P.O. MOLINETTE

Evento residenziale

Il Paziente oncologico a rischio di tossicità cardiovascolare

SEDE DEL CORSO

Torino, Via Rosmini 4/A
terzo piano

Evento organizzato con il pat
A.R.C.A.

Corso accreditato s
Sistema ECM Regione Pie
COD. 20492 - Crediti calc

AREA TEMATICA

Oncologica

FINALITA'

cardiaca nel paziente oncologico

ARTICOLAZIONE

Il Corso si articola in formula mista

Mauro GIORGI
S.C. CARDIOLOGIA 2 - OSP. MOLINETTE
CITTA' della SALUTE e della SCIENZA di TORINO

PROGRAMMA

1° giorno

9.00-9.30 Le dimensioni del problema e il modello di rete (O. Bertetto)
9.30-11.00 Il rischio di tossicità riguardo a:
- terapie oncologiche (M. Mistrangelo)
- terapie ematologiche (P. Pregno)
- trattamenti radianti (M. Levis)

il ruolo del cardiologo e dell'oncologo (A. Fava, M. Mistrangelo)

2° giorno

9.00-13.00 Suddivisione dei partecipanti in gruppi di lavoro con gestione casi clinici supportati da un leader (M. Giorgi, A. Fava, P. Lusardi, E. Coletti Moia, A. Bonzano, A. Milan, I.

esi delle proposte e con raccomandazioni finali

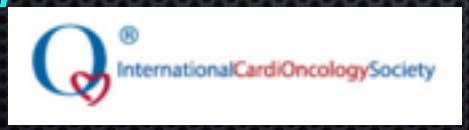
16.30-17.00 Valutazione

CARDIO-ONCO(EMATO)LOGIA

Una nuova branca della Cardiologia che studia:

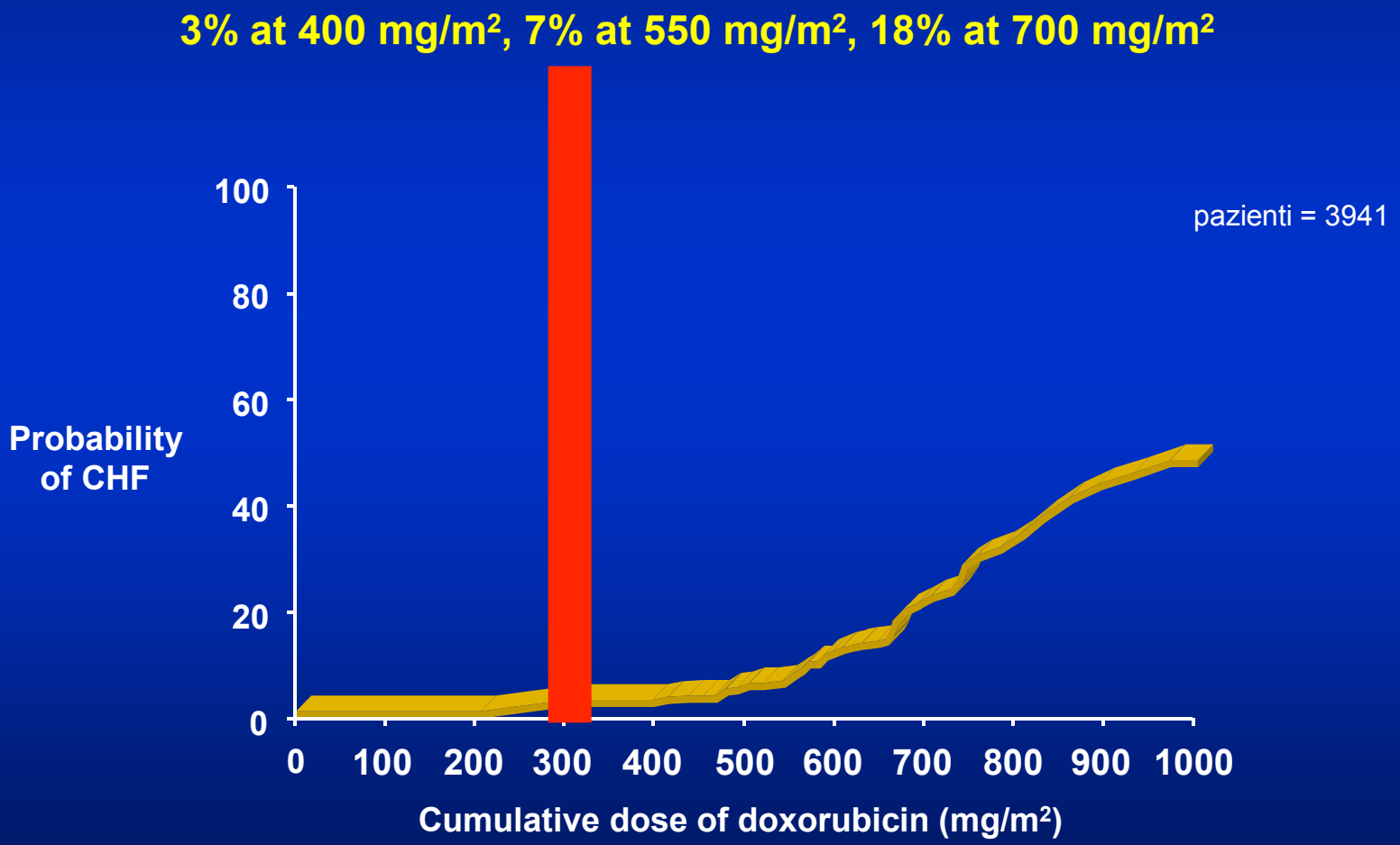
- la **cardiotossicità** provocata da terapie antitumorali (CHTh e RXTh) ed ematologiche
- la possibilità di **diagnosticarla precocemente** e a livello subclinico
- strategie di **cardioprotezione**

fino a pochi anni fa i punti di contatto tra Cardiologi e Oncologi (ed Ematologi) erano assai scarsi: il Malato di tumore era considerato un malato con poche speranze e aspettativa di vita di pochi mesi



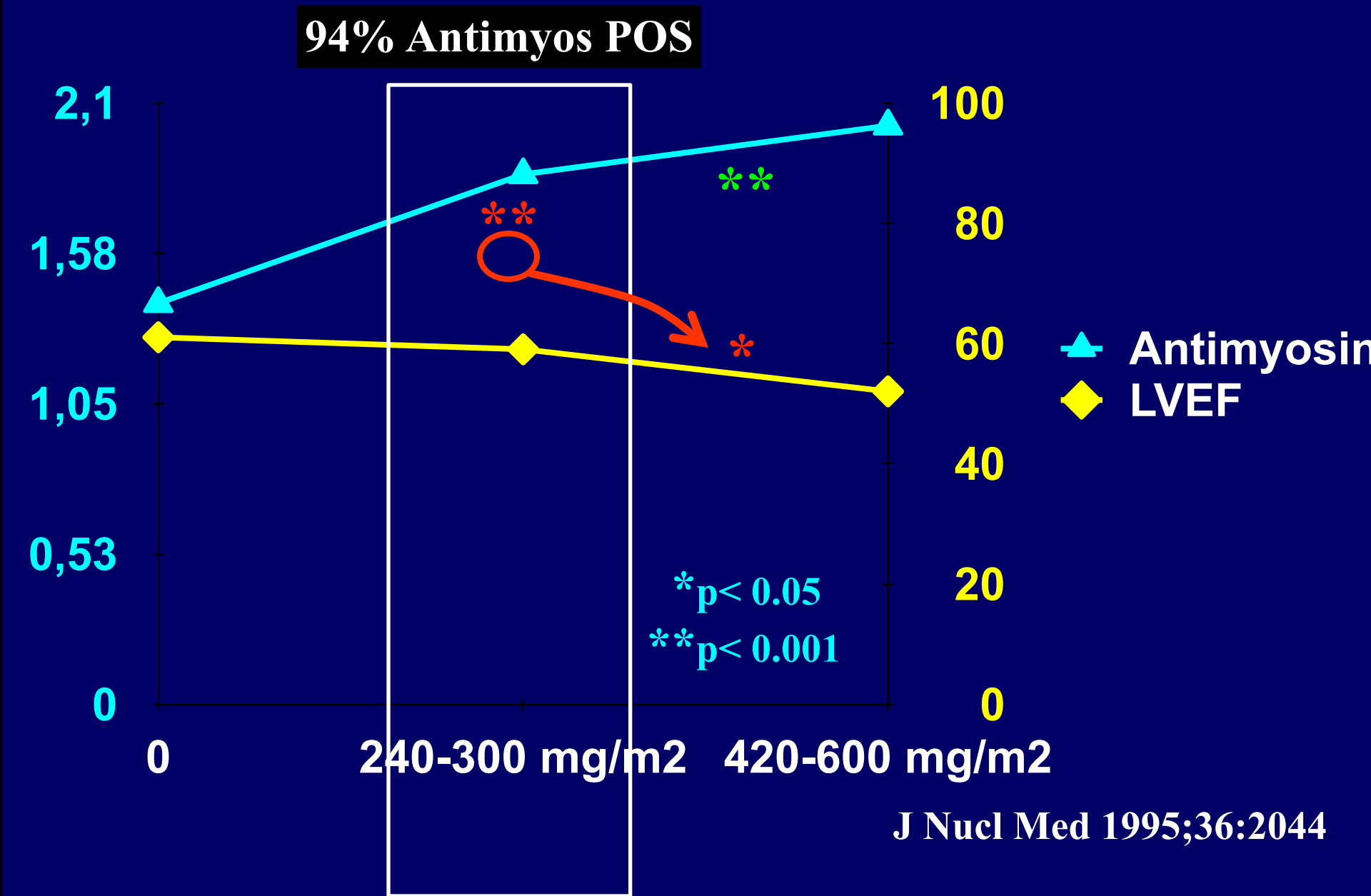
CARDIONCOLOGIA: Cosa abbiamo imparato nel corso degli anni?

Dose cumulativa di doxorubicina e insorgenza di CHF



Von Hoff DD *et al. Ann Intern Med* 1979; 91: 710–7

Early Assessment of Doxorubicin Cardiotoxicity

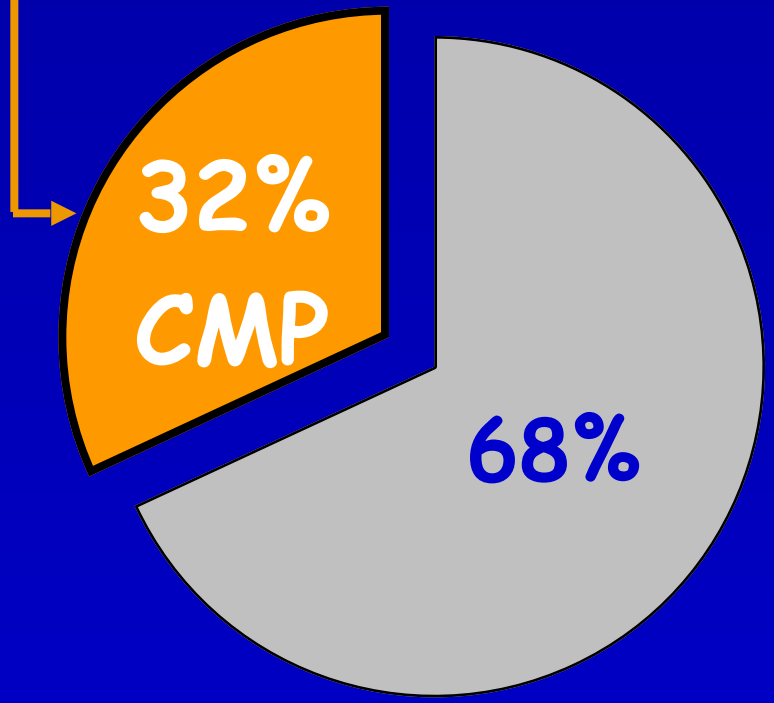


J Nucl Med 1995;36:2044

Subclinical Late Cardiomyopathy (CMP) after Doxorubicin Therapy for Lymphoma in Adults.

J Clin Oncol. 2004;22:1864

Risultati



Discussione

1. Basse dosi di Dox.
2. Studio retrospettivo

11 anni di F.U.

7 anni di F.U.

Un po' di storia…
CTX da DOXORUBICINA a BASSI DOSAGGI

- **TOSSICITÀ ANCHE A BASSI DOSAGGI**
  - 240-300 mg/m^2:
    - *EF > 55%...*
      - ★ *…ma Scinti Ac Antimiosina ⊕ nel 94% dei Pts*

Carioni, J Nucl Med 1995

- **TOSSICITÀ ANCHE TARDIVA**
  - Follow Up a 11 aa (analisi retrospettiva):
    - ★ *significativa riduzione EF (< 40%) nel 32 %*

J Clin Oncologic 2004

Cosa abbiamo imparato?

- Il **cancro** è **malattia sociale**: in Europa 1 persona su 4 manifesta un tumore nel corso della vita
- L'**allungamento della vita media** aumenta il rischio di **concomitanza** tra malattie cardiovascolari e cancro
- **Maggior efficacia** sia delle terapie cardiologiche sia di quelle oncoematologiche —> **miglior sopravvivenza**
- **Maggior aggressività** delle terapie oncoematologiche (spesso **reiterate**) —> aumentato rischio di **danni iatrogeni** all'apparato cardiocircolatorio

Cosa abbiamo imparato?

- **La CTX è un fenomeno destinato ad espandersi :**
  - aumento del n° di nuove diagnosi tumore annuali
  - ma anche aumento del n° PTs stabilizzati
  - aumento aspettativa di vita
  - per molti di essi nuovi cicli di CHT nel corso degli anni
  - ricorso a terapie antitumorali multiple, combinate e ripetute, sempre più aggressive e potenzialmente cardiotossiche

SCOPI e SCHEMI di CHT

1. **Eliminare la malattia**
2. **CHT NEOADIUVANTE:** ridurre il volume della massa tumorale prima di un'operazione o RXTh
3. **CHT ADIUVANTE:** prevenire la recidiva dopo un intervento chirurgico o RXTh, eliminando cells tumorali staccate dal tumore e diffuse in altre parti del corpo, pur senza mts rilevabili
4. **Prolungare la sopravvivenza o ritardare la progressione della malattia** se non può essere eliminata
5. **Migliorare i sintomi provocati dalla massa tumorale** se non possibile asportazione chirurgica
6. Preparazione a **TX midollo osseo o stem cells**

DIMENSIONI del PROBLEMA

NUOVI CASI DI TUMORI / ANNO:

- Italia : > 265.000
- Europa: 2.000.000
- Mondo occidentale: 13.000.000

➔ **TRATTATI CON CHEMIO/RADIOTERAPIA: 60-80%**

CARDIOTOSSICITÀ:

- Alterata funzionalità: 30 % (It = 80.000)
- Alterazione rilevante: 15 % (It = 40.000)
- Scompenso irreversibile: 1 % (It = 3.000)

Patient Discharges with Heart Failure Diagnosis at MD Anderson Cancer Center

Fiscal Year	Total Hospital Discharges	Heart Failure Discharge Diagnosis*	30-Day Re-admission
2012	26, 233	961 (3.6%)	381 (40%)
2013	27,137	1080 (3.9%)	394 (36%)

**Discharge diagnosis includes heart failure as principal and secondary diagnoses (ICD 425, 428)*

Circa il 40% dei PTs dimessi con diagnosi di scompenso rientra in ospedale entro 40 giorni

La domanda imbarazzante del Cardiologo: che speranza di vita ha il Paziente?

