Le esigenze degli Oncologi

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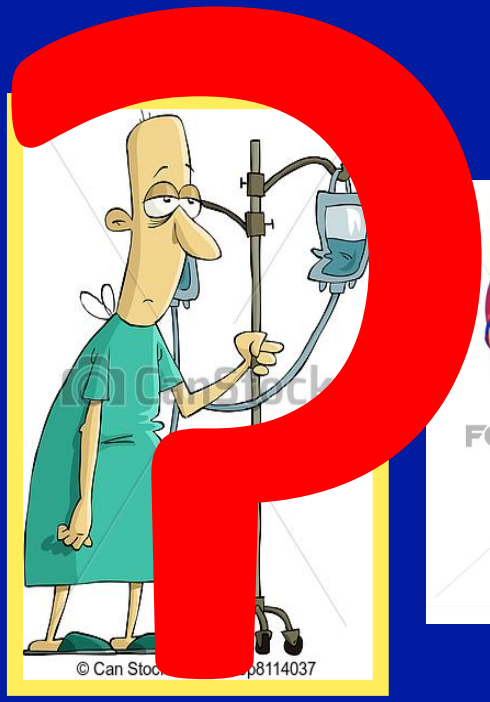
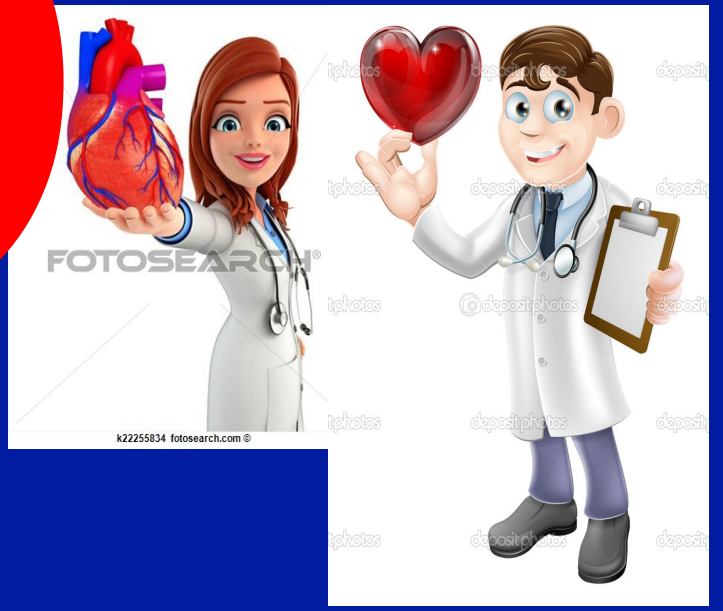
Oncologia Medica ✚

Cardiologia ✚





Alessandra Mosca, Baveno 5 maggio 2016

Farmaci oncologici e cardiotossicità

Alessandra Mosca, Baveno 5 maggio 2016

Emoclinic Symposium

CHEMOTHERAPY

TABLE 1. Potential Cardiac Toxicity Induced by Anticancer Chemotherapeutic Agents

DRUG	STUDY	TOXIC DOSE RANGE	CARDIAC TOXICITY	FREQUENCY OF OCCURRENCE[a]
Doxorubicin	Chlebowski 1979[30]	> 450 mg/m^2	Left ventricular dysfunction	Common
Epirubicin	Tjuljandin 1990[31]	> 900 mg/m^2		Common
Idarubicin	Anderlini 1995[32]	150-290 mg/m^2		Intermediate
Paclitaxel	Perez 1998[33]	Conventional dose	Left ventricular dysfunction	Intermediate
Docetaxel	Kenmotsu & Tanigawara 2015[34]			Intermediate
Cyclophosphamide	Gottdiener 1981,[35] Goldberg 1986[36]	>100-120 mg/kg	Left ventricular dysfunction	Intermediate
Ifosfamide	Kandylis 1989,[37] Tascilar 2007,[38] Cancer Care Ontario[39]	>10 mg/m^2		Uncommon
Capecitabine	Sentürk 2009[40]	Conventional dose	Cardiac ischemia	Intermediate
Fluorouracil	Sentürk 2009,[40] Schimmel 2004,[41] Chanan-Khan 2004[42]			Intermediate
Paclitaxel	Perez 1998[33]	Conventional dose	Cardiac ischemia	Uncommon
Docetaxel	Kenmotsu & Tanigawara 2015[34]			Intermediate
Trabectedin	Lebedinsky 2011[43]	Conventional dose	Cardiac ischemia	Intermediate
Arsenic trioxide	Brana & Taberno 2010[44]	Conventional dose	QTc prolongation	Common
Paclitaxel	Perez 1998[33]	Conventional dose	QTc prolongation	Uncommon

