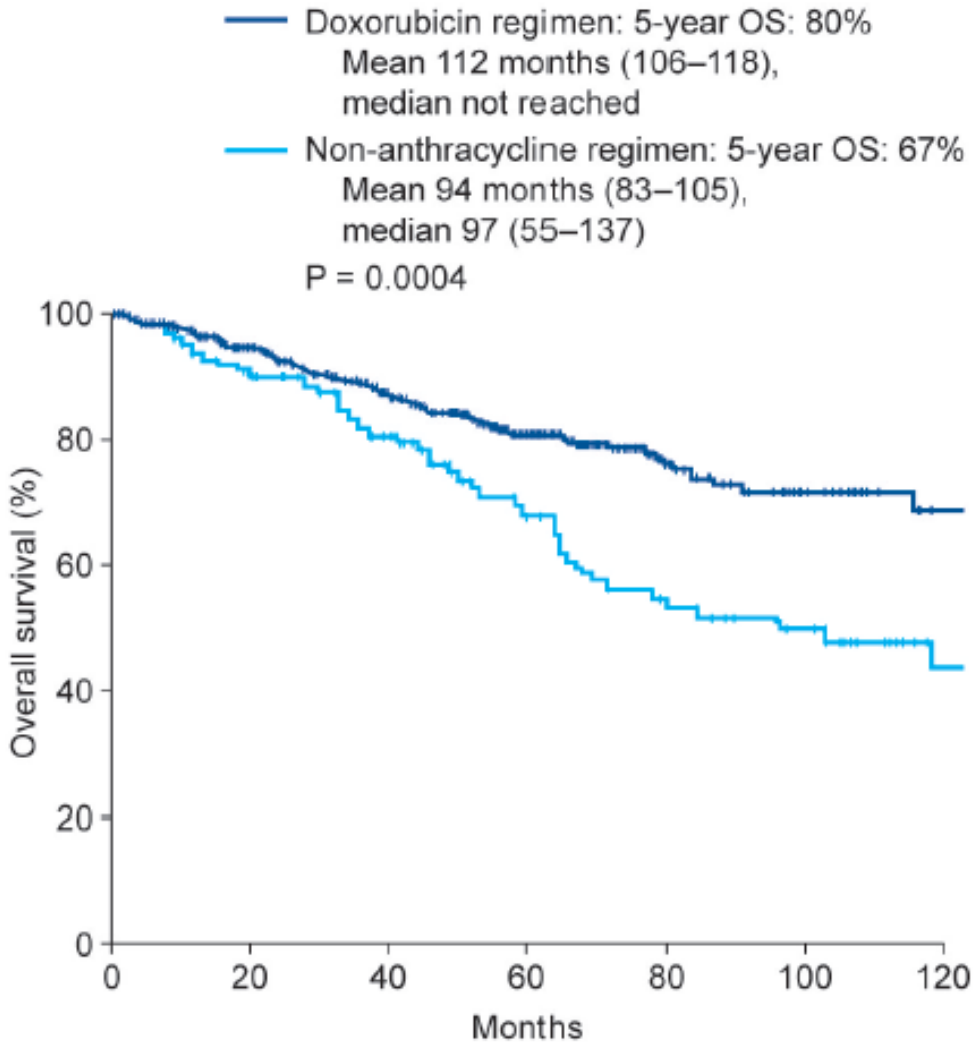
HELP FOR HEART

GESTIONE DEL PAZIENTE CON CARDIOTOSSICITA'

Stefano Oliva, Paolo Spallarossa



Aggressive NHL and cardiotoxicity
The «exit» strategies: without Doxo

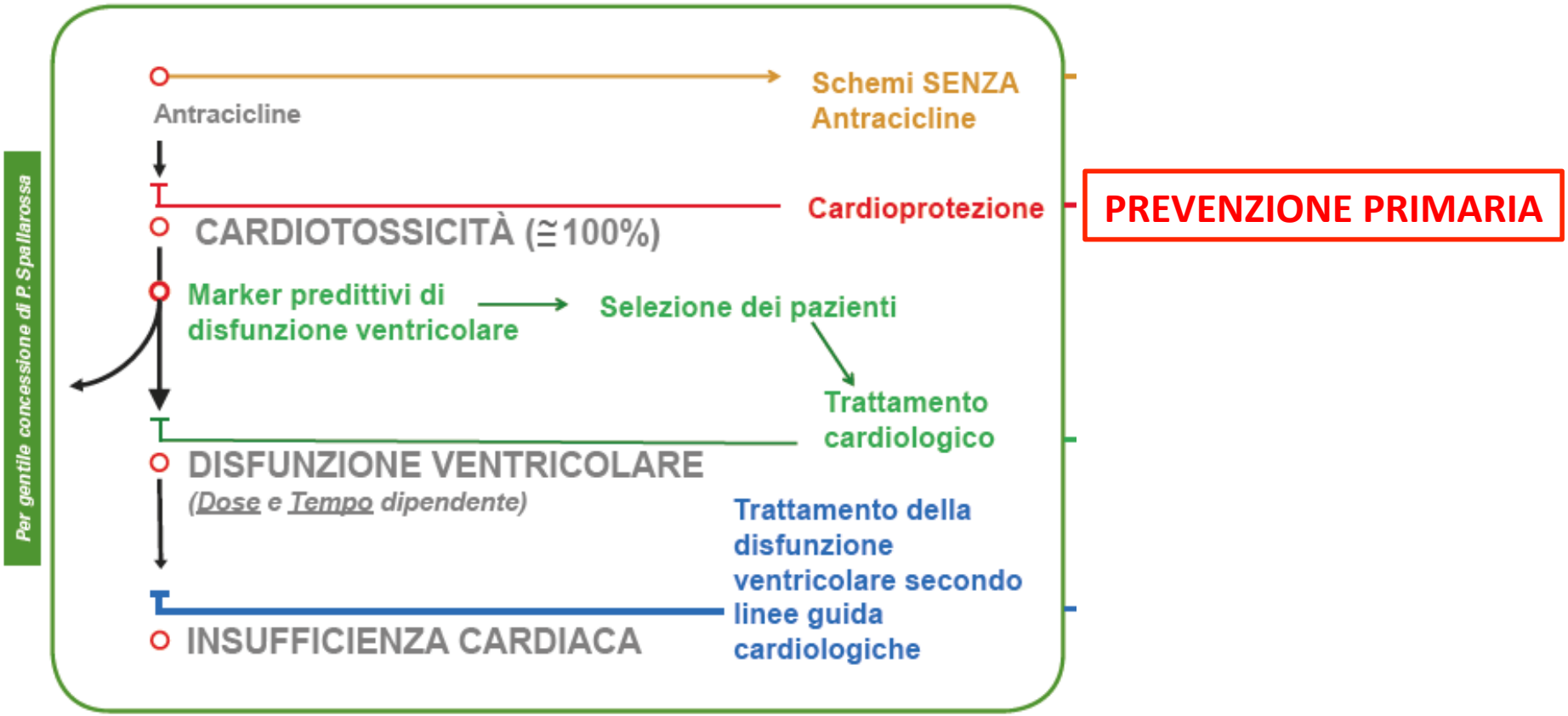


Rigacci L. et al – Leukemia Lymphoma 2003

HELP FOR HEART

GESTIONE DEL PAZIENTE CON CARDIOTOSSICITA'

Stefano Oliva, Paolo Spallarossa



La prevenzione farmacologica primaria

Table III. Liposomal doxorubicin-based regimens in aggressive non-Hodgkin lymphoma*.

Reference	Patients (*n*)	Reasons for LD choice	Treatment	Drug	Outcome	LVEF post-treatment	Cardiac events
Visani *et al.*, 2008 [26]	20	Median age (range): 73 years (61–82) Hypertension: 50% Cardiac	R-COMP × 4–6	NPLD 50 mg/m^2	CR: 65% DFS: 83% at 2 years OS: 90% at 2 years	No change in 17/20 patients; − 20% in 2 patients (10%)	2 cases of CHF; 1 case of fatal pulmonary embolism
				NPLD 50 mg/m^2	CR: 57% PFS: 69% at 3 years OS: 72% at 3 years	No change overall; − 20% or drop < 50% in 4/72 patients (5%)	4% grade 3–4 cardiac events; 1 case of fatal CHF
				NPLD 50 mg/m^2	76% % at 1 year hs	No change in 20/21 patients; − 30% in 1 patient (5%)	1 case of CHF
					% 36% at 2 years? OS: 87% at 2 years	No change overall	No clinical events
				NPLD 50 mg/m^2	CR: 68% TTF: 49% at 4 years OS: 67% at 4 years	No change overall; < 40% in 3/41 patients (7%)	17% grade 3–4 cardiac events
Gimeno *et al.*, 2011 [94]	35†	Median age (range): 76 years (61–88) Hypertension: 63% Cardiac comorbidities§: 87%	R-CMyOP × 4–6	NPLD 30 mg/m^2	CR: 69% PFS: 58% at 2 years OS: 70% at 2 years	No change overall; < 50% in 4/35 patients (11%)	14% cardiac events; 2 cases of CHF