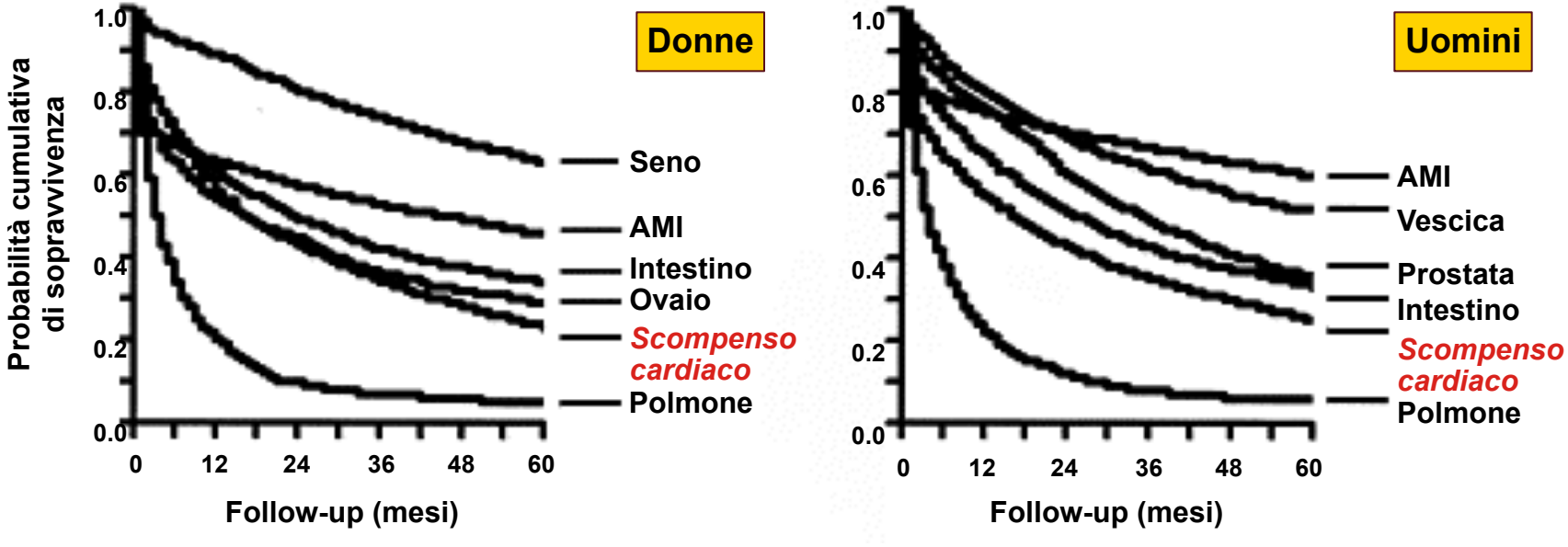
La malattia CANCRO sta diventando una malattia CRONICO-DEGENERATIVA e pone problematiche NUOVE

SCENARI ODIERNI

- Pts con cardiopatia in atto che si ammalano di cancro
- Pts oncologici che manifestano malattie cardiocircolatorie
- Terapie oncologiche che causano cardiopatie
- Cardiopatie in lungosopravviventi e guariti
- Compatibilità tra terapie oncologiche e cardiologiche

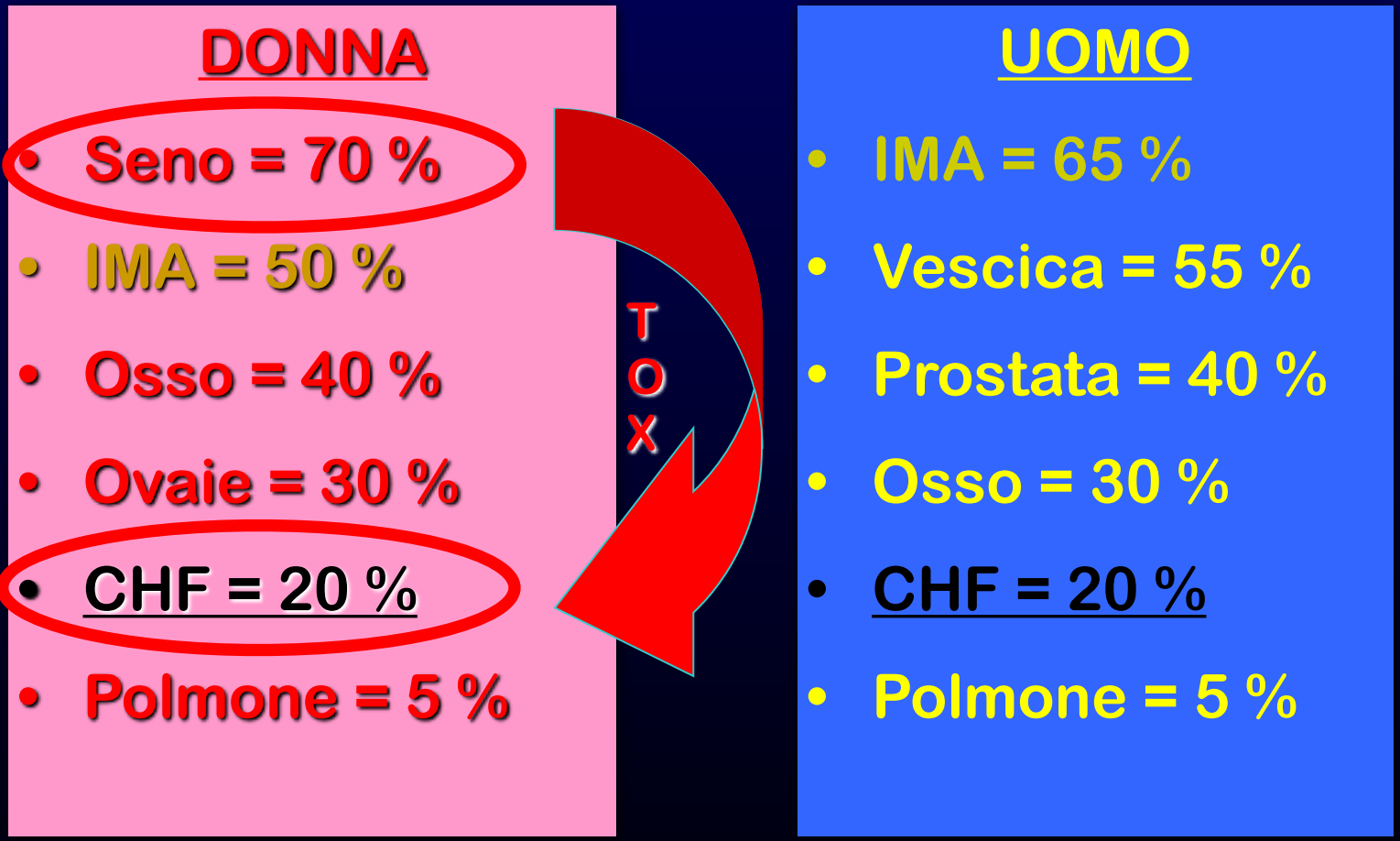
More "Malignant" than Cancer?

Probabilità media di sopravvivenza a 5 anni dalla diagnosi nello scompenso cardiaco e nelle forme di cancro più frequenti nei due sessi



Eur J Heart Fail. 2001 Jun;3:315-22

CHF vs TUMORI: CURVE di SOPRAVVIVENZA



CHF vs TUMORI: CURVE di SOPRAVVIVENZA

More "malignant" than cancer ?

Five year survival following a first admission for heart failure

Stewart S., MacIntyre K., Hole DJ., Capewell S., McMurray JJ.

With the notable exception of lung cancer, heart failure is "malignant" as many common types of cancer and is associated with a comparable number of expected life-years old

(Eur. J. Heart Fail 2001)

Le curve di sopravvivenza per scompenso cardiaco sono peggiori di quelle della > parte dei tumori

LINEE GUIDA ONCOLOGICHE

INTERROMPERE C.T. se:

↓ EF > 10p% + EF < 50%

LIMITAZIONE delle OPPORTUNITÀ della CHEMIOTERAPIA

- **STOP se:**
  - **↓ EF > 10p%**
  - **EF < 40%**

CARDIOTOSSICITÀ: CONSEGUENZE

- Condizionamento dell'oncologo nella scelta della terapia
- Riduzione della dose per evitare danni permanenti (riduzione dose = limitazione efficacia)
- Limitazione della potenziale efficacia della cura

TERAPIE ONCO EFFICACI. MA MENO DANNOSE

DIAGNOSI PRECOCE di CARDIOTOX

CARDIOPROTEZIONE

VALUTAZIONE dell'EF: LIMITI

- ↓ *EF = perdita di cardiomiociti (danno irreversibile)*
- *EF normale anche con alterazioni cinesi segmentaria*
- ***EF = indice tardivo, poco sensibile e poco specifico, con bassa accuratezza diagnostica e scarso potere predittivo***

OBIETTIVO DEL CARDIONCOLOGO:

- identificazione precoce dei **Pts a rischio** di sviluppare una disfunzione VS → personalizzazione del programma terapeutico cht e cardioprotezione

  (= identificazione del danno in **fase pre-clinica**)

Classificazione AHA/ACC dello scompenso

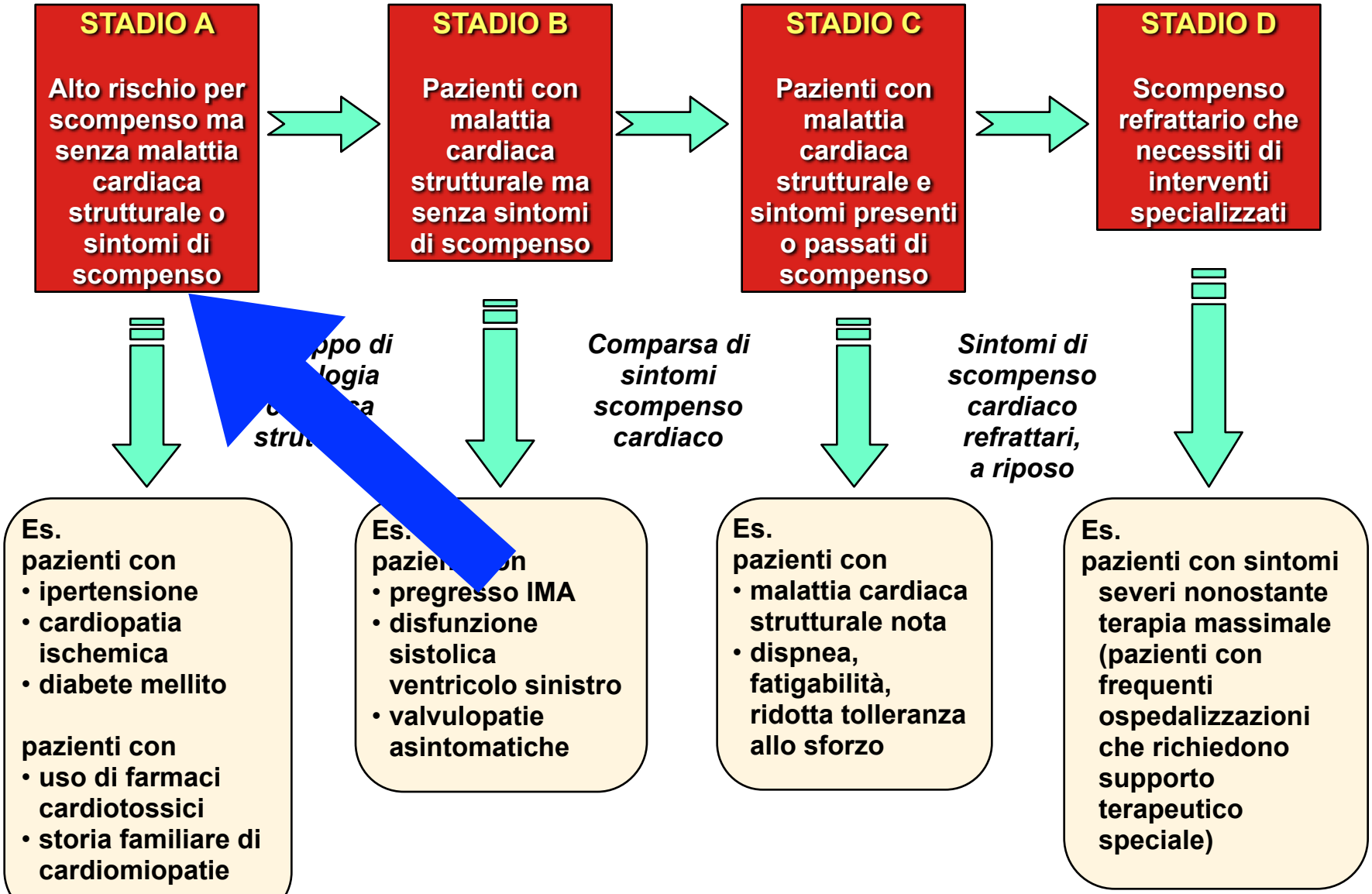


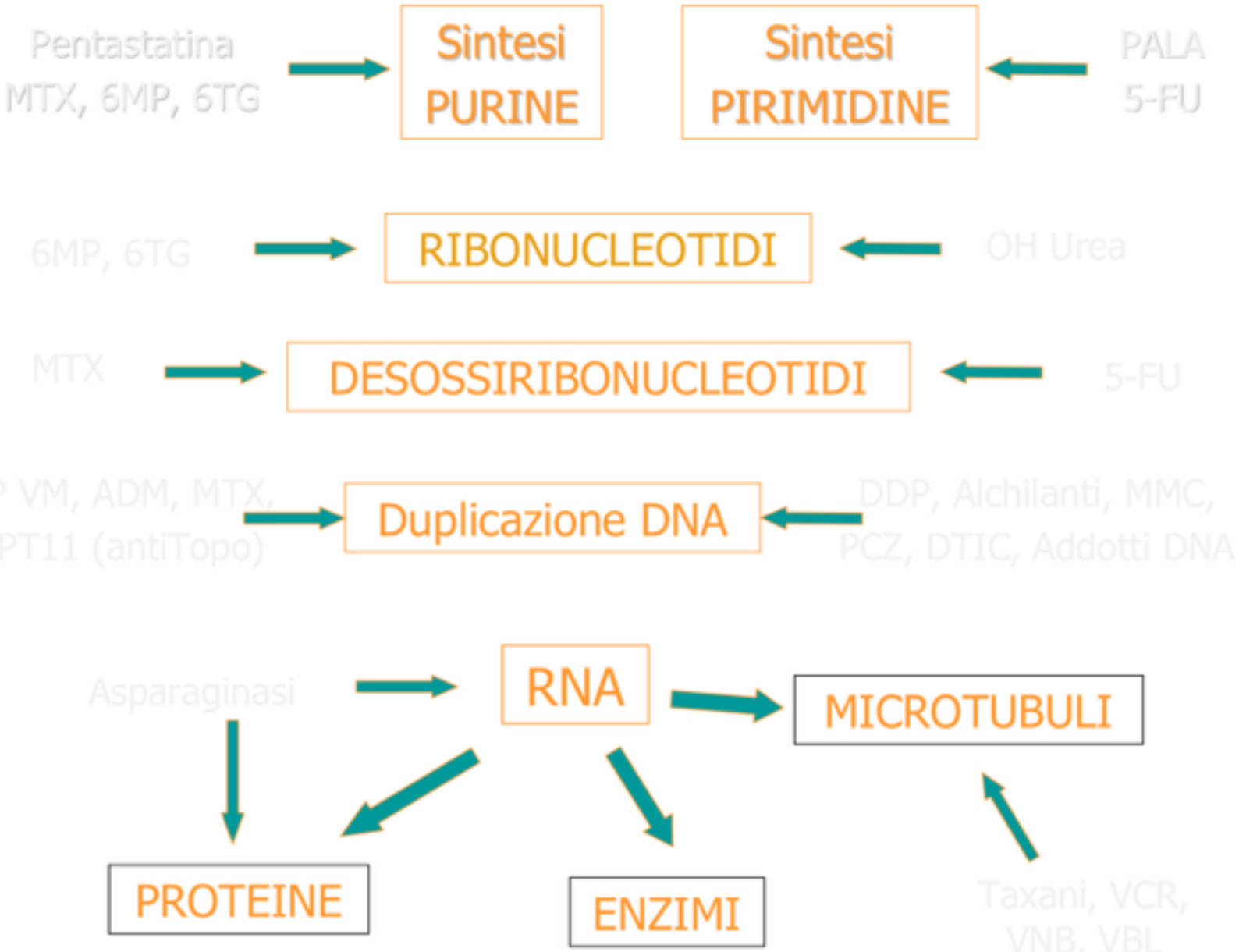
TABLE 83–3 Cardiotoxicity of Antineoplastic Agents