[a]Common indicates that more than 5% reported incidence; intermediate, between 1% and 5% reported incidence; uncommon, less than 1% reported incidence.

CA CANCER J CLIN 2016;

TARGETED THERAPY -I-

Table I. Representative tyrosine kinase inhibitors that caus cardiotoxicity

Target no.	Agent (trade name)	Class	Targets	Malignancies	Cardiotoxicity incidence	First FDA approval	Molecular mechanism
Single	Trastuzumab (Herceptin)	mAb	ErbB2 (HER2)	HER2+ breast cancer	LVD: 3-7% as a single agent and ≤64% in combination regimens (>6 months administration)	1998	LVD: inactivation of HER2/Erk/Akt pathway in cardiomyocytes; prevention of HER2 receptor dimerization; tumor cell death; downregulation of HER2 receptor
	Bevacizumab (Avastin)	mAb	VEGF	mCRC, nsNSCLC, mRCC, GBM	LVD: 1.7-3%; HTN: 16-47%	2004[a]	HTN: inhibition of VEGF-eNOS to weaken vasodilation; overproliferation of vascular SMCs Thrombosis: increased platelet aggregation and proinflammatory gene expression in endothelial cells
Multiple	Imatinib (Gleevec)	Small molecule	ABL1/2, KIT, PDGFR α/β	CML, RCC, GIST, HES	HF: 0.5-1.7%	2001	HF: inhibition of ABL causes cardiomyopathy, increased apoptosis and ER stress
	Sunitinib (Sutent)	Small molecule	VEGFRs, PDGFR α/β, KIT, FLT3	RCC, imatinib resistant GIST	HF: 2.7-11%; HTN: 5-47%	2006	HF: abnormal mitochondrial biogenesis, increased apoptotic cell death, inhibition of AMPK and PDGFRs

[a]Approved for breast cancer and revoked in 2011. FDA, Food and Drug Administration; mAb, monoclonal antibody; HER2, human epidermal growth factor receptor 2; LVD, left ventricular dysfunction; mCRC, metastatic colorectal cancer; nsNSCLC, non-squamous non-small-cell lung cancer; mRCC, metastatic renal cell carcinoma; GBM, glioblastoma multiforme; VEGF, vascular endothelial growth factor; eNOS, endothelial nitric oxide synthase; HTN, hypertension; SMC, smooth muscle cell; PDGFR, platelet-derived growth factor receptor; VEGFR, VEGF receptor; CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumor; HES, hypereosinophilic syndrome; HF, heart failure; ER, endoplasmic reticulum; FLT-3, Fms-like tyrosine kinase 3; AMPK, AMP-activated protein kinase.