LA FORMULAZIONE LIPOSOMIALE NON PEGILATA CONSENTE L'UTILIZZO DELLA ANTRACICLINA ANCHE NEI PAZIENTI NEI QUALI L'USO SAREBBE SCONSIGLIATO, CON PECENTUALI DI CARDITOSSICITA' ACCETTABILI

Zinzani P.L. et al – Leukemia Lymphoma 2015

ORIGINAL RESEARCH ARTICLE

Nonpegylated liposomal doxorubicin combination regimen in patients with diffuse large B-cell lymphoma and cardiac comorbidity. Results of the HEART01 phase II trial conducted by the Fondazione Italiana Linfomi

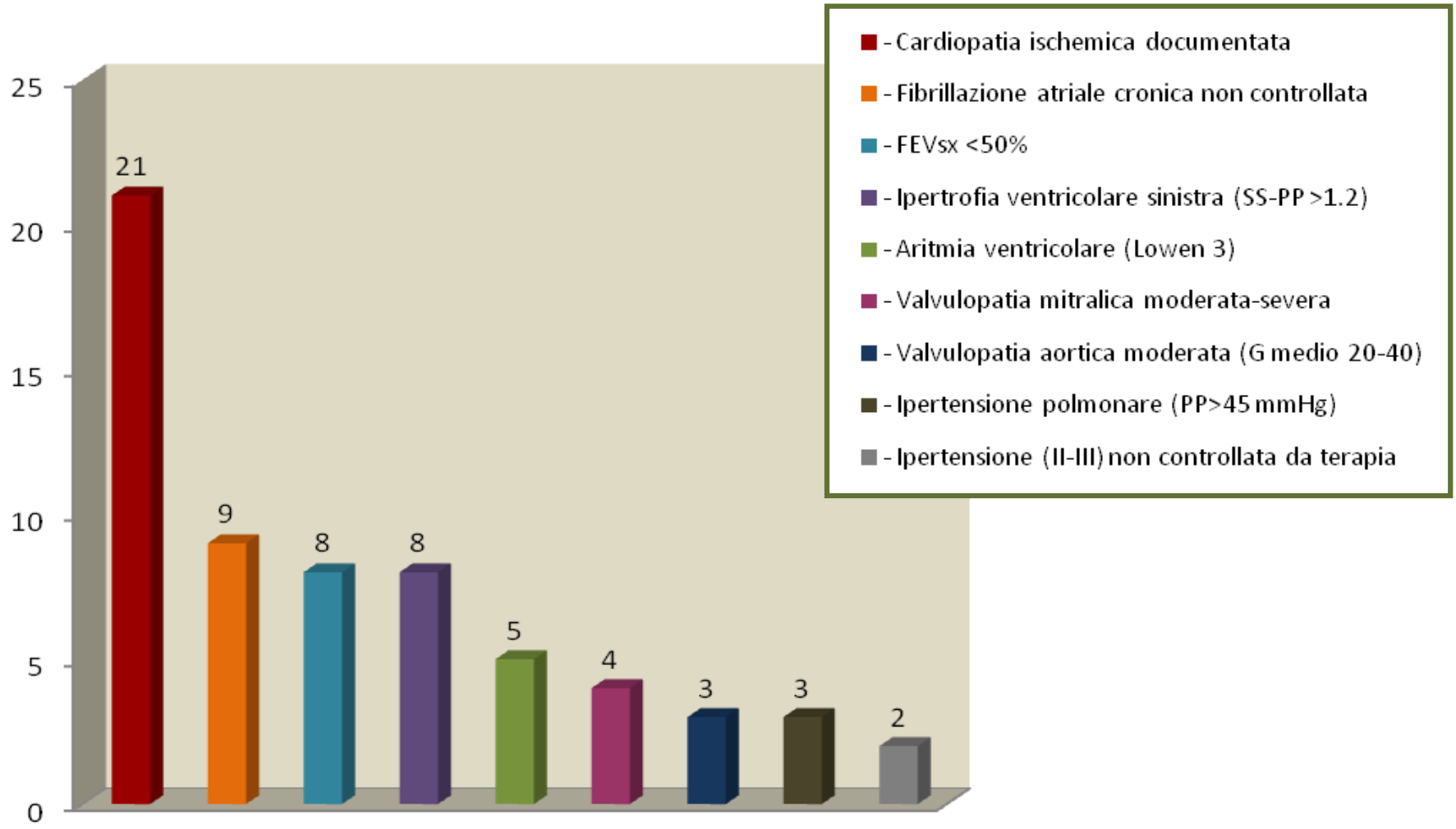
Stefano Luminari[1,2] | Elda Viel[3] | Andrés José Maria Ferreri[4] | Francesco Zaja[5] | Emanuela Chimienti[6] | Gerardo Musuraca[7] | Alessandra Tucci[8] | Monica Balzarotti[9] | Monica Tani[10] | Francesca Salvi[11] | Emanuela A. Pesce[12] | Angela Ferrari[1] | Anna M. Liberati[13] | Antonio Spadea[14] | Dario Marino[15] | Maria Bruno-Ventre[4] | Stefano Volpetti[5] | Chiara Bottelli[8] | Elena Ravaioli[6] | Francesco Merli[1] | Michele Spina[6]

CRITERI DI CARDIOPATIA

- ✓ **FEVS < 50%**
- ✓ **Ipertrofia ventricolare sinistra (SS-PP>1.2)**
- ✓ **Ipertensione arteriosa moderata-severa non controllata dalla terapia**
- ✓ **Cardiopatia ischemica documentata**
- ✓ **Aritmie ventricolari significative note (Lown 3)**
- ✓ **Fibrillazione atriale cronica non controllata**
- ✓ **Ipertensione polmonare (PP > 45 mmHg)**
- ✓ **Valvulopatia mitralica moderata-severa**
- ✓ **Valvulopatia aortica moderata (G medio 20-40)**

FONDAZIONE ITALIANA LINFOMI

PATOLOGIA CARDIACA
(N=63*)



*Concomitanza di due diversi tipi di cardiopatie = 4 casi
Concomitanza di tre diversi tipi di cardiopatie = 4 casi

VARIAZIONE FEV

FONDAZIONE ITALIANA LINFOMI

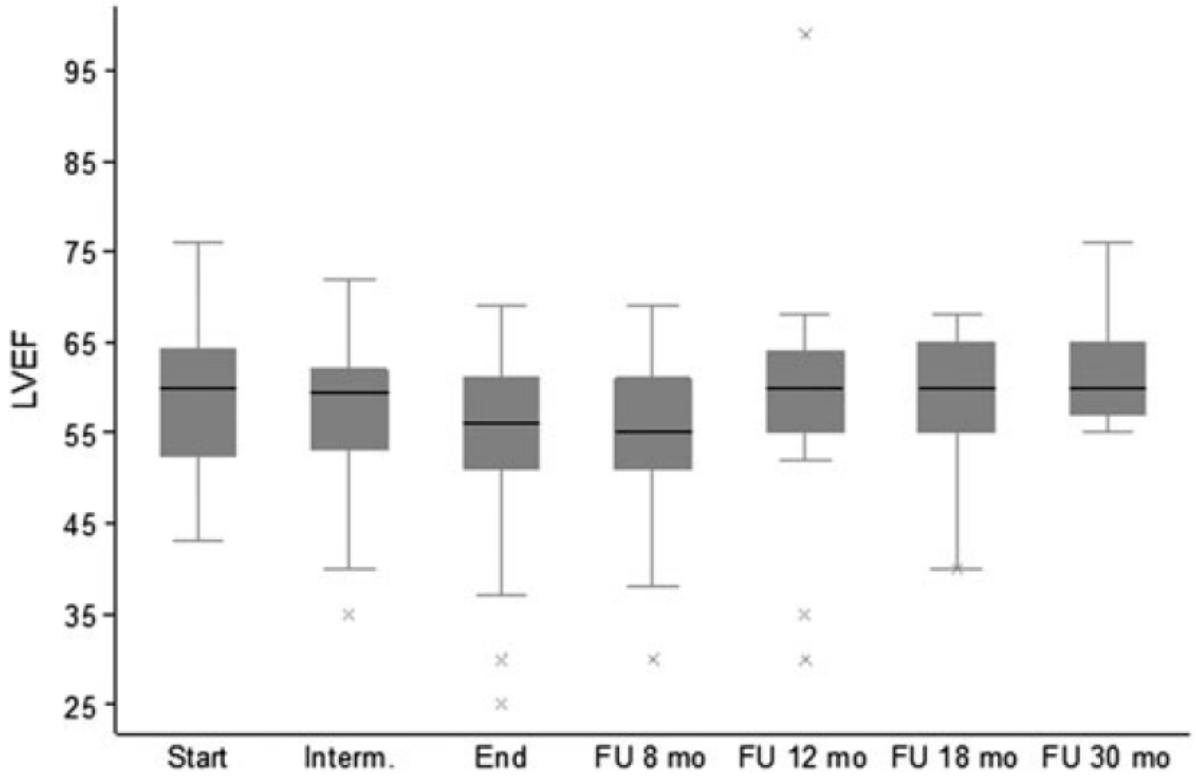


FIGURE 2 Left ventricular ejection fraction trend from baseline to end of follow up

TABLE 4 Summary of cardiac events during treatment

	Population (N = 50)	
Cardiac disorder	**Grades 1-2, n (%)**	**Grades 3-4, n (%)**
Heart failure	1(2)	1(2)
LVEF drop ≥20%	2(4)[a]	3(6)
Increased troponin	2(4)	-
Angina	-	1(2)
Atrial fibrillation	-	1(2)
Tot	**5(10)**	**6(12)**

Abbreviations: LVEF, left ventricular ejection fraction.