Implicated Agent	Comments
Anthracyclines	
Doxorubicin or daunorubicin	CHF at cumulative doses above 450 mg/m^2, arrhythmias
Mitoxantrone, idarubicin	CHF, decreases in left ventricular ejection fraction
Alkylating agents	
Cyclophosphamide	Produces a hemorrhagic myopericarditis 1-2 weeks after marrow transplant doses
Busulfan	Endocardial fibrosis
Cisplatin	Acute myocardial ischemia
Other cytotoxics	
Paclitaxel (Taxol)	Exacerbates anthracycline-associated CHF, bradycardia
5-Fluorouracil	Angina/myocardial infarction
Vincristine, vinblastine, vinorelbine (Navelbine)	Myocardial infarction
Biologics	
Trastuzumab (Herceptin)	Exacerbates anthracycline-associated CHF
Interferons	Exacerbates underlying cardiac disease
Interleukin-2	Acute myocardial injury, ventricular arrhythmias, hypotension
Hormones	
Megestrol (progestin)	Cardiomyopathy
Estramustine (androgen antagonist [Emcyt])	Myocardial infarction, CHF
Goserelin (gonadotropin-releasing hormone analog [Zoladex])	Myocardial infarction, CHF
Diethylstilbestrol (estrogen)	Myocardial infarction
Toremifene (antiestrogen [Fareston])	Myocardial infarction
Bicalutamide (antiandrogen [Casodex])	Angina, CHF, myocardial infarction
All-*trans*-retinoic acid	Myocardial dysfunction, heart failure, fever, shortness of breath, pleural and pericardial effusions, pulmonary infiltrates, and peripheral edema
Hematopoietic growth factors	
Granulocyte macrophage colony-stimulating factor (sargramostim [Leukine])	Capillary leak syndrome
Antiemetic	
Granisetron	Sinus bradycardia, atrioventricular block and increased PR interval or a Wenckebach block (Mobitz I).

CHF = congestive heart failure.

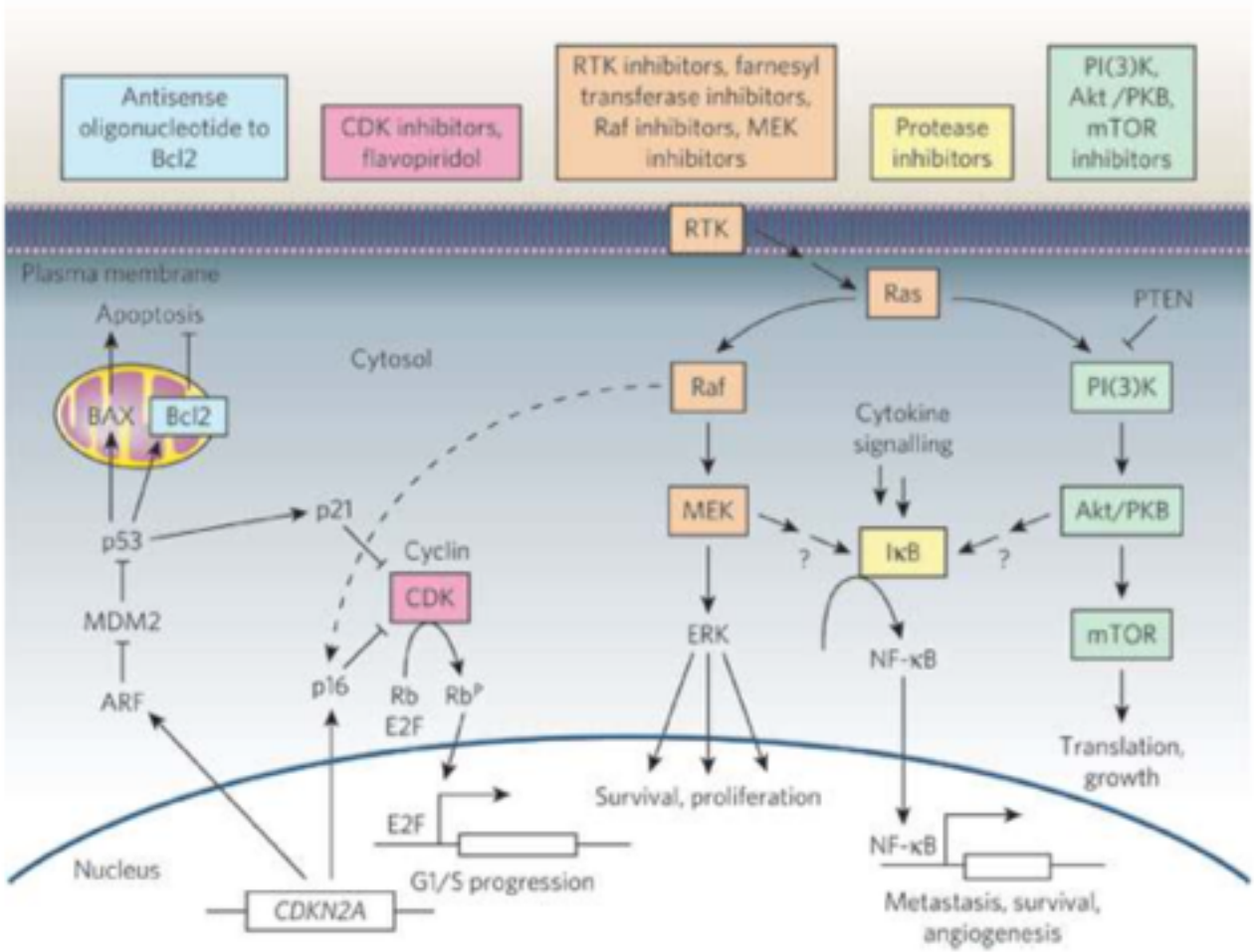
EFFETTI dei FARMACI ANTITUMORALI

- **ANTRACICLINE** (Doxo, Epi, Ida) → CHF
- **ANTIMETABOLITI** (5 fluorouracile, capecitabina) → spasmo coronarico (S.C.A. = angina, infarto)
- **AGENTI ALCHILANTI** (ciclofosfamide, cisplatino) → CAD
- **TAXANI** (Taxolo, Paclitaxel, Docetaxel-Taxotere) → aritmie (spt bradicardia, BAV I-III), CHF
- **AC MONOCLONALI*** (trastuzumab, rituximab) → CHF
- **INIBITORI TIROSINCHINASI*** (lapatinib, sunitinib, sorafenib): HP, CHF, aterosclerosi (arteriopatia periferica, CAD)
- **INTERFERONE , INTELEUKINA** → aritmie, CHF
- **ANTIESTROGENI** (tamoxifene, in. aromatasi) →CHF
- **ALCALOIDI VINCA** (vinblastina, vinorelbina) →CHF


Pentastatina
MTX, 6MP, 6TG
Sintesi PURINE
Sintesi PIRIMIDINE
PALA
5-FU
6MP, 6TG
RIBONUCLEOTIDI
OH Urea
MTX
DESOSSIRIBONUCLEOTIDI
5-FU
VP VM, ADM, MTX,
CPT11 (antiTopo)
Duplicazione DNA
DDP, Alchilanti, MMC,
PCZ, DTIC, Addotti DNA
Asparaginasi
RNA
MICROTUBULI
PROTEINE
ENZIMI
Taxani, VCR,
VNB, VBL

Bersagli Target Therapy

(AC. MONOCLONALI e INIBITORI TKI)



Early Breast Cancer Therapy and Cardiovascular Injury

Lee W. Jones, PHD,* Mark J. Haykowsky, PHD,‡ Jonas J. Swartz, BS,* Pamela S. Douglas, MD,† John R. Mackey, MD§

(J Am Coll Cardiol 2007;50:1435–41)

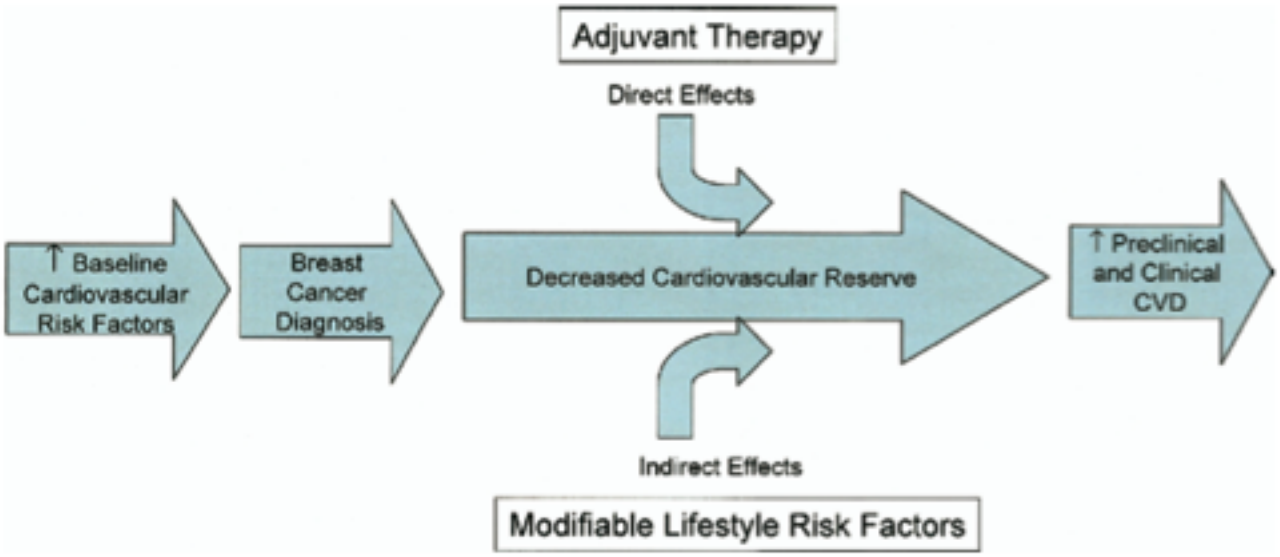


Figure 1 **The "Multiple-Hit" Hypothesis**

A schematic representation describing the "multiple-hit" hypothesis. At diagnosis, a significant proportion of early breast cancer patients present with pre-existing or heightened cardiovascular disease (CVD) risk factors, which increase the risk of adjuvant therapy-associated cardiovascular injury. Independently, many adjuvant therapies used in breast cancer are associated with unique and varying degrees of direct adverse effects on the cardiovascular system. These direct effects occur in the context of concomitant lifestyle perturbations (indirect effects) that combine to reduce cardiovascular reserve. Collectively, these changes may leave the patient more susceptible to further cardiovascular insults and at higher risk of premature death due to cardiovascular mortality.