MOLECULAR AND CLINICAL ONCOLOGY 4: 675-681, 2016

TARGETED THERAPY -II-

TABLE 3. Rates of Hypertension With Selected Angiogenesis Inhibitors

DISEASE	DRUG	STUDY	GRADE 3/4 HYPERTENSION RATES, %	
			ANTIANGIOGENIC	CONTROL
Colon cancer	Bevacizumab	Dewdney 2012,[65] Mir 2011[66]	11	2.3
Renal cell cancer	Bevacizumab	Fraeman 2013[67]	36	NA
Lung cancer	Bevacizumab	Mir 2011,[66] Chen 2015[68]	7	0.7
Breast cancer	Bevacizumab	Fraeman 2013,[67] Gampenrieder 2014[69]	14.8	14.6
Ovarian cancer	Bevacizumab	Fraeman 2013[67]	26.4	16.7
Renal cell cancer	Sunitinib	Larochelle 2012[71]	8	1
GIST	Sunitinib	George 2012[72]	3	0
Breast cancer	Sunitinib	Sungyub & Chamberlain 2015[73]	6	NA
Breast cancer	Sorafenib	Funakoshi 2013[74]	17	12
Lung cancer	Cediranib	Langenberg 2009[75]	35	NA
Breast cancer	Cediranib	Langenberg 2009[75]	42	NA
Phase 1	Sorafenib and bevacizumab	Castellano 2013,[76] Azad 2008[70]	33	NA

GIST, gastrointestinal stromal tumor; NA, not available.

CA CANCER J CLIN 2016;

HORMONE-THERAPY -I-

BREAST CANCER

✓30.023 postmenopausal women

✓Aromatase Inhibitors (AI) and Tamoxifen (T) as primary adjuvant horm-ther

→5 yrs AI or T or T+AI: non-statistically significant increased risk of CV disease (OR 1.11, p=.09)

→≥5 yrs AI: increased risk of CV disease (OR 1.26, p<.001)

Amir et al, *JNCI* 2011

✓Postmenopausal women

✓AI and/or T as primary adjuvant horm-therapy

→no difference between AI (mono- or sequenced ther) and T for CV disease;

→sequenced therapy (T->AI) compared with AI alone: lower risk of CV events (moderate level of evidence) -> CV events related to AI deserve further attention