[a]Asymptomatic.

Conclusions

The substitution of conventional doxorubicin with non pegilated liposomal doxorubicin in the R-CHOP regimen is a safe and active option for patients with DLBCL presenting with concomitant moderate/severe cardiac disorders.

European Journal of Cancer 58 (2016) 112–121

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Clinical Trial

Cardiotoxicity with rituximab, cyclophosphamide, non-pegylated liposomal doxorubicin, vincristine and prednisolone compared to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone in frontline treatment of patients with diffuse large B-cell lymphoma A randomised phase-III study from the Austrian Cancer Drug Therapy Working Group *[Arbeitsgemeinschaft Medikamentöse Tumortherapie AGMT]* (NHL-14)

Michael A. Fridrik [a,*], Ulrich Jaeger [b], Andreas Petzer [c], Wolfgang Willenbacher [d], Felix Keil [e], Alois Lang [f], Johannes Andel [g], Sonja Burgstaller [h], Otto Krieger [i], Willi Oberaigner [j], Kurt Sihorsch [k], Richard Greil [l]

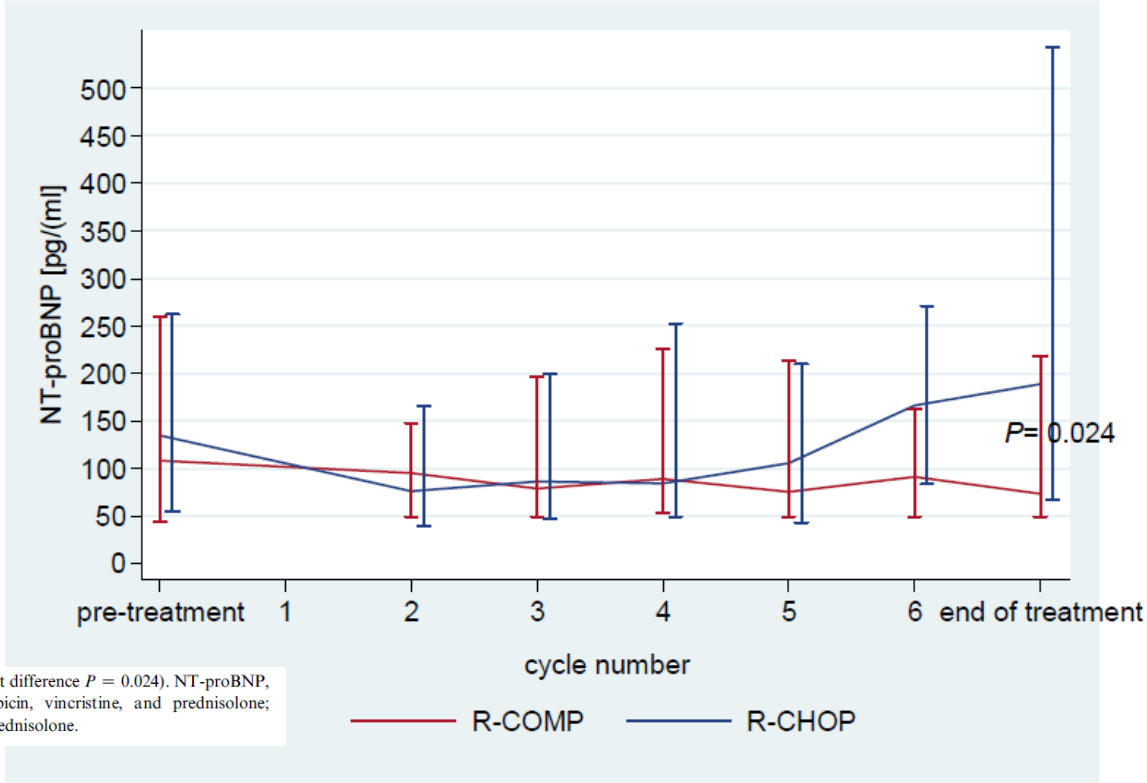
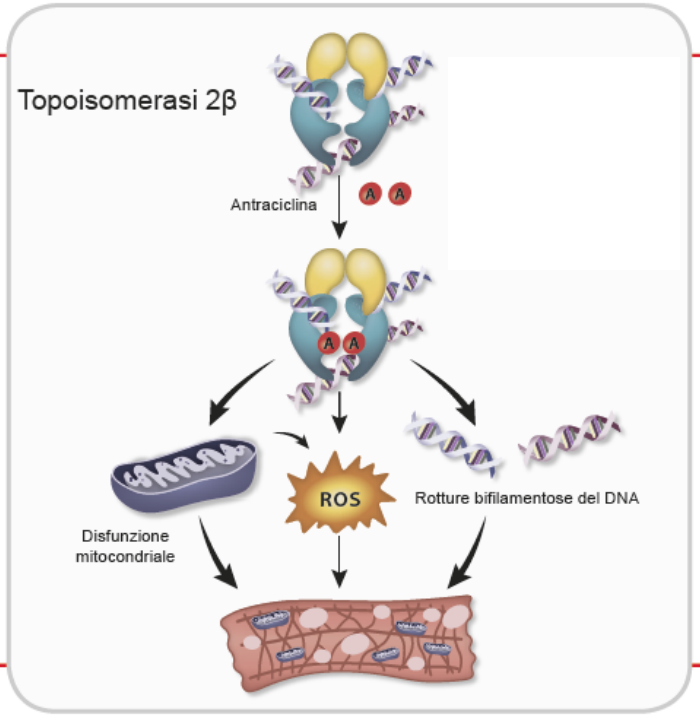


Fig. 2. Median NT-proBNP levels and interquartile range 25–75% during therapy (end of treatment difference $P = 0.024$). NT-proBNP, N-terminal pro B-type natriuretic peptide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-COMP, rituximab, cyclophosphamide, non-pegylated liposomal doxorubicin, vincristine and prednisolone.

HELP FOR HEART

CARDIOTOSSICITA' DA ANTRACICLINE

Giorgio Minotti, Stefano Oliva, Paolo Spallarossa



Da Rif. 5

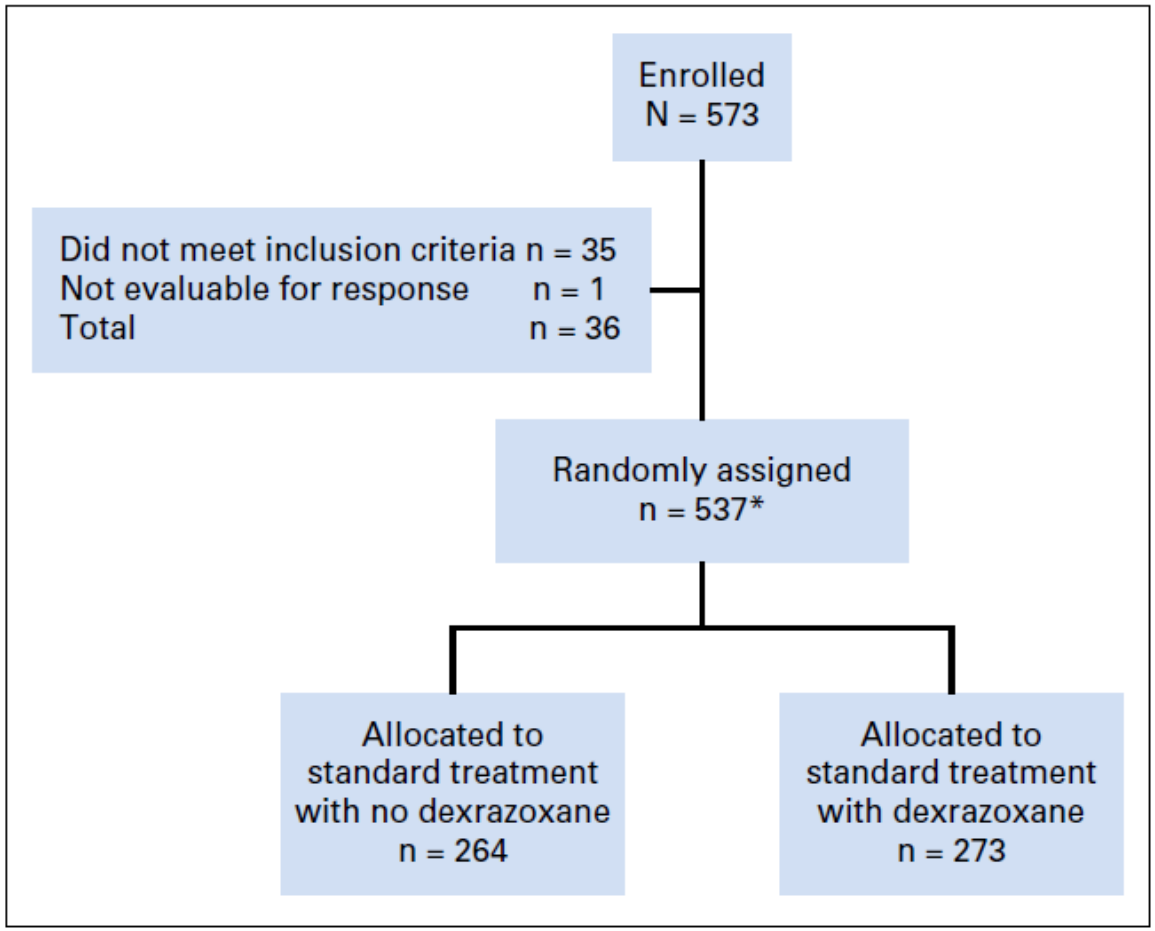
NUOVA TEORIA - Cardiotossicità mediata dall'inibizione di una topoisomerasi 2ß espressa costitutivamente nei cardiomiociti: Nel cuore, la stabilizzazione di un complesso ternario topoisomerasi 2ß-DNA-antraciclina determina rotture bifilamentose del DNA, con conseguenti alterazioni globali della trascrizione genica e, in ultima analisi, un'alterata biogenesi e funzione mitocondriale, con inadeguata produzione di ATP nel miocardio. Il ruolo dei ROS è tardivo e non esclusivo rispetto ad altri meccanismi[5]