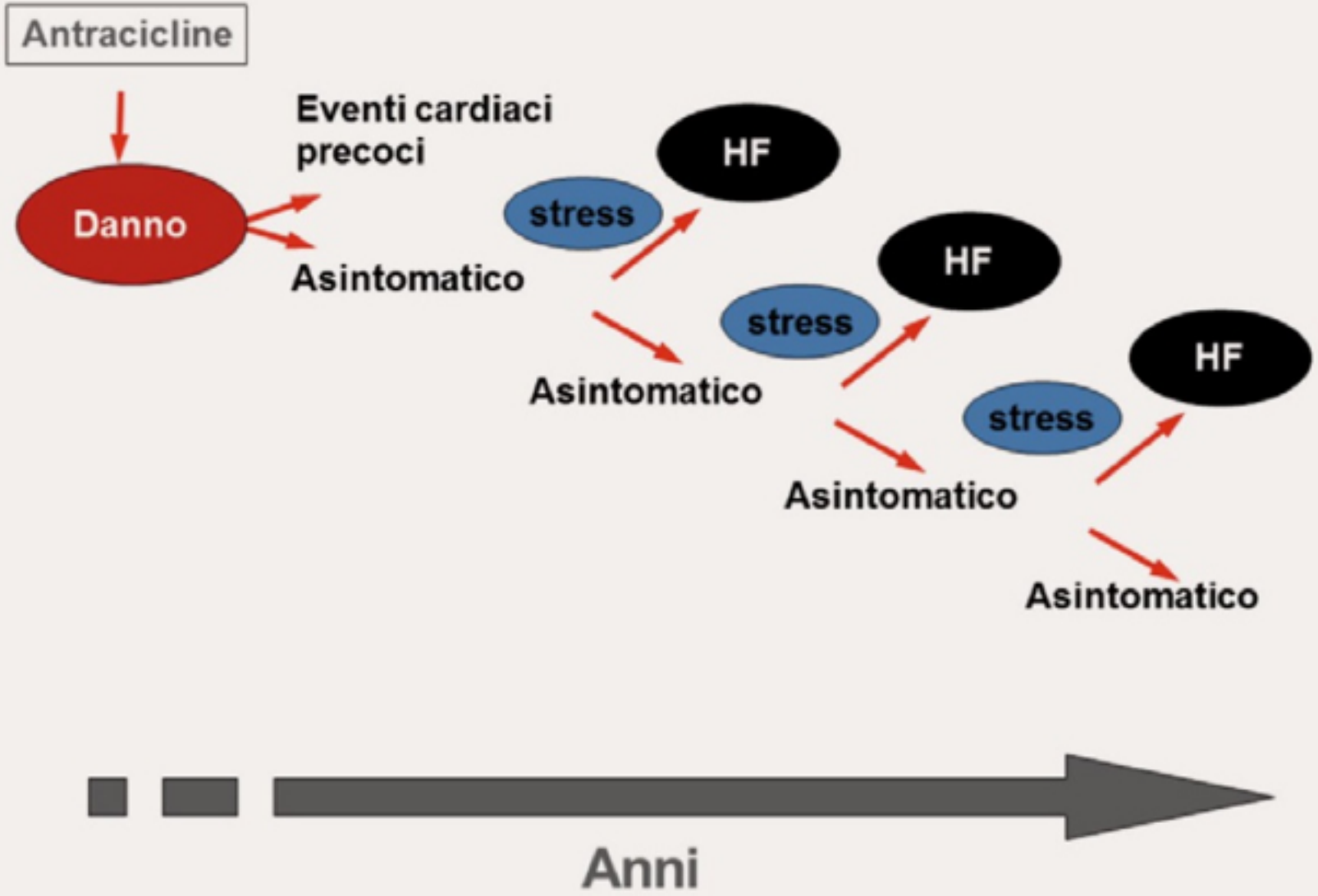
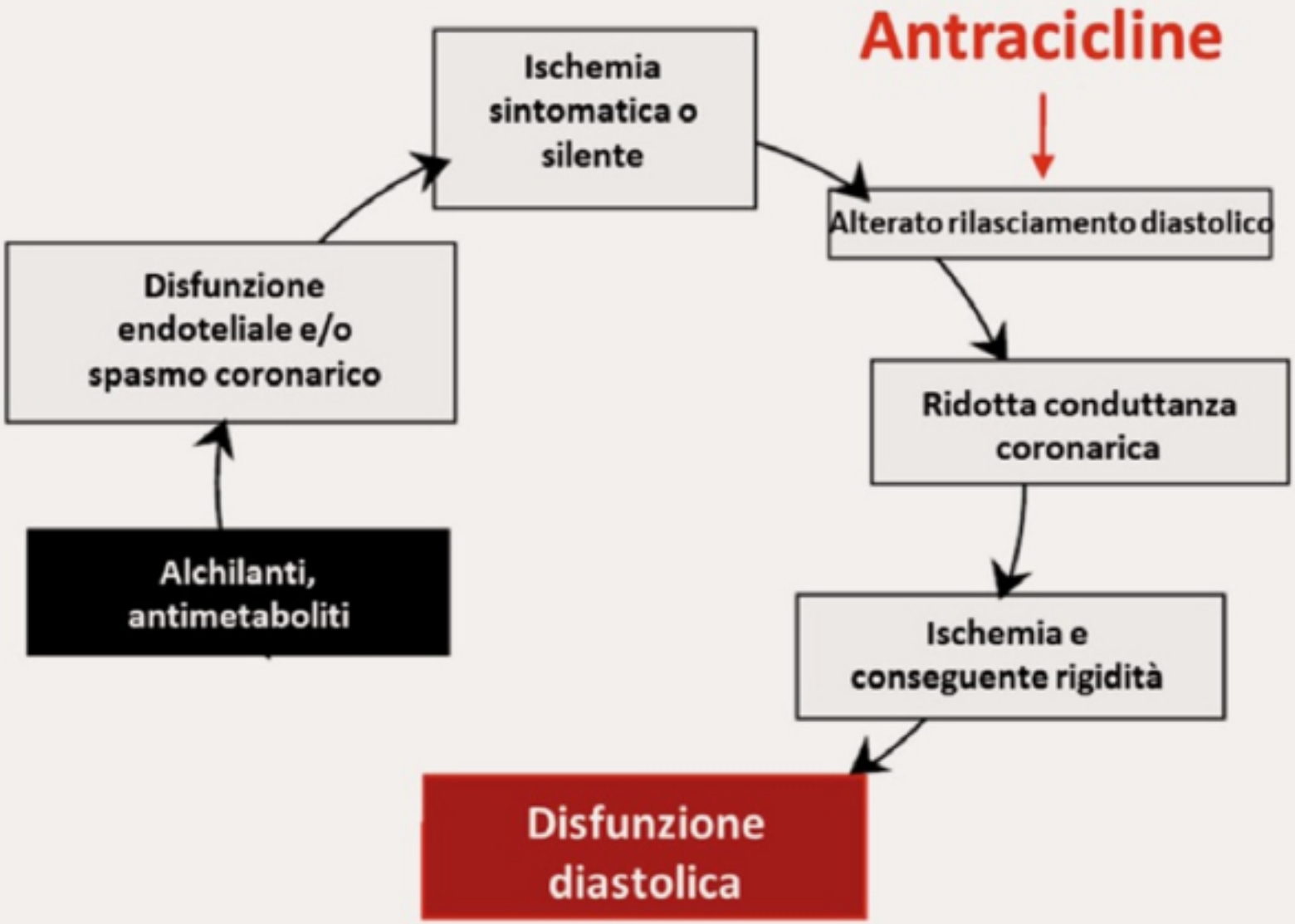
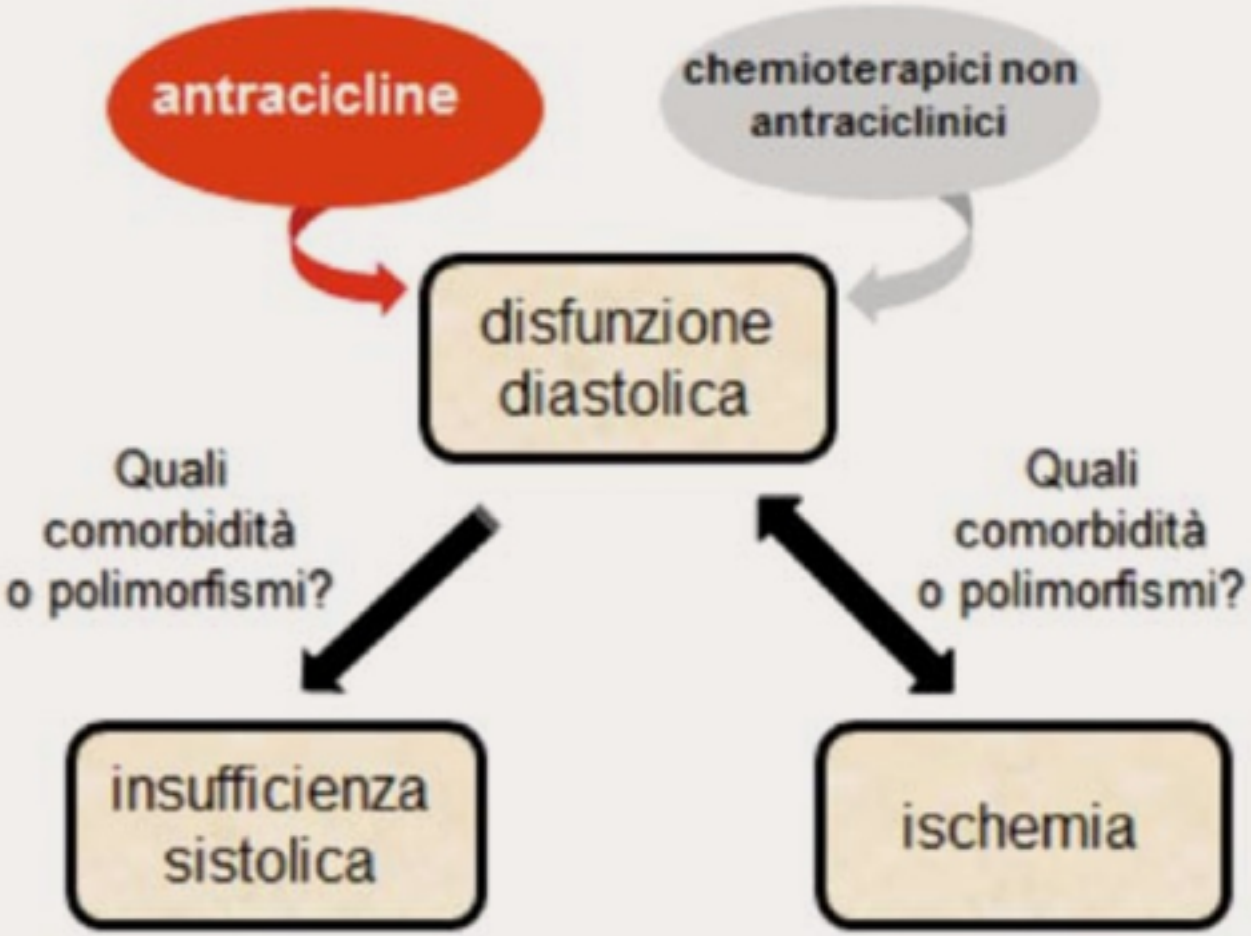


Figura 2.1 **Teoria degli stress multipli.** Secondo tale teoria, il danno da antracicline può rimanere asintomatico fino a che non si verificano, anche a distanza di anni, eventi stressogeni che possono determinare scompenso (Hearth Failure, HF)

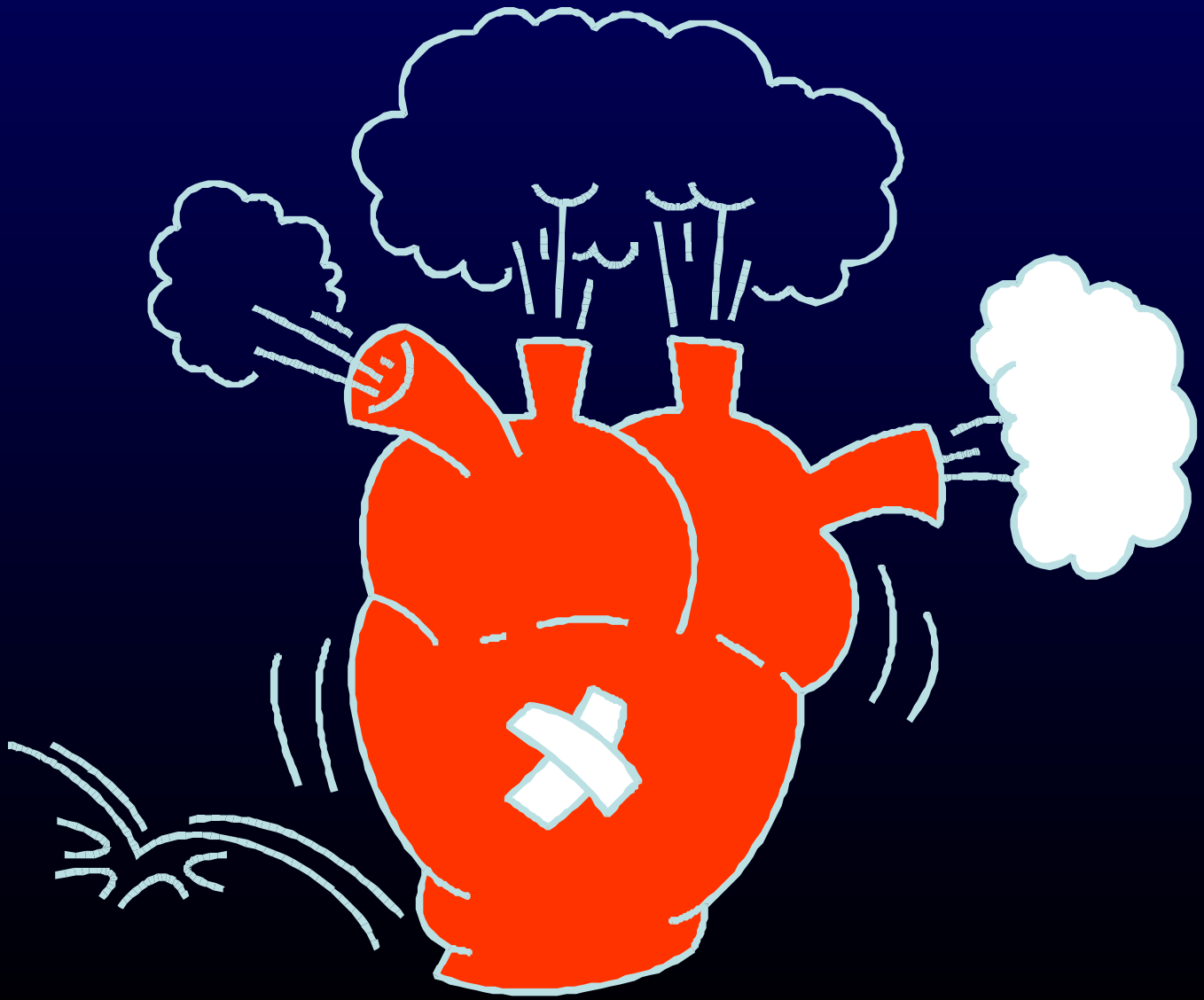
INTERAZIONE TRA AC E FARMACI NON AC: UN CIRCOLO VIZIOSO



INTERAZIONE TRA AC E FARMACI NON AC: UN CIRCOLO VIZIOSO



CARDIOTOX: quadri morfologici



CARDIOTOSSICITÀ ACUTA

- Aritmie
- Alterazioni ECG
- Disfunzione VS

} REVERSIBILI

- Pericardite
- Miocardite
- Infarto
- Morte improvvisa

} GRAVI o FATALI

CARDIOTOSSICITÀ CRONICA

- Tachicardia sinusale
- Aritmie
- Versamento pericardico
- Disfunzione VS
- CMP
- CHF da bassa portata
- **Dose dipendente** (cumulativa doxo <550 mg/m^2, <330 mg/m^2 se RXTh)
- **Sensibilità individuale**
- **F.R.: età, pregressa RXTh, cardiopatia, infezioni virali, th antitumorali multiple**

"LATE ONSET" CMP

- Possibili candidati a **TX cardiaco**
- **Fattori "triggeranti"**: sovraccarico circolatorio di liquidi, gravidanza, calo/aumento peso, chirurgia, anestesia generale, abuso alcool, cocaina, anemia, infezioni acute (virali), ipoproteinemia
- Caratteristiche diverse secondo l'**età**:
  - Bambini → **CMP restrittiva**
  - Adulti → **CMP dilatativa** (anche se non sono da escludere le forme restrittive)

Non solo scompenso !