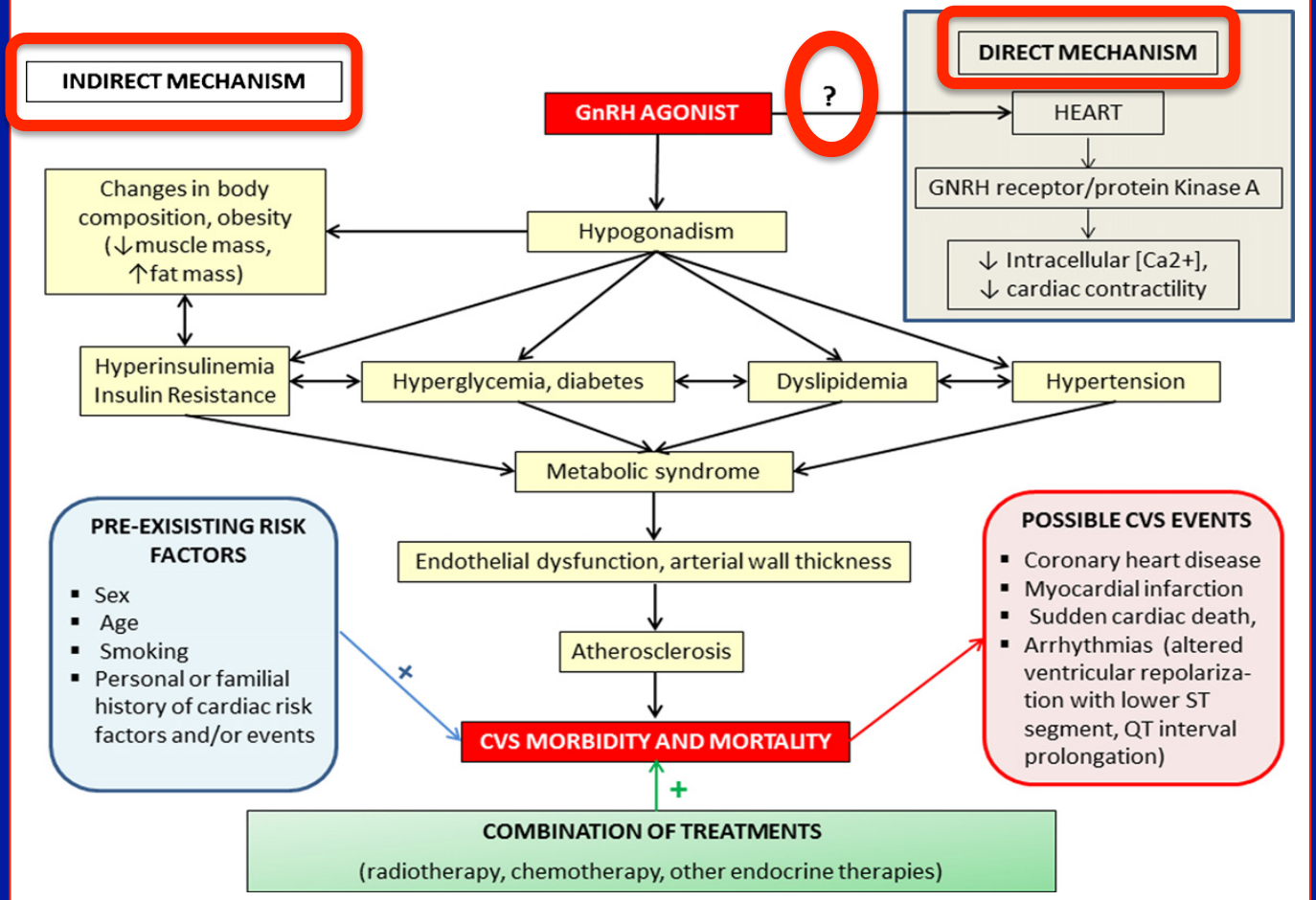
Ryden et al, *Breast* 2016

HORMONE-THERAPY -II-

PROSTATE CANCER

The cardiovascular risk of gonadotropin releasing hormone agonists in men with prostate cancer: An unresolved controversy

V. Conteduca et al. / Critical Reviews in Oncology/Hematology 86 (2013) 42–51



HORMONE-THERAPY -III-

PROSTATE CANCER

R. Iacovelli et al. / European Journal of Cancer 51 (2015) 1970–1977

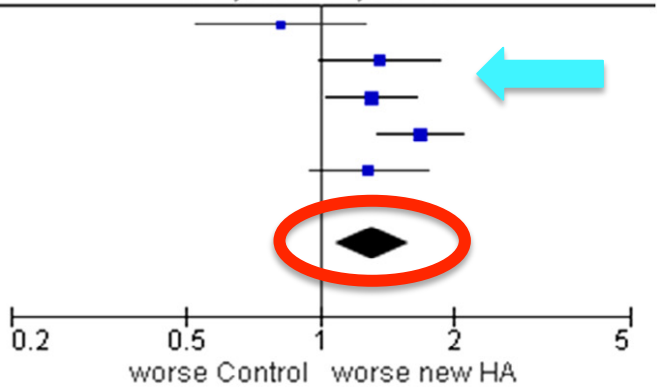
All grade CV tox

A

Study or Subgroup	new HA Events	new HA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFFIRM (Enzalutamide)		800	30	399	12.9%	0.81 [0.53, 1.26]
COU-AA-301 (Abiraterone)		791	46	394	18.9%	1.36 [1.00, 1.87]
COU-AA-302 (Abiraterone)		542	96	540	23.9%	1.31 [1.03, 1.66]
ELM-PC 4	172	784	100	770	24.8%	1.69 [1.35, 2.12]
PREVAIL (Enzalutamide)		871	66	844	19.5%	1.29 [0.95, 1.75]
Total (95% CI)		**3788**		**2947**	**100.0%**	**1.32 [1.08, 1.60]**
Total events	561		338			

Heterogeneity: Tau² = 0.03; Chi² = 9.01, df = 4 (P = 0.06); I² = 56%

Test for overall effect: Z = 2.77 (P = 0.006)



Meta-analysis in 6735 pts enrolled in 6 prospective studies

High grade CV tox

B

Study or Subgroup	new HA Events	new HA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFFIRM	7	800	8	399	11.3%	0.44 [0.16, 1.19]
COU-AA-301	41	791	9	394	17.2%	2.27 [1.11, 4.62]
COU-AA-302	45	542	23	540	23.8%	1.95 [1.20, 3.18]
ELM-PC 4	55	784	46	770	27.6%	1.17 [0.80, 1.72]
PREVAIL	24	871	18	844	20.2%	1.29 [0.71, 2.36]
Total (95% CI)		**3788**		**2947**	**100.0%**	**1.35 [0.90, 2.03]**
Total events	172		104			