VOLUME 34 · NUMBER 8 · MARCH 10, 2016

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cardioprotection and Safety of Dexrazoxane in Patients Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic Non-Hodgkin Lymphoma: A Report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404

Barbara L. Asselin, Meenakshi Devidas, Lu Chen, Vivian I. Franco, Jeanette Pullen, Michael J. Borowitz, Robert E. Hutchison, Yaddanapudi Ravindranath, Saro H. Armenian, Bruce M. Camitta, and Steven E. Lipshultz

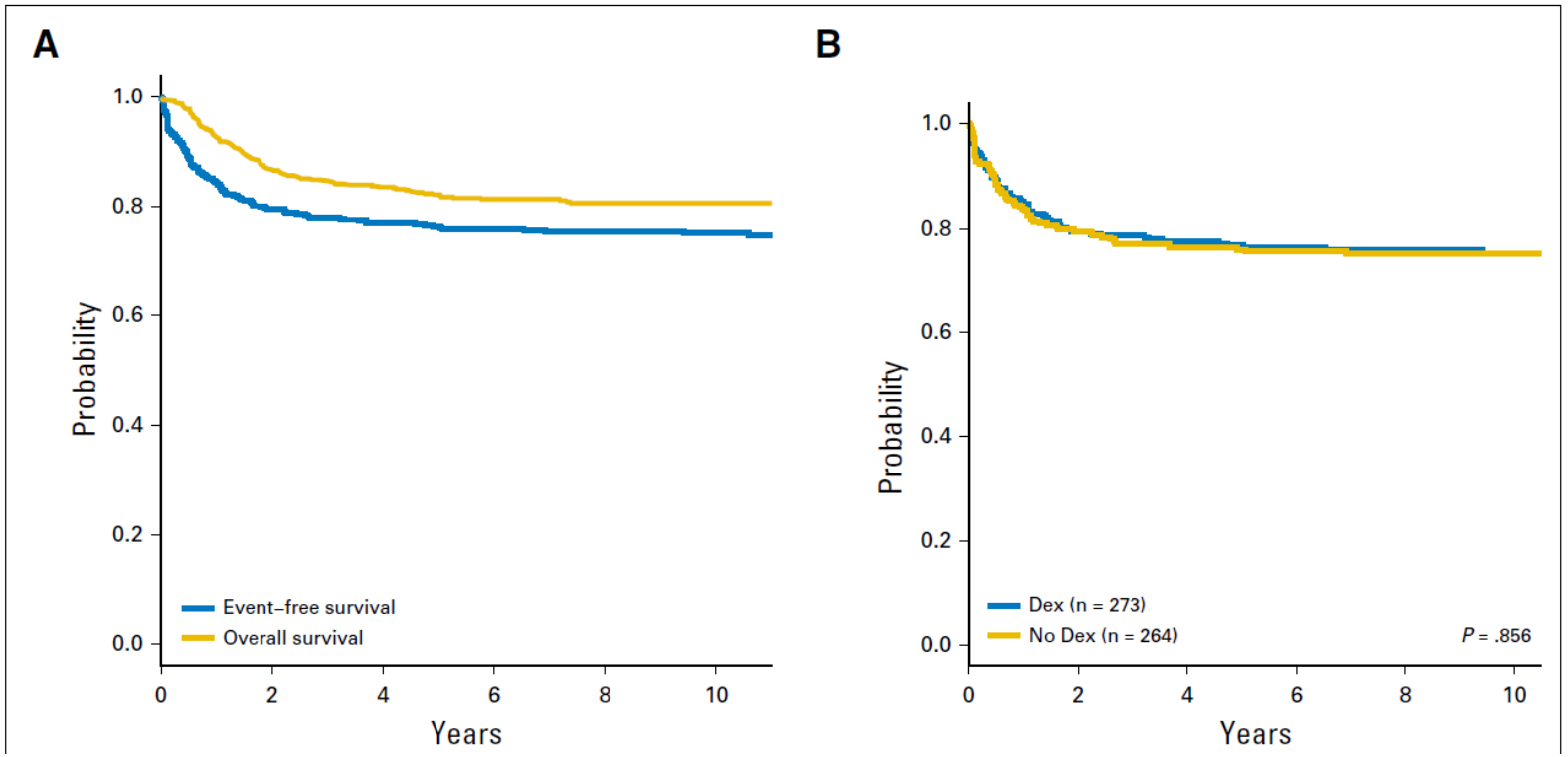


VOLUME 34 · NUMBER 8 · MARCH 10, 2016

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cardioprotection and Safety of Dexrazoxane in Patients Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic Non-Hodgkin Lymphoma: A Report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404

Barbara L. Asselin, Meenakshi Devidas, Lu Chen, Vivian I. Franco, Jeanette Pullen, Michael J. Borowitz, Robert E. Hutchison, Yaddanapudi Ravindranath, Saro H. Armenian, Bruce M. Camitta, and Steven E. Lipshultz