Molecular Targeted Therapies

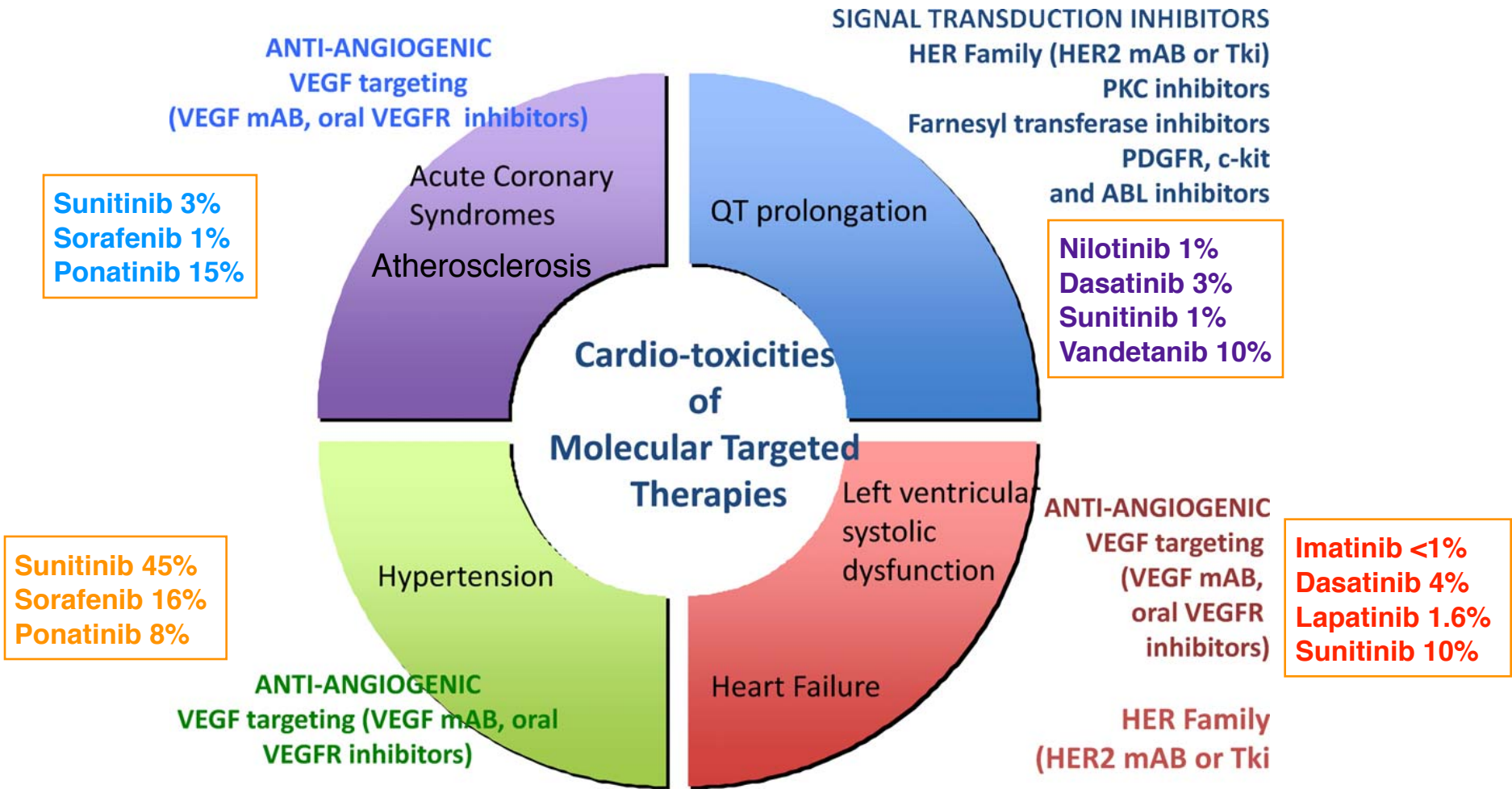
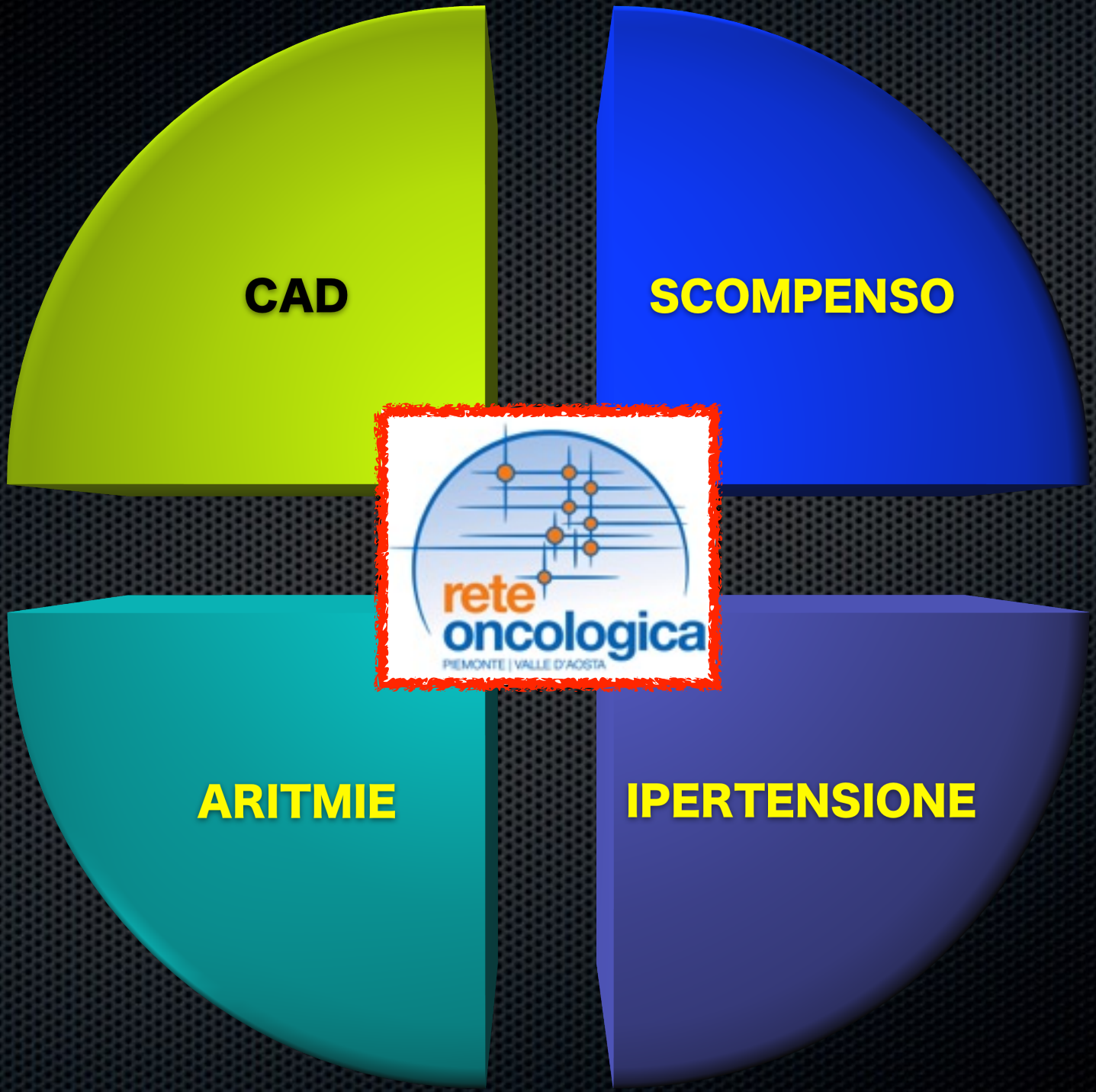


Fig. 1. Spectrum of cardiotoxicity associated with MTTs. Abbreviations: FTPase, farnesyl transferase protein; HER, human epidermal growth factor receptor; mAb, monoclonal antibody; MTT, molecular targeted therapy; PDGFR, platelet-derived growth factor receptor; PKC, phosphokinase C; TKI, tyrosine kinase inhibitor; VDA, vascular-disrupting agents; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.


CAD
SCOMPENSO
rete
oncologica
PIEMONTE | VALLE D'AOSTA
ARITMIE
IPERTENSIONE

Stratificazione, prevenzione e monitoraggio del rischio cardiovascolare nei pazienti con leucemia mieloide cronica o leucemia linfoblastica acuta Ph1 positiva che hanno indicazione alla terapia con Ponatinib

Documento di Raccomandazioni di Consenso di Esperti

Eleonora ARBOSCELLO, Giovanni BAROSI, Fabio CICERI, Mauro GIORGI, Alberto GROSSI, Mario MALLARDO, Giorgio MINOTTI, Savina NODARI, Patrizia PREGNO, Carla SALA, Paolo SPALLAROSSA, Giovanni TORTORELLA

Quale paziente dobbiamo curare?

Differenza di popolazione tra K mammella e CML

Epidemiologia della CML

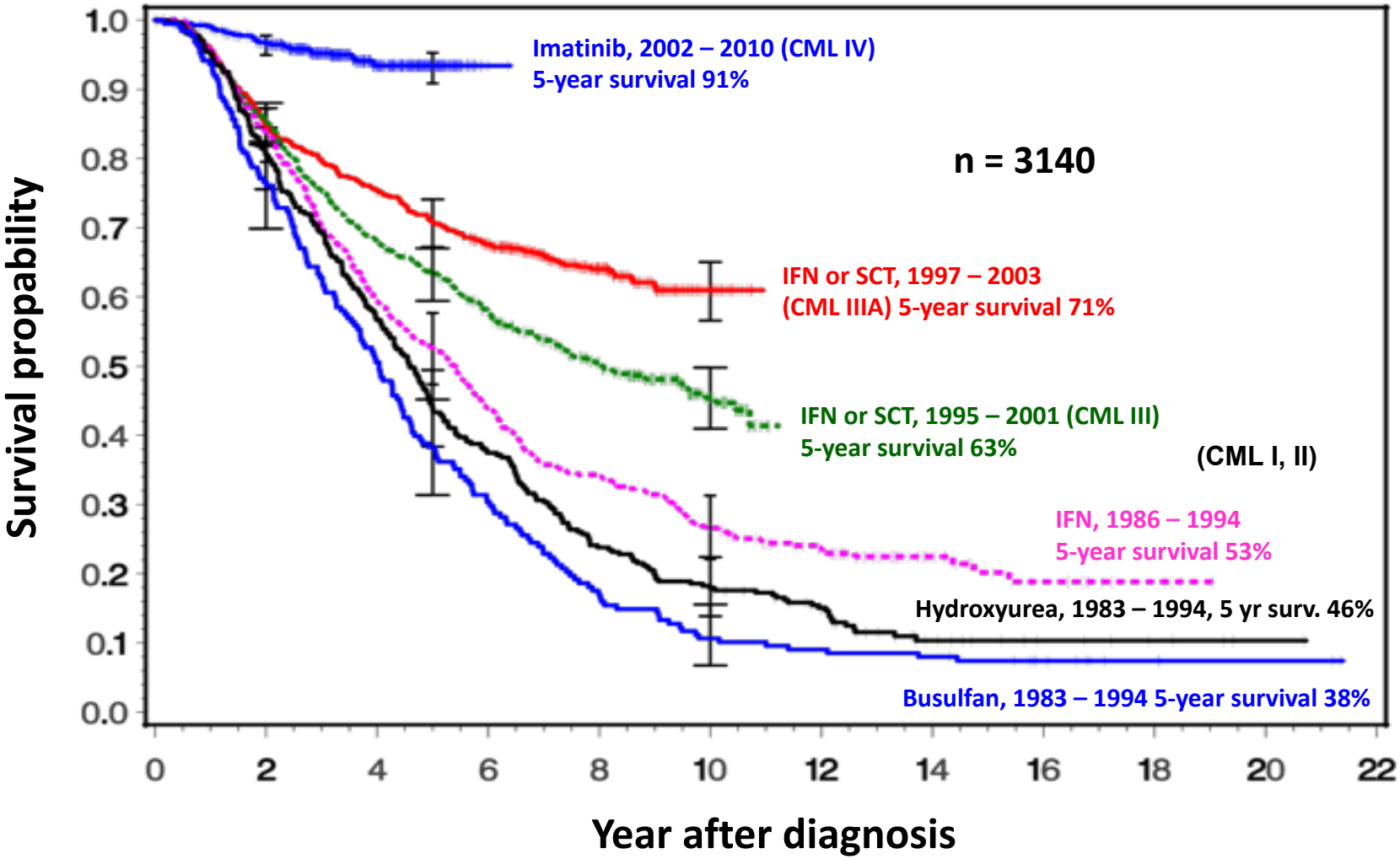
- **Incidenza aumenta con l'età con mediana a 45-55 anni**
  - **fino al 30% dei pz hanno >60 aa**
  - **in Piemonte 1.0/100000 nel 2013**

- **incidenza lievemente + elevata nei maschi**
  - **Maschio-femmina ratio 1.3:1**

- **Alla diagnosi**
  - **50% diagnosi in corso di test di routine**
  - **85% diagnosi in fase cronica di malattia**

Sawyers. *N Engl J Med*. 1999;340:1330.
Faderl et al. *Ann Intern Med*. 1999;131:207.

Improvement of survival of CML 1983 – 2010



German CML Study Group

L’età è un problema?

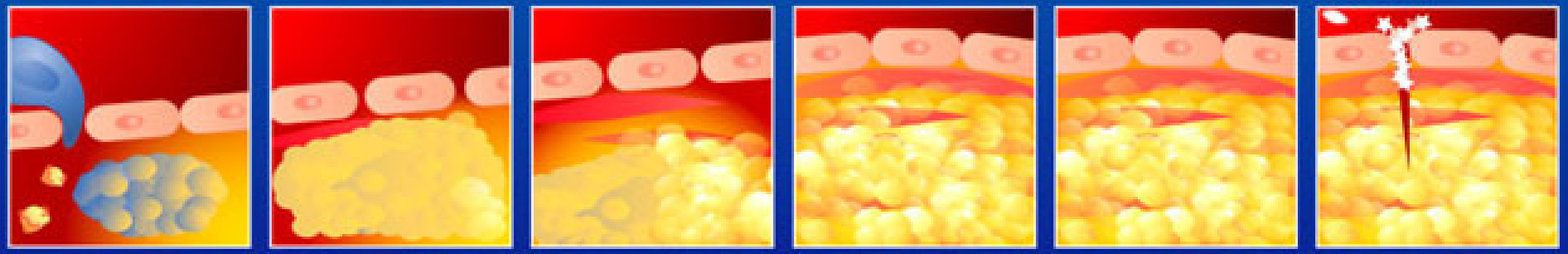
- La LMC è più frequente nel soggetto anziano

- L’età da sola non è un problema, conta l’aspettativa di vita

Vi è maggiore probabilità di

- Ipertensione
- Patologie cardiovascolari
- Patologie metaboliche
- Patologie respiratorie

Atherosclerotic cardiovascular disease (CVD) is a chronic disorder developing insidiously throughout life and usually progressing to an advanced stage by the time symptoms occur