Heterogeneity: Tau² = 0.12; Chi² = 9.58, df = 4 (P = 0.05); I² = 58%

Test for overall effect: Z = 1.46 (P = 0.15)

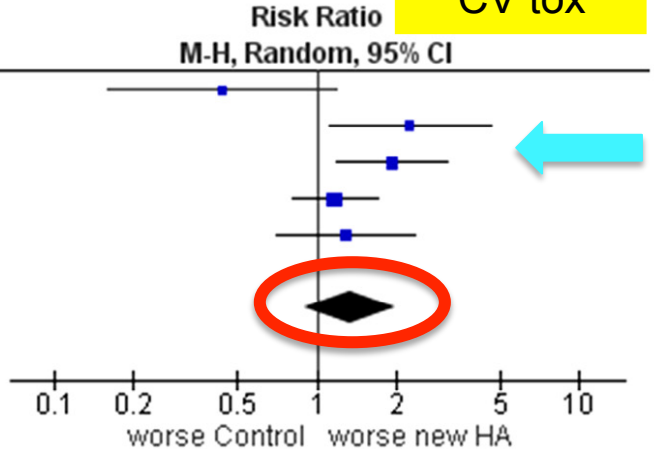


Fig. 2. Relative risk for (A) all- and (B) high-grade cardiac toxicity in patients treated with new hormonal agents (HA) or control.

Neoplasie solide
e
farmaci cardiotossici

Alessandra Mosca, Baveno 5 maggio 2016

Emoclinic Symposium

NEOPLASIE MAMMARIE

CT:

-ANTRACICLINE, ANTRACICLINE LIPOSOMIALI (peghilate e non peghilate: minore cardiotossicità ma indicate solo nella malattia mts)

-5-FLUOROURACILE e CAPECITABINA

HT:

-TAMOXIFENE, INIBITORI AROMATASI

TT:

-antiHER2 (TRASTUZUMAB, PERTUZUMAB, LAPATINIB): cardiotossicità reversibile, ma indispensabile monitoraggio di FE;

CARDIOXANE:

-quale ruolo nella prevenzione della cardiotossicità da antracicline?

(in collaborazione con Dr.ssa Saggia, Dr.ssa Rossi, Dr.ssa Giglione)

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NEOPLASIE POLMONARI

CT:

-CISPLATINO -> premedicazione con abbondante quantità di liquidi -> rischio scompenso cardiaco

TT:

-BEVACIZUMAB -> ipertensione, insufficienza cardiaca, IMA

-CRIZOTINIB e CERITINIB (ALK inibitori)-> allungamento QT (predisposizione a torsioni di punta)

-NIVOLUMAB -> aritmie

-NINTEDANIB (triplo inibitore orale dell'angiochinasi) -> ipertensione

(in collaborazione con Dr.ssa Buosi, Dr.ssa Borra, Dr.ssa Genestroni)

Alessandra Mosca, Baveno 5 maggio 2016

NEOPLASIE GASTRO-ENTERO-PANCREATICHE

CT:

-5-FLUOROURACILE (5FU) e CAPECITABINA (in mono-poliCT)

→ meccanismo vasospastico endotelina mediato

→ cardiotox: infarto del miocardio, angina, shock cardiogeno, morte improvvisa, prolungamento QT, aritmia cardiaca (fibrillazione ventricolare, torsione di punta e bradicardia), insufficienza cardiaca e cardiomiopatia

→ più a rischio i pazienti con anamnesi di cardiopatia, aritmia e angina pectoris significative

TT:

-BEVACIZUMAB E AFLIBERCEPT: ipertensione, insufficienza cardiaca, disaccoppiamento della fosforilazione mitocondriale nei cardiomiociti -> tachicardia sopraventricolare ed eventi trombotici

-REGORAFENIB: ischemia e infarto del miocardio, ipertensione

(in collaborazione con Dr.ssa Forti, Dr.ssa Negru, Dr.ssa Bertona)

NEOPLASIE TESTA-COLLO E MELANOMA

CT:

-CISPLATINO, 5FU

TT:

-DABRAFENIB (BRAF inibitore) +/- TRAMETINIB (MEK inibitore): riduzione FEV

(in collaborazione con Dr Sponghini, Dr Rondonotti)

NEOPLASIE UROLOGICHE E NEUROENDOCRINE

CT:

-CISPLATINO

TT:

-SUNITINIB, SORAFENIB, (PAZOPANIB, CABOZANTINIB, NIVOLUMAB)

HT:

-LHRH-AGONISTI, ABIRATERONE, ENZALUTAMIDE

Tipologia di paziente/fase di malattia oncologica e cardiotossicità

cardiotossicità

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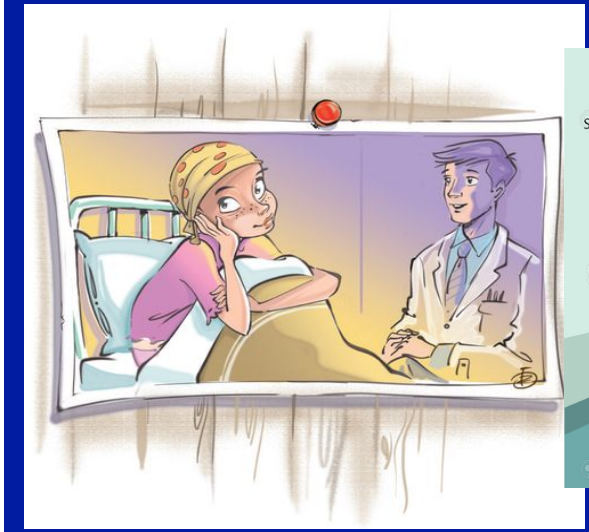

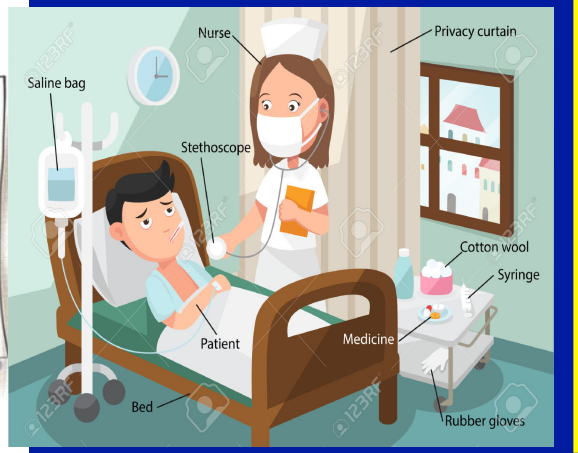

-Giovane
-No comorbidità cardiologiche
-M0, CT adiuvante
-> lunga aspettativa di vita
-> NB: danni CV acuti/tardivi

-Anziano
-Comorbidità (anche cardiologiche)
-M1, CT palliativa
-> ridotta aspettativa di vita
-> NB: danni CV acuti/tardivi

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Valutazione cardio-oncologica del paziente (cardio-)oncologico