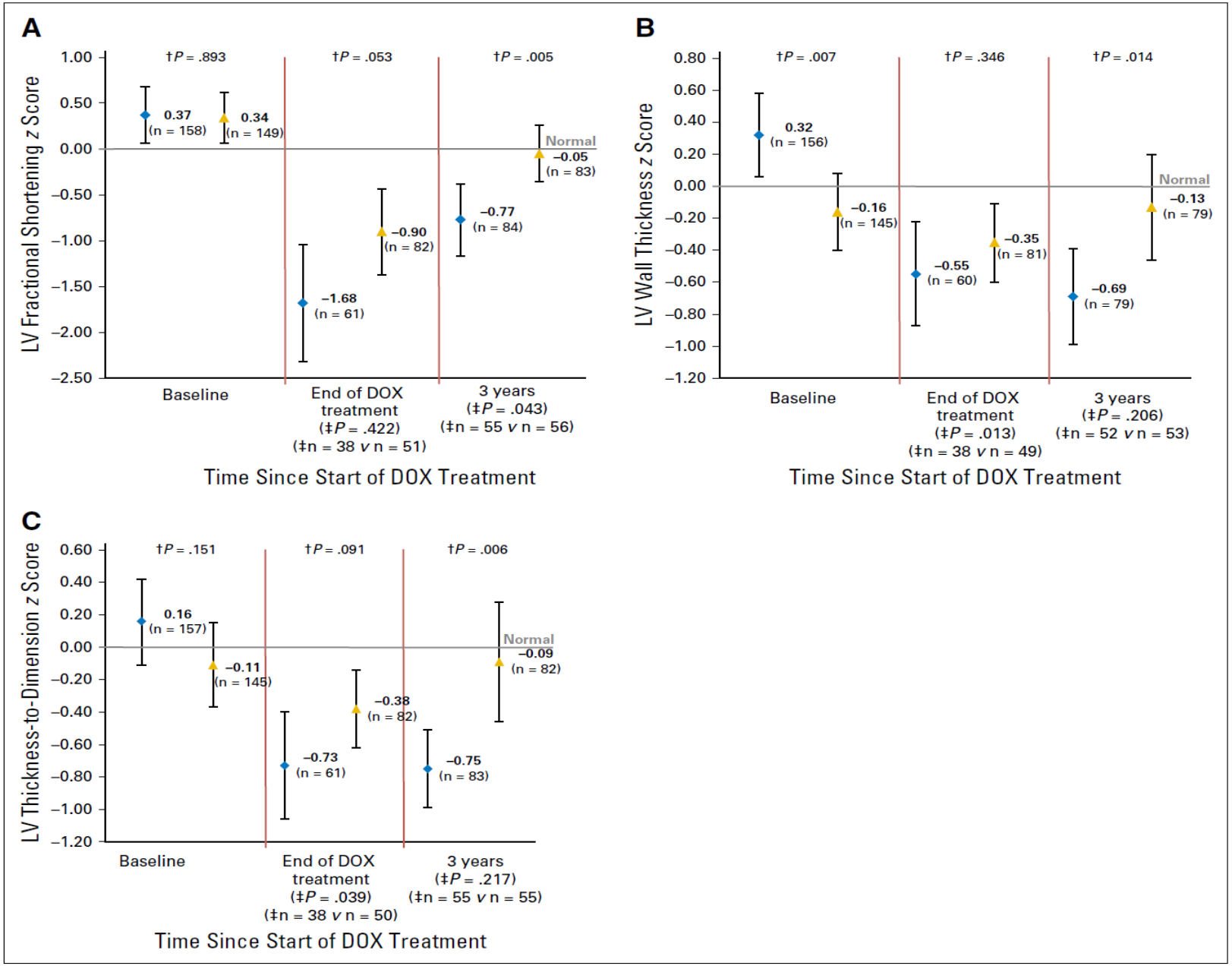
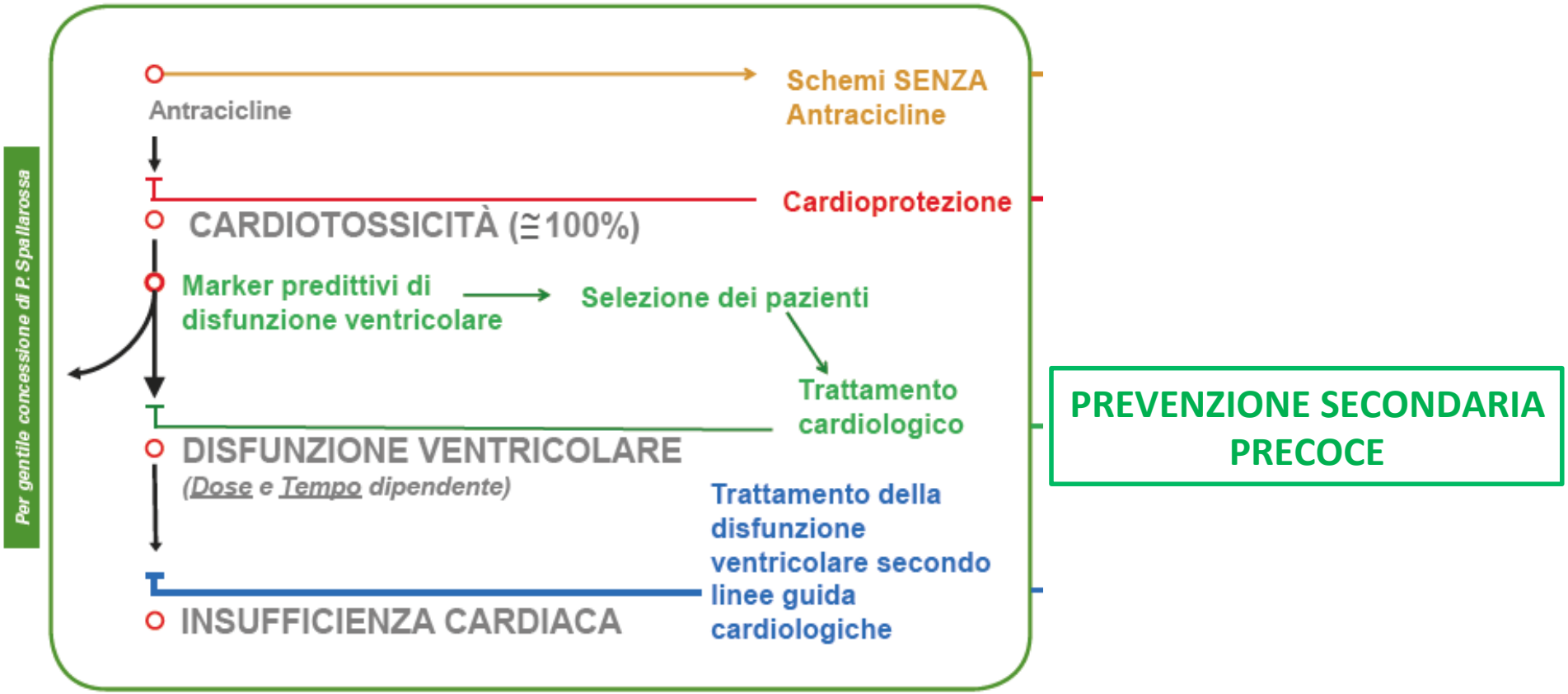


Fig 3. Estimated mean *z* scores by treatment group among 307 children with T-cell acute lymphoblastic leukemia or advanced-stage lymphoblastic non-Hodgkin lymphoma at baseline (n = 307), at end of therapy (n = 143), and at 3 years (n = 167). Comparison of change from baseline at each time point is noted at the bottom of the figure. (A) LV fractional shortening. (B) LV wall thickness. (C) LV thickness-to-dimension ratio. Bars represent 95% CIs; blue diamond, standard treatment only (doxorubicin [DOX]); gold triangle, dexrazoxane plus standard treatment (DRZ + DOX). †*P* values comparing the two groups at each time point (baseline, end of DOX treatment, and 3 years). ‡*P* values for differences in change in mean *z* scores since baseline in DOX- versus DOX- + DRZ-treated patients, for those patients with values at baseline and a second time point. n indicates number of patients with paired studies in each treatment group. Only patients with paired baseline and end-of-therapy or 3-year *z* scores were included in these analyses.

HELP FOR HEART

GESTIONE DEL PAZIENTE CON CARDIOTOSSICITA'

Stefano Oliva, Paolo Spallarossa



HELP FOR HEART

GESTIONE DEL PAZIENTE CON CARDIOTOSSICITA'