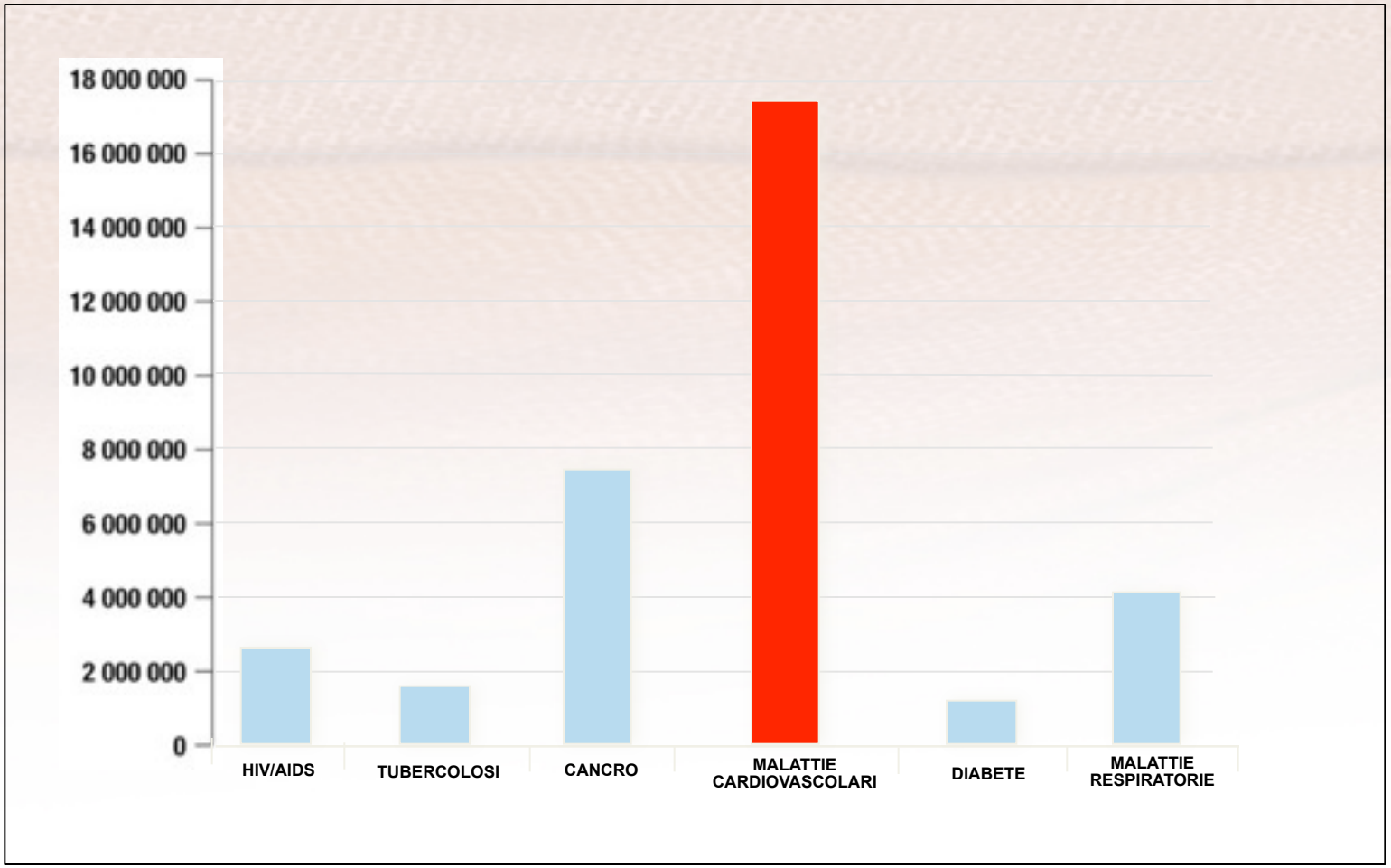
- Intra- and extracellular accumulation of lipids
- Formation of lipid core

Development of fibrosis surrounding lipid core

- Plaque growth
- Atherothrombosis
- Plaque rupture

Asymptomatic — **Eventual clinical events**

Le malattie cardiovascolari sono ancora la prima causa di morte in Europa e in USA !

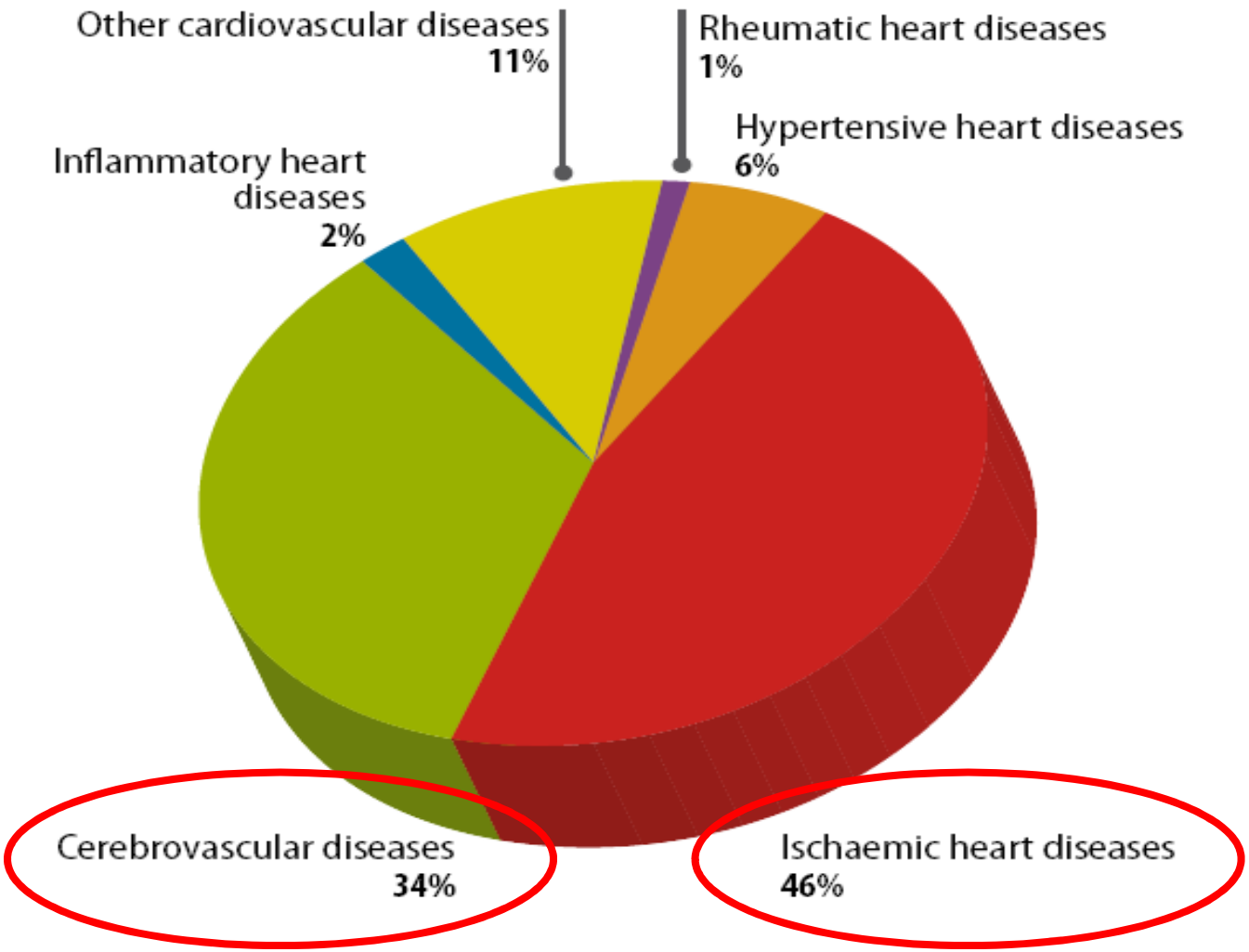


Projections of Global Mortality and Burden of Disease from 2002 to 2003 PLoS Med 3(11): e442. doi:10.1371/journal.pmed.0030442.

Impatto globale della malattia cardiovascolare

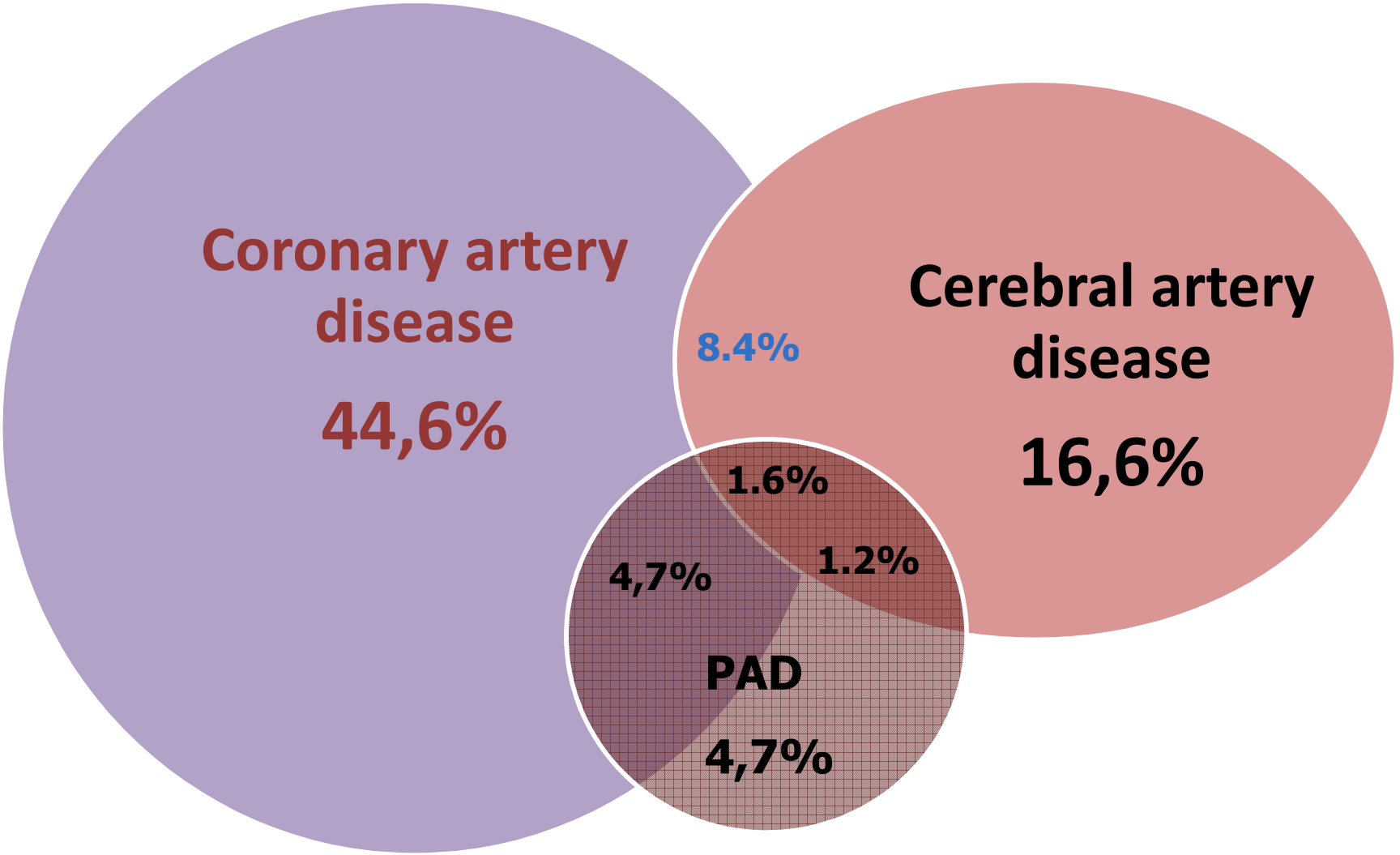
- 16,6 milioni di persone muoiono per CVD ogni anno nel mondo:
  - 7,2 milioni di morti per CVD
  - 5,5 milioni di morti per infarto
- Le CVD contribuiscono a circa un terzo della totalità dei decessi
- Nell'ultima decade riduzione CVD in molti paesi Europei, ma aumento in quelli in via di sviluppo (EST)
- La cura clinica della CVD è costosa e di lunga durata ➜ mass disability e perdita di produttività

DISTRIBUTION OF CARDIOVASCULAR DISEASES DEATHS



Global Atlas on cardiovascular disease prevention and control, WHO Geneva, 2011

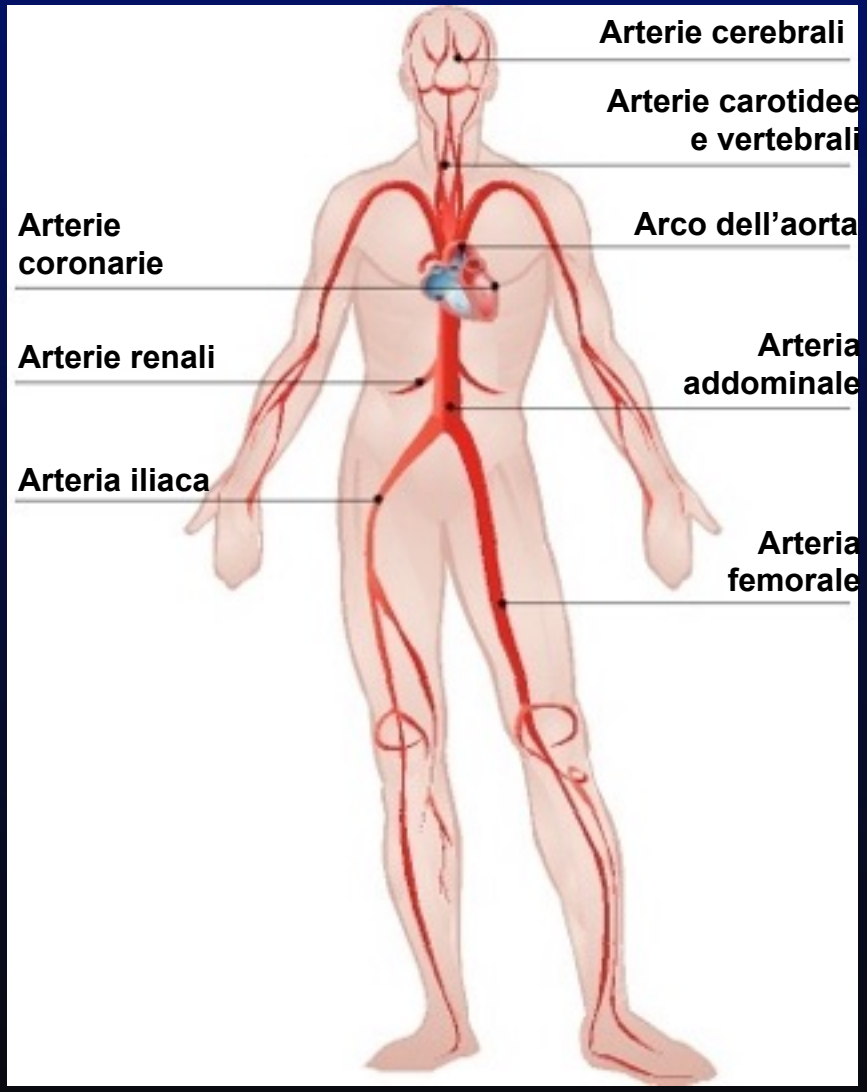
COEXISTENCE OF CARDIOVASCULAR DISEASES



Data from REACH study, Batth et al. JAMA 2006

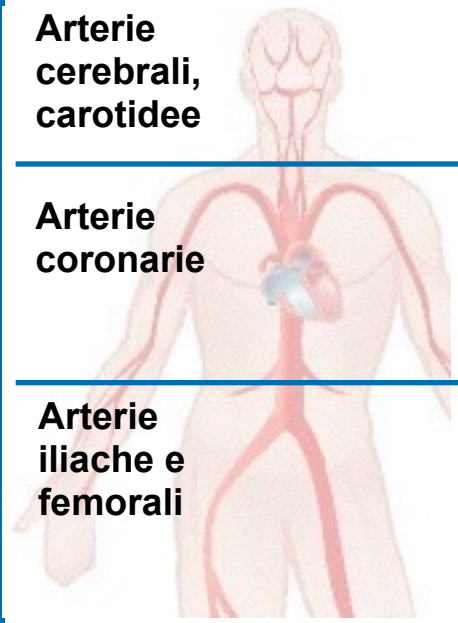
SITI di SVILUPPO delle PLACCHE ATEROMASICHE

Le placche aterom. tendono a formarsi nei punti di **ramificazione** del sistema vascolare arterioso, dove il flusso del sangue è più **turbolento** ed è più probabile che si verifichi un danno all'endotelio.