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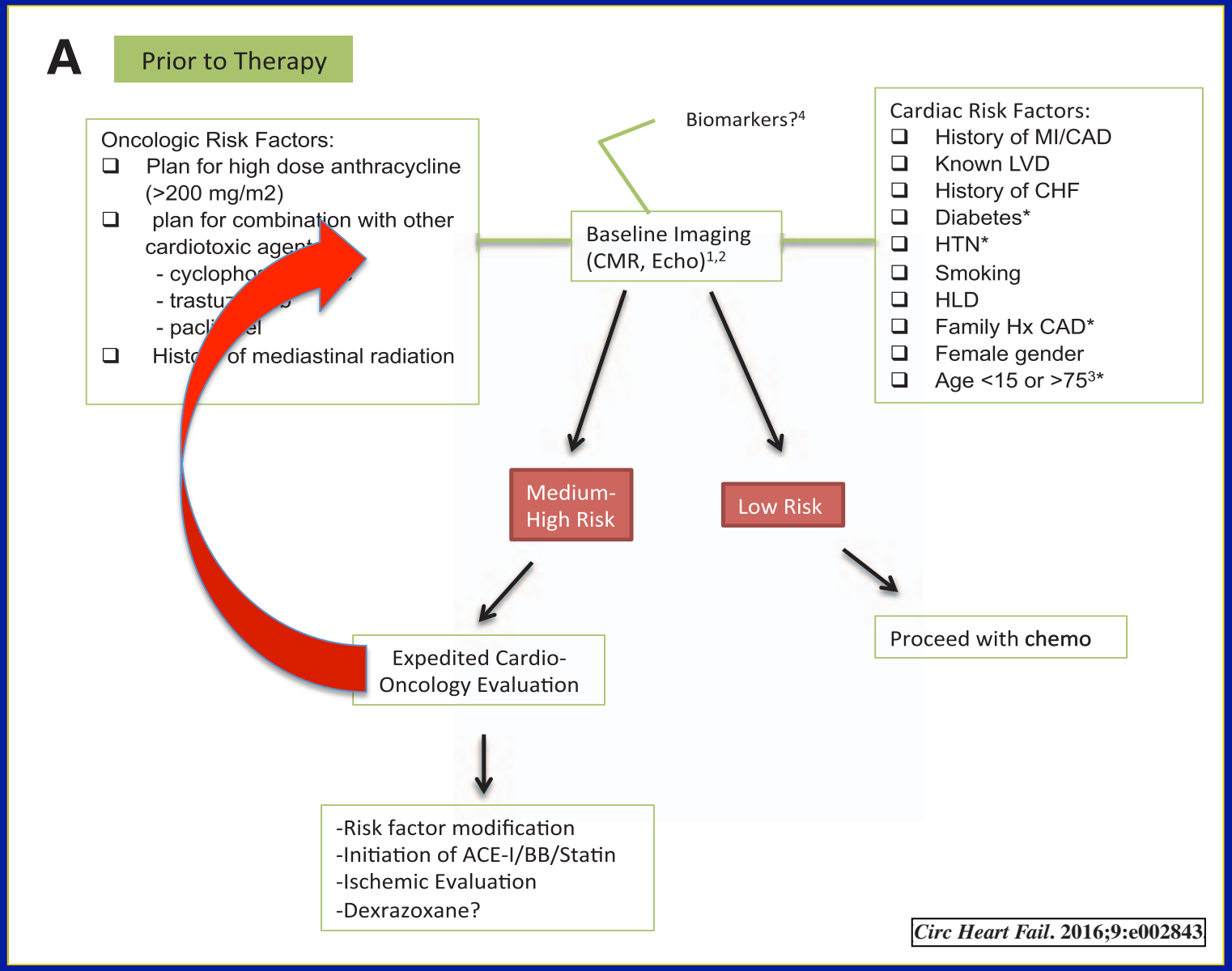
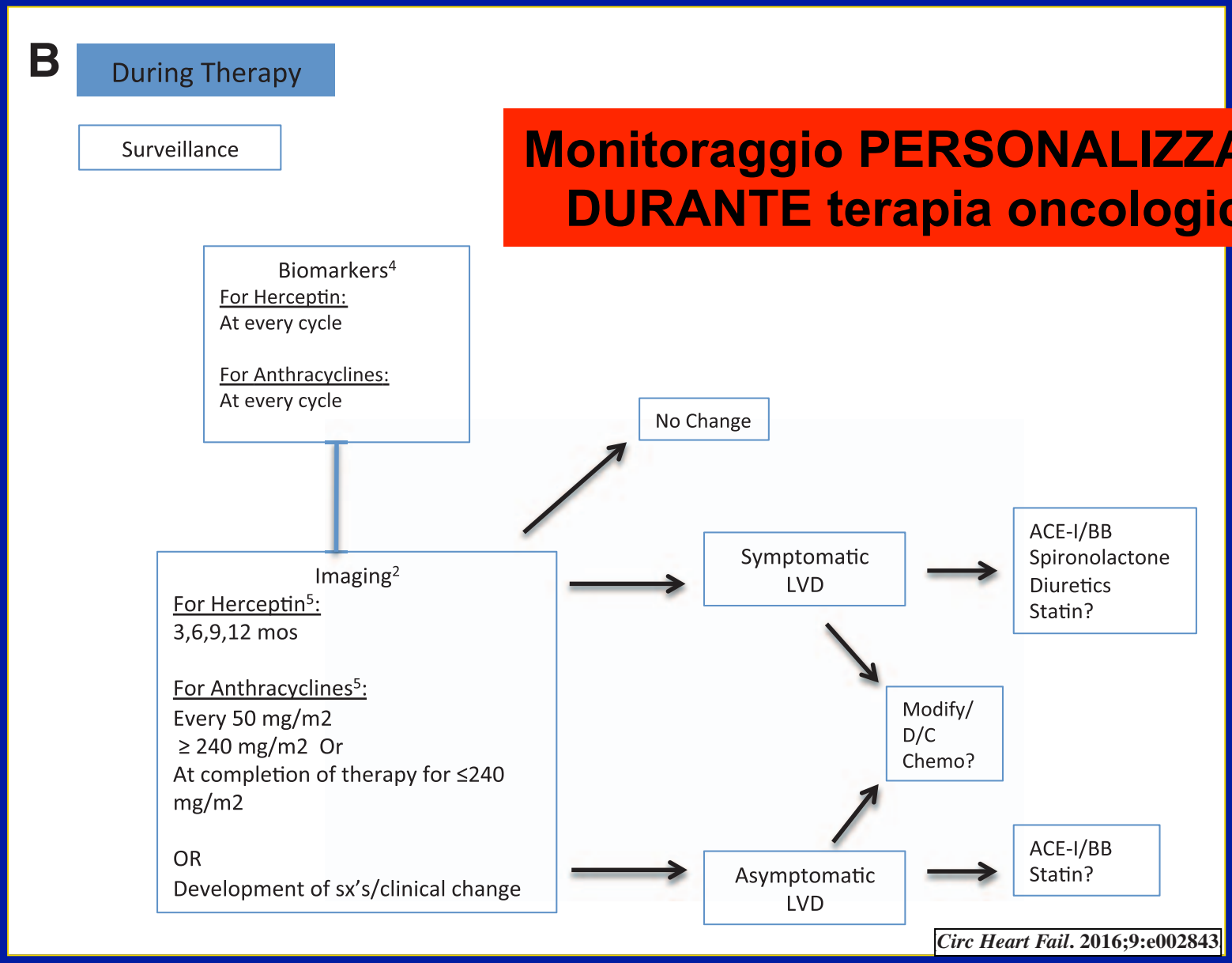
Le esigenze degli Oncologi: PRIMA della terapia oncologica