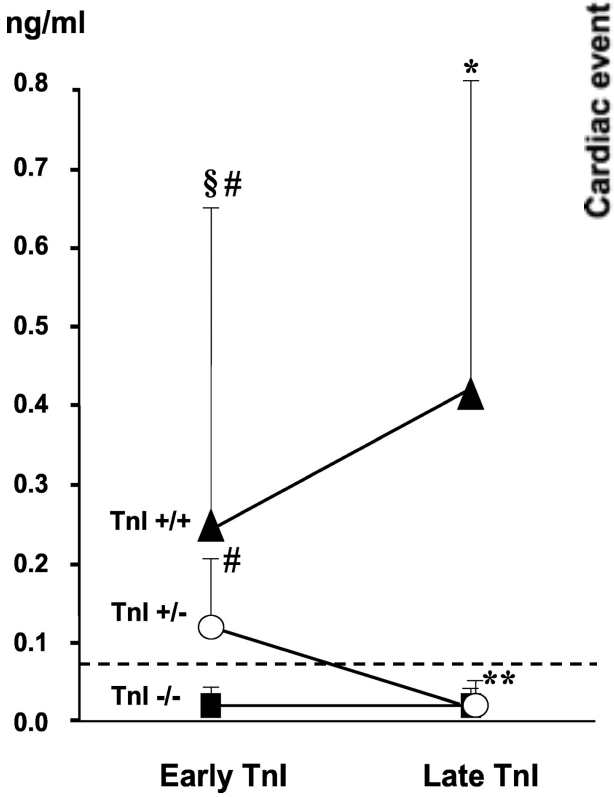
Stefano Oliva, Paolo Spallarossa

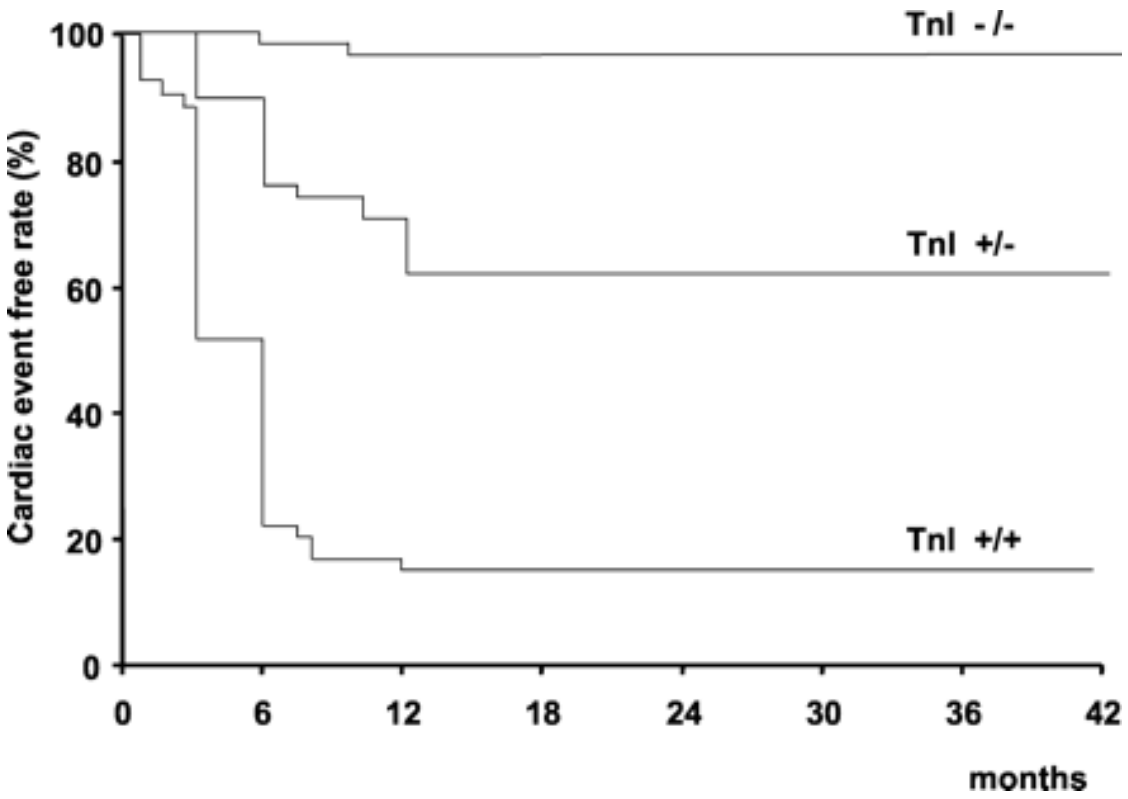
STUDIO DEI BIOMARCATORI PER IDENTIFICARE LA CARDIOTOSSICITÀ INDOTTA

BIOMARCATORE	COME RICERCARLO	VALORE SOGLIA	CHE COSA EVIDENZIA	ATTENDIBILITÀ
Troponina cardiaca I	Mediante prelievo venoso	0,08 ng/ml Nella pratica quotidiana, si può fare riferimento ai valori soglia adottati dal proprio laboratorio	Predittivo della disfunzione del ventricolo sinistro: un suo innalzamento precoce correla con un aumentato rischio di eventi cardiovascolari a 42 mesi, quindi nel lungo termine[34,35]	- Con valori permanentemente > valore soglia, maggiore incidenza di eventi cardiaci nell'84% dei pazienti[34,35] - Secondo le linee guida ESMO, possibile marcatore di identificazione del rischio cardiovascolare (evidenza e grado di raccomandazione 3)[23]
I pazienti individuati con questa metodica devono essere avviati al trattamento cardiovascolare sotto la gestione del cardiologo				

Per i pazienti in cui il dosaggio della troponina cardiaca I si mantenga **costantemente inferiore al valore soglia, il rischio di eventi cardiaci è praticamente nullo**[34,35]

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





The early elevation of TnI is associated with an increased risk for cardiovascular events at 42 months

Cardinale D. et al.- Circulation 2004

Prospective observational study on the use of anthracyclines and monitoring of cardiotoxicity in patients with diffuse large B-cell lymphoma (Cardio DLBCL)

S. Luminari
G. Gini

FONDAZIONE ITALIANA LINFOMI

Primary objective

- Assess the cardiotoxicity of chemotherapy by the analysis of serum markers and cardiac function.

Secondary objective

- Analyze the therapeutic choice among conventional anthracyclines and liposome and evaluate the toxicity of the treatments.
- Evaluate the efficacy of treatment in terms of overall response rate (ORR) and overall survival (OS).
- Evaluate the frequency and severity of adverse events as assessed by Common Toxicity Criteria for Adverse Effects (CTCAE) 4.0

INCLUSION CRITERIA

S. Luminari
G. Gini

- Patients with untreated DLBCL aged ≥18 years
- Planned full dose R-CHOP or R-CHOP-like (CEOP, COMP, CNOP)
- Stage I-IV
- ECOG performance status 0-3
- Left ventricular ejection fraction (LVEF) > 40%
- No prior treatment for lymphoma with the exception IF-RT
- HIV negativity
- No SNC involvment
- No active heart disease
- Written Informed Consent

FONDAZIONE ITALIANA LINFOMI

CARDIOTOXICITY ASSESSMENTS

S. Luminari
G. Gini

FONDAZIONE ITALIANA LINFOMI

	Baseline	Each Cycle	After cycle 3	End of therapy	Follow up
ECG*	●	●	●	●	●
Echocardiogram	●		●*	●	●
Serum sample for biomarkers**	●	●	●	●	
DLCO*	●			●	

* **Recommended if available, not mandatory**

** **Troponin I, BNP (centralized analysis)**

STATISTICAL CONSIDERATIONS

S. Luminari
G. Gini

- Primary endpoint: rate of cardiac events (Lenihan et al Cancer 2013)
- Probability of event: 20%
- Confidence interval of 95%
- 124 patients treated with anthracycline to observe between 16 and 35 events.
- Drop out rate 10-15%

FONDAZIONE ITALIANA LINFOMI

Planned total sample size of 150 patients

2017: il Progetto «Cardioscore»

Stefano Oliva, Guido Gini

FONDAZIONE ITALIANA LINFOMI

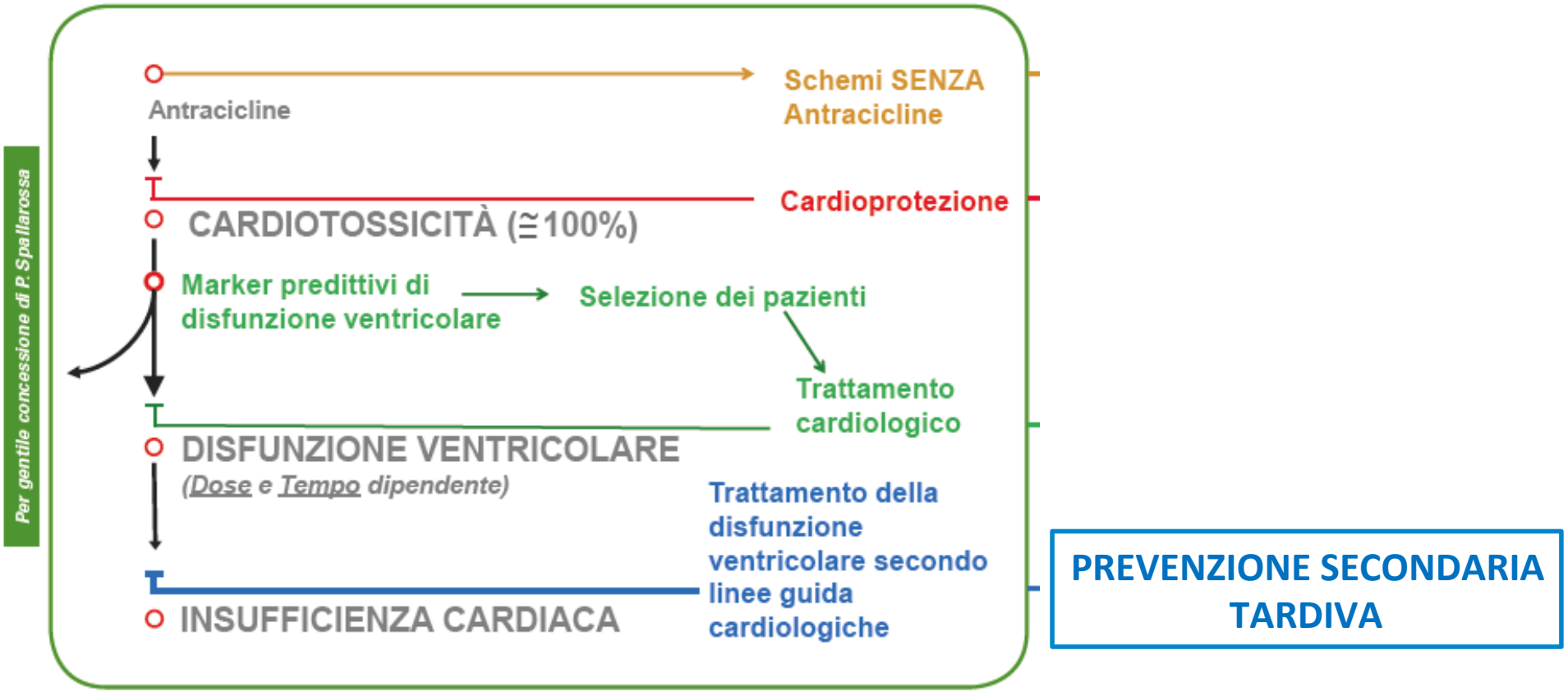
- **PRESUPPOSTI**: i fattori di rischio legati al paziente incidono significativamente sul rischio cardioncologico a distanza ma, ancora oggi, non è chiaro QUANTO incidano!
- **METODO E OBIETTIVO**: In una popolazione selezionata di pazienti con lungo follow up verificare l'incidenza della cardiotossicità e legarla alle caratteristiche del paziente per definire uno «score di rischio futuro»…

MISURABILE PREVEDIBILE TRATTABILE

HELP FOR HEART

GESTIONE DEL PAZIENTE CON CARDIOTOSSICITA'