TIPI DI MANIFESTAZIONE CLINICA in RELAZIONE al GRADO di STENOSI e all'ARTERIA COLPITA

ARTERIE COLPITE	GRADO DI STENOSI		
	 Stenosi	 Stenosi occlusiva (o trombosi)	 Distacco di embolo
Arterie cerebrali, carotidee	TIA	Ictus	TIA Ictus
Arterie coronarie	Angina pectoris	Infarto del miocardio	Infarto del miocardio
Arterie iliache e femorali	Claudicatio intermittens	Dolore ischemico a riposo Necrosi ischemica	Dolore ischemico a riposo Necrosi ischemica



PATOLOGIE CONSEGUENTI alla PROGRESSIONE dell'ATEROSCLEROSI

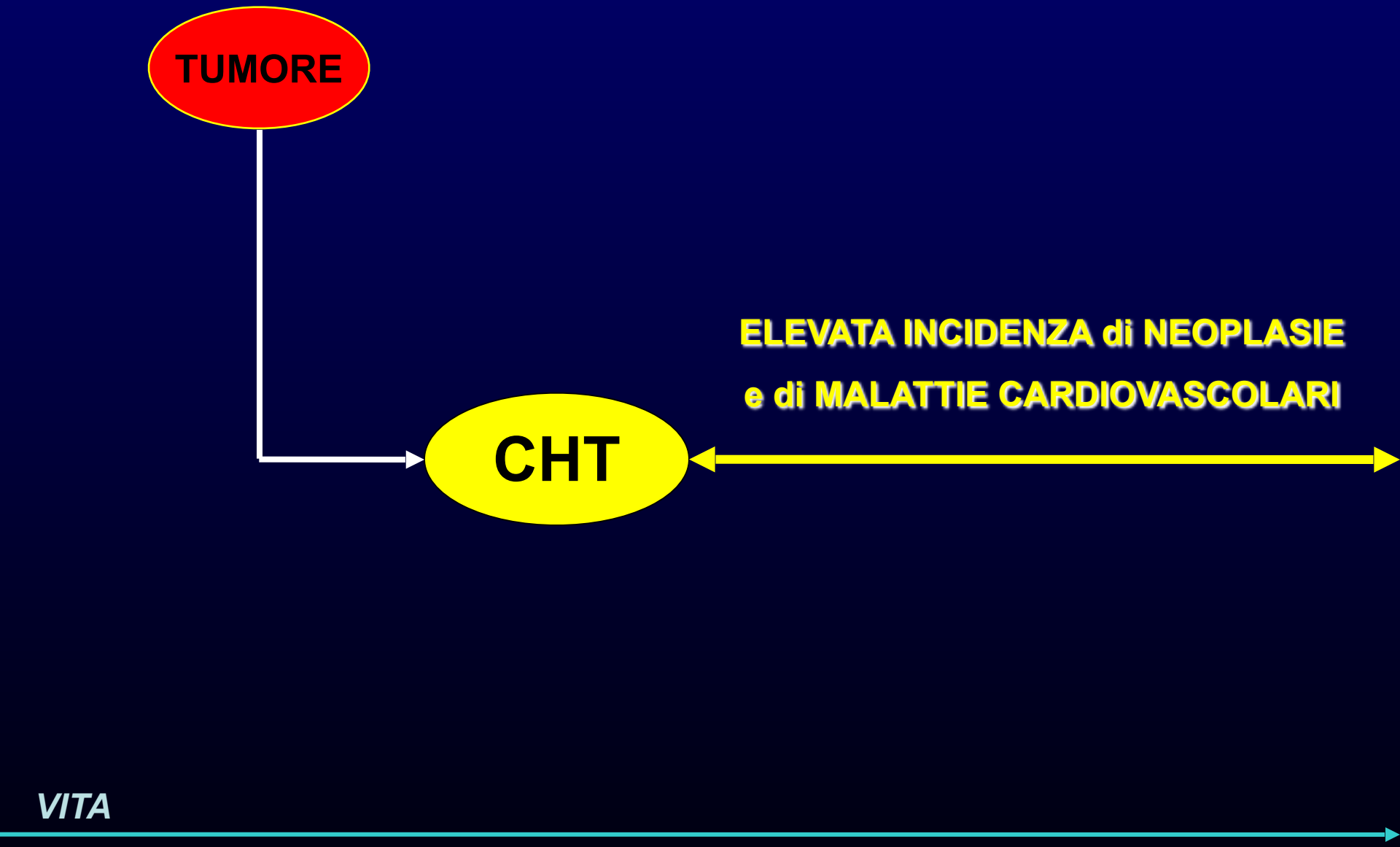
- **Cardiopatia ischemica** (CVD):
  - angina instabile (SCA) - NSTEMI
  - infarto del miocardio (STEMI)
- **Malattia cerebrovascolare** (CBVD)
  - attacchi ischemici transitori (TIA)
  - ictus
- **Arteriopatia periferica** (PAD)
  - claudicatio intermittens
  - dolore ischemico a riposo
  - necrosi ischemica

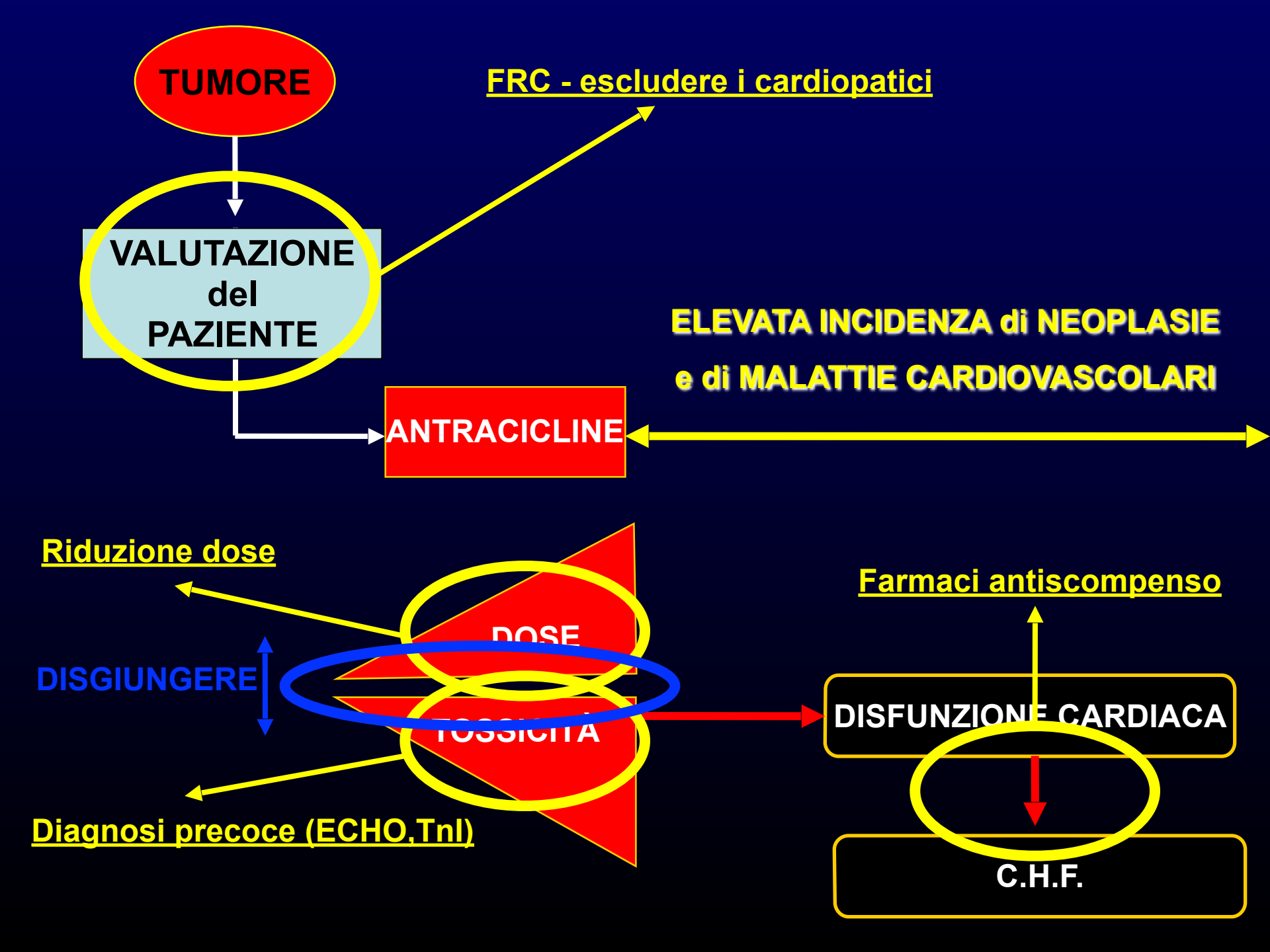
MANAGEMENT

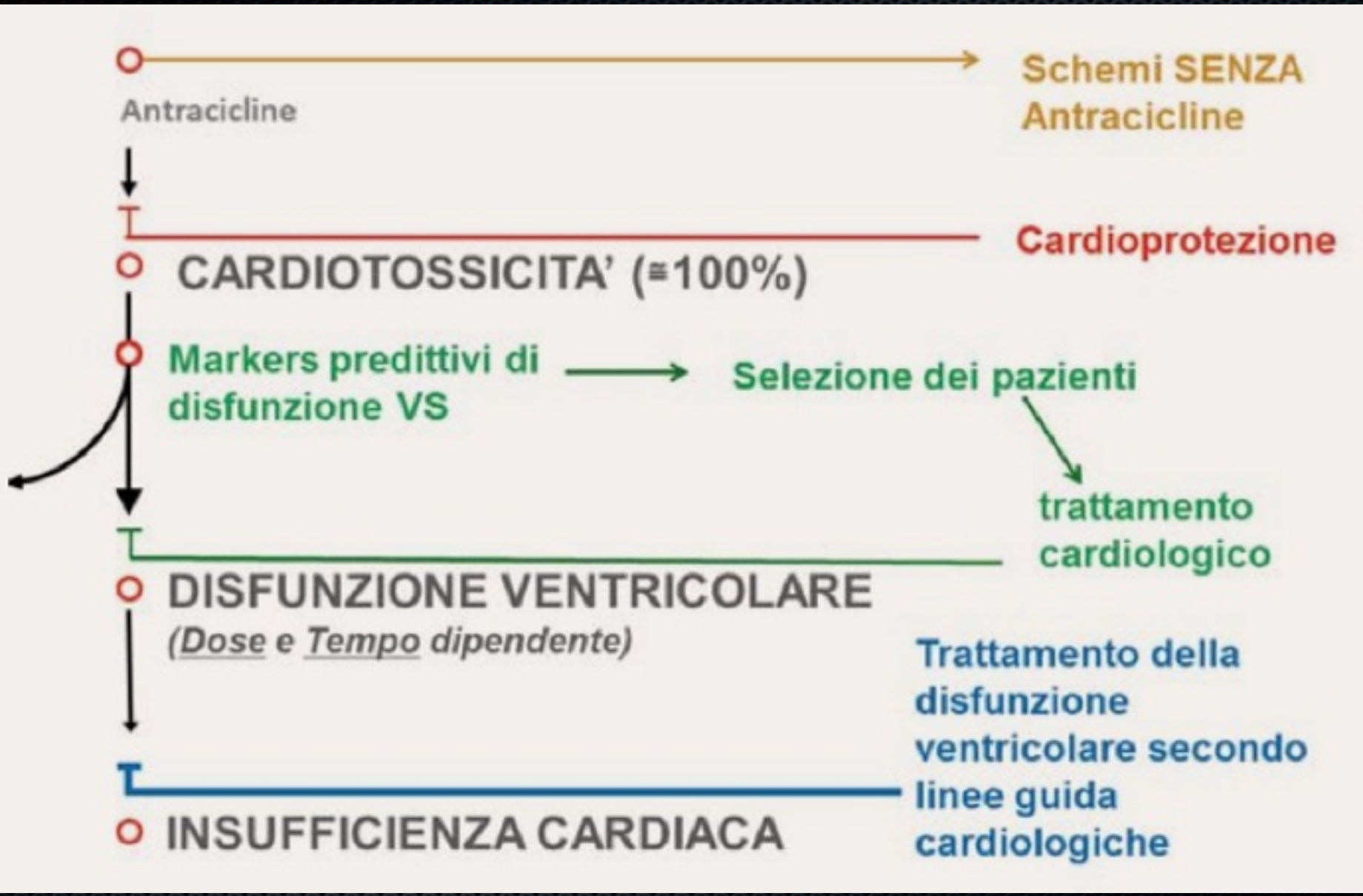
La definizione del profilo cardiovascolare, del rischio individuale e la messa in atto di un monitoraggio clinico continuo sono essenziali nella gestione dei pazienti in trattamento con TKIs

Ruolo del Cardioncologo

- **DURANTE CHT** :
  - modulare la dose del farmaco in modo da somministrare la **dose più alta possibile**, senza causare severo danno cardiaco
- **DOPO CHT** :
  - identificare il danno cardiaco in uno **stadio precoce** per prevenire un ulteriore deterioramento


TUMORE
CHT
ELEVATA INCIDENZA di NEOPLASIE
e di MALATTIE CARDIOVASCOLARI
VITA


TUMORE
FRC - escludere i cardiopatici
VALUTAZIONE del PAZIENTE
ELEVATA INCIDENZA di NEOPLASIE
e di MALATTIE CARDIOVASCOLARI
ANTRACICLINE
Riduzione dose
Farmaci antiscompenso
DISGIUNGERE
DOSE
TOSSICITÀ
DISFUNZIONE CARDIACA
Diagnosi precoce (ECHO,TnI)
C.H.F.


Antracicline
Schemi SENZA Antracicline
Cardioprotezione
CARDIOTOSSICITA' (≅100%)
Markers predittivi di disfunzione VS
Selezione dei pazienti
trattamento cardiologico
DISFUNZIONE VENTRICOLARE
(Dose e Tempo dipendente)
Trattamento della disfunzione ventricolare secondo linee guida cardiologiche
INSUFFICIENZA CARDIACA

CLINICAL WORK UP

- Anamnesi personale e famigliare
- Individuazione e correzione dei FRC
- Visita / esame obbiettivo
- Profilo biochimico completo *(funzionalità renale ed epatica, assetto lipidico, HbA1C)*
- ECG (+ ECG Holter e stress test se CAD nota)
- ECHO
- EcoDoppler arterioso (se FRC) e venoso - ABI
- BNP / Troponina (?)