Le esigenze degli Oncologi: DURANTE la terapia oncologica



Le esigenze degli Oncologi: DOPO la terapia oncologica

C

Following Therapy

Surveillance

Monitoraggio PERSONALIZZATO DOPO terapia oncologica

Low Risk

Medium-High Risk

2D/3D echo with strain at therapy completion

No need for further post-chemo imaging if asymptomatic

Trastuzumab/Other "Type II" Agents:

2D/3D Echo with strain at completion of therapy (further surveillance not established)

Anthracyclines alone or with Trastuzumab +/- RT

2D/3D Echo with strain at completion of therapy, 6-12 mos vs 12 mos, 18mos post rx
(Further surveillance not established)

Circ Heart Fail. 2016;9:e002843

CONCLUSIONI

-Diversi farmaci oncologici per diverse neoplasie solide, con diverse tossicità CV

-I pazienti oncologici sono molto eterogenei

-Non esistono attualmente Linee Guida validate per ottimali Inquadramento clinico e monitoraggio della tossicità cardiaca prima/durante/dopo terapia oncologica

MULTIDISCIPLINARY APPROACH TO ONCOLOGICAL PATIENTS

ONCOLOGIST

PATHOLOGIST

CARDIOLOGIST

SURGEON

RADIOTHERAPIST

PSYCHOLOGIST

ENDOCRINOLOGIST

Grazie per l'attenzione!

Alessandra Mosca, Baveno 5 maggio 2016