Stefano Oliva, Paolo Spallarossa



HELP FOR HEART

GESTIONE DEL PAZIENTE CON CARDIOTOSSICITA'

Stefano Oliva, Paolo Spallarossa

L'ecocardiografia rappresenta lo strumento di valutazione complementare o alternativo all'uso dei biomarcatori

L'ECOCARDIOGRAFIA RILEVA IL GRADO DI DISFUNZIONE VENTRICOLARE

INDICE ECOCARDIOGRAFICO	VALORE NORMALE	CHE COSA EVIDENZIA	ATTENDIBILITÀ
Frazione di eiezione del ventricolo sinistro (FEVS)	> 50-55%	Indice della funzione sistolica	Non sufficientemente sensibile da rilevare minime alterazioni: nella progressione della disfunzione ventricolare sinistra, è l'ultimo parametro a subire alterazioni[24]
Tempo di rilasciamento isovolumetrico (IVRT)	60-90 msec	Indice della funzione diastolica I pazienti con IVRT < 80 msec entro 3 mesi dal termine della chemioterapia con antracicline, 3 anni e mezzo dopo manifesteranno una FEVS più ridotta[36]	Il valore "precoce" di IVRT correla con il valore "tardivo" di FEVS: la disfunzione diastolica precede la disfunzione sistolica
Global Longitudinal Strain (GLS)	< -16%	Modificazioni del grado di stiramento della fibra, misurato con Speckle-Tracking Echocardiography bidimensionale	Raccomandato dalle società scientifiche, una sua riduzione precoce del 12-15% rispetto al basale sembra essere il parametro più utile per predire la cardiotossicità (riduzione della FEVS o insufficienza cardiaca), se misurato in corso di trattamento o immediatamente dopo[24,37]
I pazienti individuati con questa metodica devono essere avviati al trattamento cardiovascolare sotto la gestione del cardiologo			

L'**ecocardiografia**, meglio se utilizzando nuovi indici di disfunzione sistolica o diastolica precoce, rappresenta tuttora lo **standard per il monitoraggio cardioncologico**

Journal of the American College of Cardiology

Available online 2 April 2014

In Press, Accepted Manuscript — Note to users

Use of Myocardial Strain Imaging by Echocardiography for the Early Detection of Cardiotoxicity in Patients During and After Cancer Chemotherapy – A Systematic Review

Paaladinesh Thavendiranathan, MD[1, 2], Frédéric Poulin, MD[1], Ki-Dong Lim, MD[1], Juan Carlos Plana, MD[3], Anna Woo, MD[1], Thomas H. Marwick, MD[4].

Abstract

The literature exploring the utility of advanced echocardiographic techniques (such as deformation imaging) in the diagnosis and prognostication of patients receiving potentially cardiotoxic cancer therapy has involved relatively small trials in the research setting. In this systematic review of the current literature, we describe echocardiographic myocardial deformation parameters in 1504 patients during or after cancer chemotherapy for three clinically relevant scenarios. The systematic review was performed following the PRISMA guidelines using EMBASE (1974 to November 2013) and MEDLINE (1946 to November 2013) databases. All studies of early myocardial changes with chemotherapy demonstrate that alterations of myocardial deformation precede significant change in LVEF. Using tissue Doppler-based strain imaging, peak systolic longitudinal strain rate has most consistently detected early myocardial changes during therapy, while with speckle tracking echocardiography (STE), peak systolic global longitudinal strain (GLS) appears to be the best measure. A 10-15% early reduction in GLS by STE during therapy appears to be the most useful parameter for the prediction of cardiotoxicity defined as a drop in left ventricular ejection fraction (LVEF) or heart failure. In late survivors of cancer, measures of global radial and circumferential strain are consistently abnormal, even in the context of normal LVEF, but their clinical value in predicting subsequent ventricular dysfunction or heart failure has not been explored. Thus, this systematic review confirms the value of echocardiographic myocardial deformation parameters for the early detection of myocardial changes and prediction of cardiotoxicity in patients receiving cancer therapy.

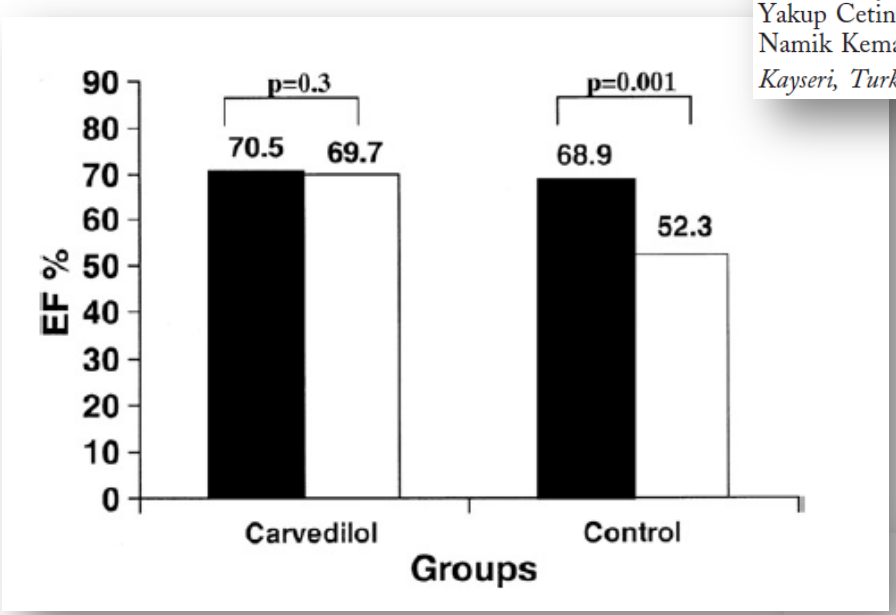
La prevenzione farmacologica primaria

La prevenzione primaria

Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy

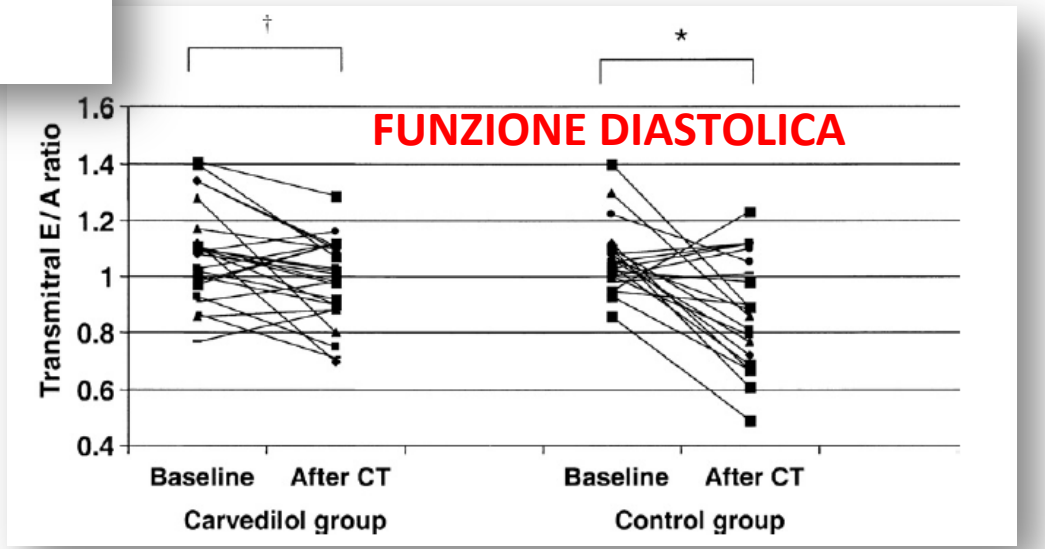
Nihat Kalay, MD,* Emrullah Basar, MD,* Ibrahim Ozdogru, MD,* Ozlem Er, MD,† Yakup Cetinkaya, MD,* Ali Dogan, MD,* Tugrul Inanc, MD, Abdurrahman Oguzhan, MD,* Namik Kemal Eryol, MD,* Ramazan Topsakal, MD,* Ali Ergin, MD*

Kayseri, Turkey



FUNZIONE SISTOLICA

Il carvedilolo, somministrato prima della chemioterapia, è efficace nel proteggere il cuore dai danni provocati



FUNZIONE DIASTOLICA

JACC 2006

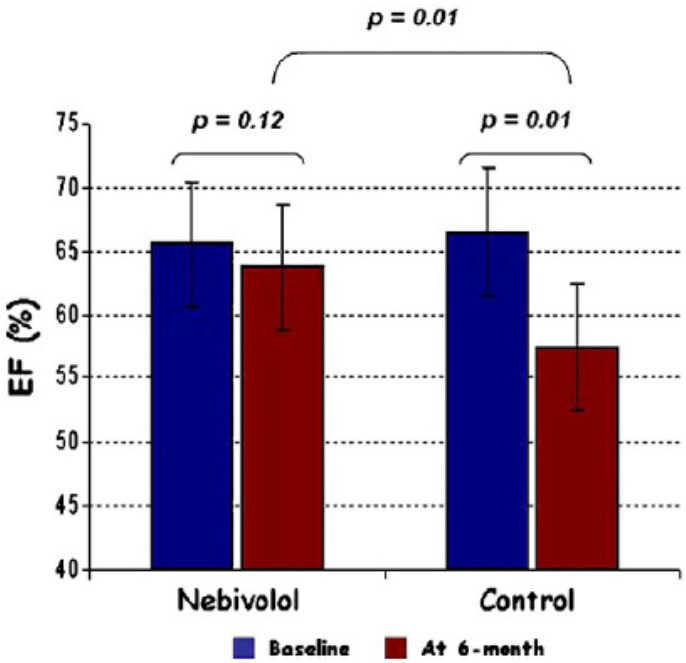
Contents lists available at SciVerse ScienceDirect

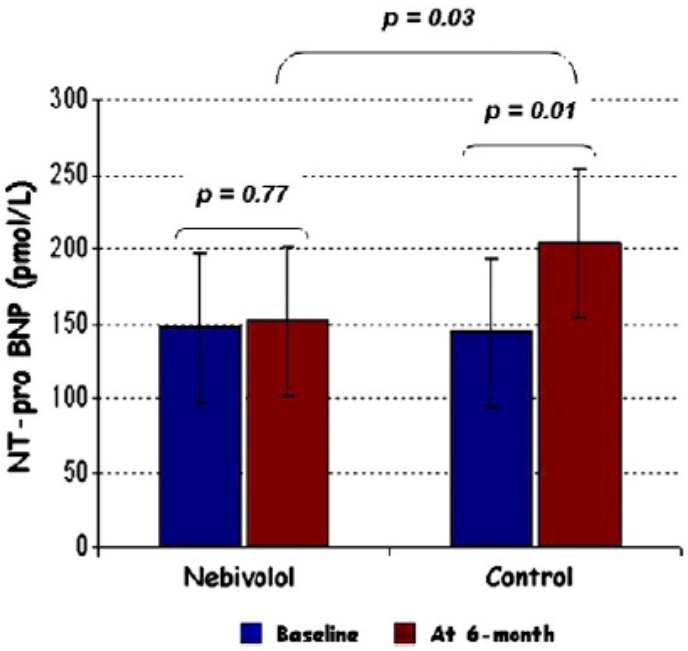
International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Protective effects of nebivolol against anthracycline-induced cardiomyopathy: A randomized control study ☆

Mehmet G. Kaya [a], Metin Ozkan [b], Ozgur Gunebakmaz [a], Hasan Akkaya [a], Esma G. Kaya [c], Mahmut Akpek [a], Nihat Kalay [a], Mustafa Dikilitas [b], Mikail Yarlioglues [a], Halit Karaca [b], Veli Berk [b], Idris Ardic [a], Ali Ergin [a], Yat Yin Lam [d,*]

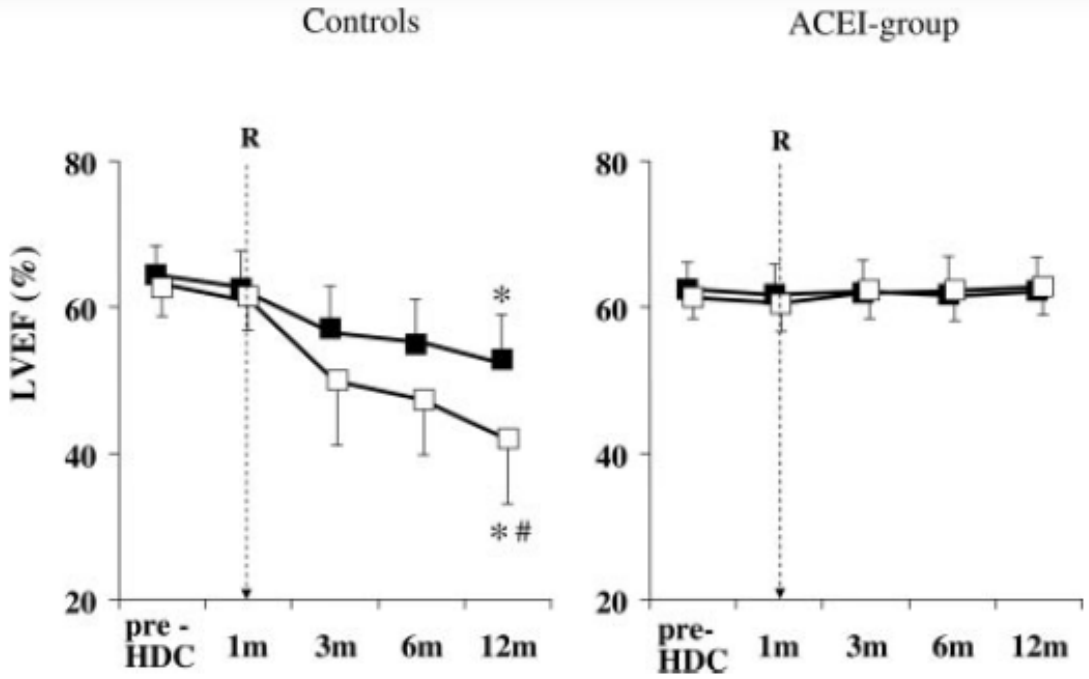




Int Journal of Cardiol, 2012

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

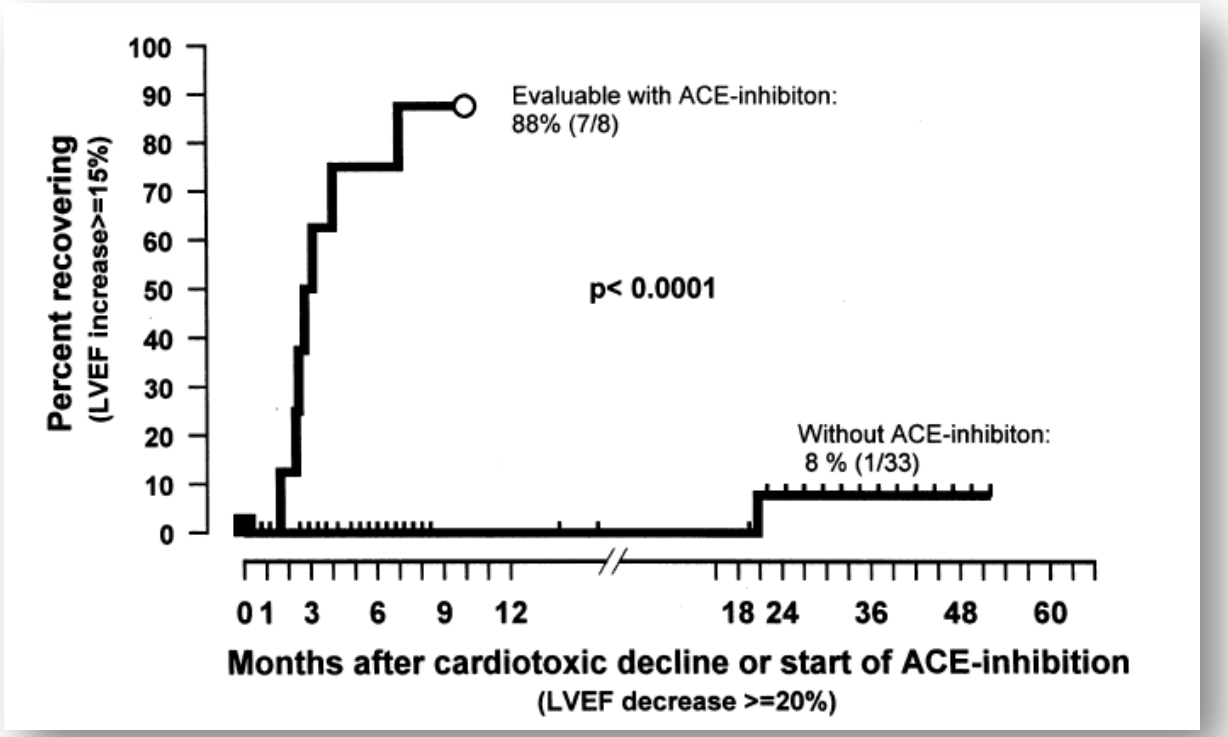


L'enalapril migliora la FEVS se somministrato in pazienti con danno preclinico (TnI)...

L'efficacia dei trattamenti farmacologici

Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients

B. V. Jensen[1]*, T. Skovsgaard[1] & S. L. Nielsen[2]



...ma anche con danno evidente

Annals of Oncology 2002

Conclusioni

- La fisiopatologia del danno da antracicline ha ancora aspetti poco conosciuti;
- Le strategie preventive più efficaci si sono finora dimostrate quelle che hanno utilizzato analoghi meno tossici delle antracicline;
- Dove non è possibile utilizzarle, la stratificazione del rischio è utile per prevenire la tossicità «early» ma soprattutto quella «late»;
- L'ecocardiografia, meglio se utilizzando nuovi indici di disfunzione sistolica o diastolica precoce, rappresenta tutt'ora lo standard per il monitoraggio cardioncologico;