WHO Trial

Heart Protection Study

CARE

Coronary Drug Project

Progetto Cuore

Scandinavian Simvastatin Survival Study

Oslo Study

La "EVIDENCE BASED MEDICINE": PREVENZIONE CARDIOVASCOLARE

Framingham Study

Helsinki Heart Study

LRC Trial

LIPID

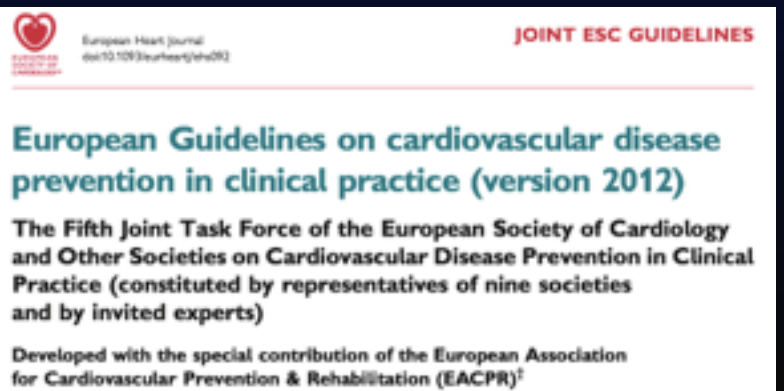
Seven Countries Study

MRFIT

WOSCOPS

AFCAPS

Lipid Research Clinics Program Prevalence Study


European Heart Journal
doi:10.1093/eurheartj/ehs092

JOINT ESC GUIDELINES

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)‡

FATTORI di RISCHIO CARDIOVASCOLARE

FATTORI NON MODIFICABILI

ETÀ (> 50 anni)

SESSO MASCHILE (♀menopausa)

FAMILIARITÀ

FATTORI di RISCHIO CORONARICO

FATTORI MODIFICABILI

DISLIPIDEMIA

FUMO

IPERTENSIONE

DIABETE

SOVRAPPESO-OBESITÀ

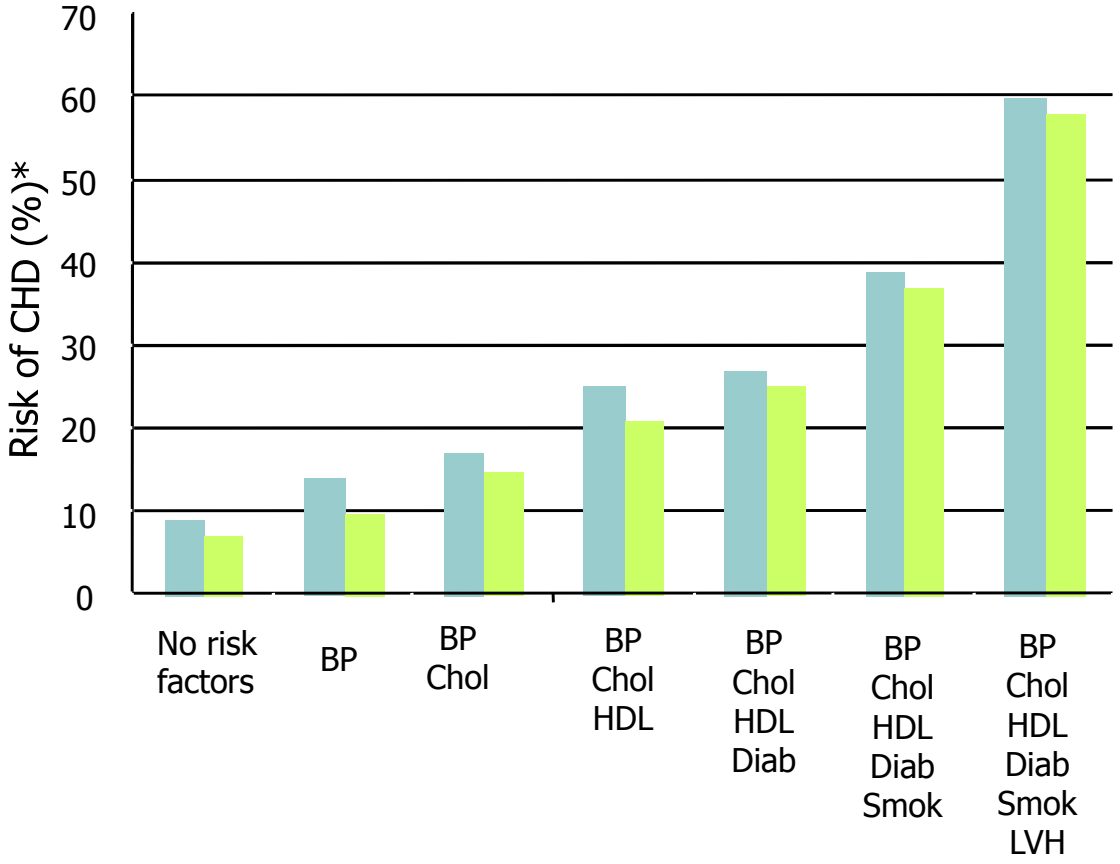
SEDENTARIETÀ

STRESS


DISLIPIDEMIA
OBESITÀ
DIABETE
PROCESSO ATEROGENETICO
FUMO
SEDENTARIETÀ
IPERTENSIONE
STRESS

RISK OF CORONARY HEART DISEASE INCREASES WITH MULTIPLE RISK FACTORS

Analysis of data from the Framingham Heart Study



Risk factors

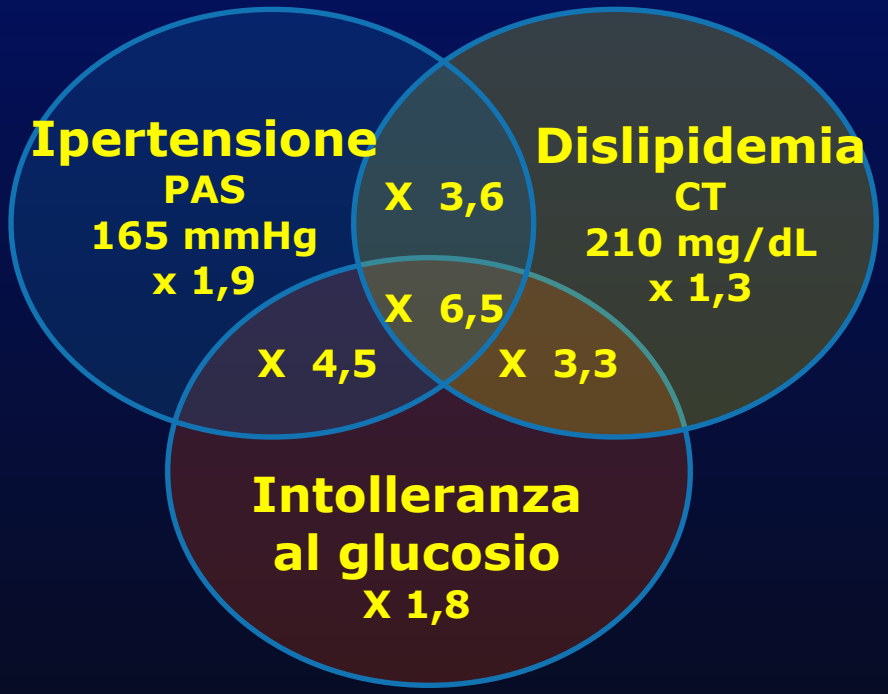
- Systolic Blood Pressure (>160 mm Hg)
- Cholesterol (>260 mg/dL)
- HDL cholesterol (<35 mg/dL)
- Diabetes
- Smoking
- Left ventricular hypertrophy confirmed by ECG

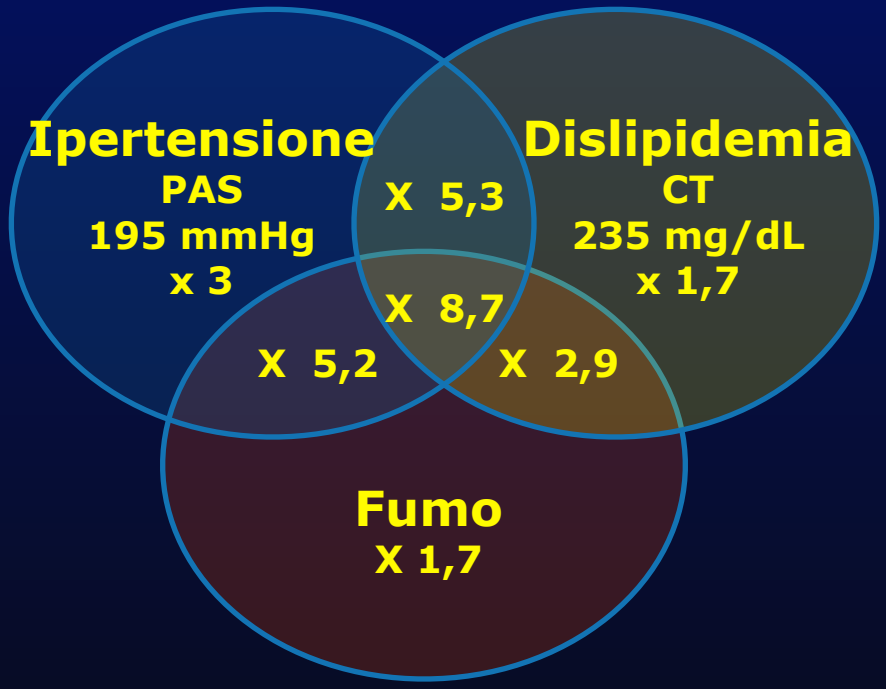
Men

Women

Kannel, Hypertens Res 1995

Il rischio CV globale





<u>Effetto esponenziale</u>

dell'interazione di più fattori di rischio

Il rischio globale

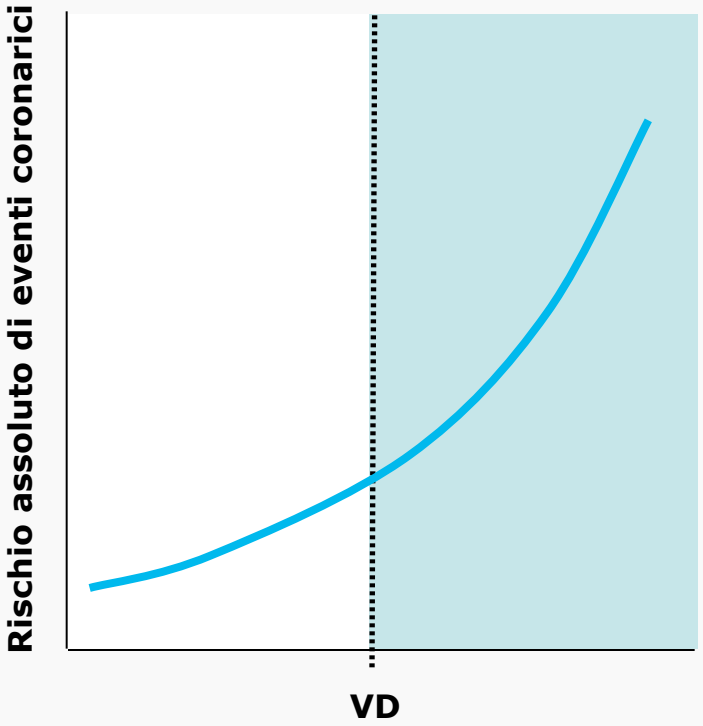
I fattori di rischio interagiscono comportando un AUMENTO ESPONENZIALE del rischio cardiovascolare

Per ridurre il RISCHIO CARDIOVASCOLARE GLOBALE è necessario identificare e trattare i principali fattori di rischio COESISTENTI nello stesso paziente

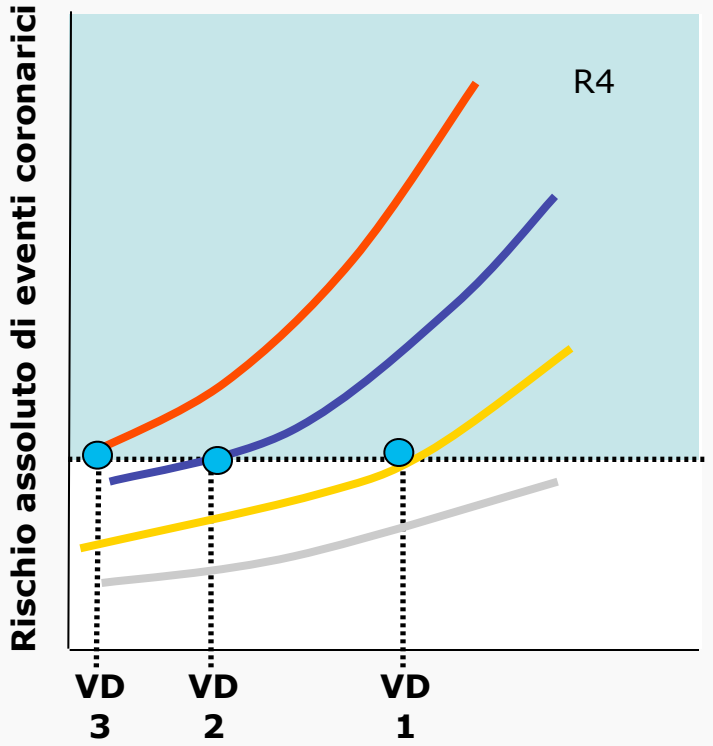
Il nuovo approccio ai F.R.C.

A

VD= valore decisionale



B



Poli A. Rischio Cardiovascolare globale, 2002

TREAT TO TARGET

THE HIGHER THE RISK, THE GREATER THE BENEFIT

FROM PREVENTIVE EFFORTS

OBIETTIVO

Identificare
i soggetti a rischio
moderato/elevato

STILE di VITA

PREVENZIONE

TRATTAMENTO FARMACOLOGICO

Perché é necessaria la prevenzione cardiovascolare?

- La malattia cardiovascolare (CVD) rimane la **principale causa di morte** in Europa
- Più dell' 80% della CVD oggi si manifesta nei Paesi in via di sviluppo
- La CVD é causa di disabilità di massa (**DALYs**: Disability Adjusted Life Years): da 85 milioni nel 1990 a 150 milioni nel 2020
- → **perdita di produttività !**

Perché é necessaria la prevenzione cardiovascolare?

- La CVD é strettamente correlata allo **stile di vita** (***FRC***)
- Oltre il **75%** di tutta la mortalità per CVD può essere **prevenuto** grazie ad un cambiamento nello stile di vita
- **"LIFELONG APPROACH"**: la prevenzione dovrebbe iniziare fin dall'infanzia e continuare per sempre
- "Daily practice": concentrazione su età media e PTs alto rischio ➽ potenziale grande beneficio se prevenzione attuata su **giovani** (e molto anziani) e Pts **rischio basso-moderato**

2. Why is prevention of cardiovascular disease needed?

Terapia vs Prevenzione

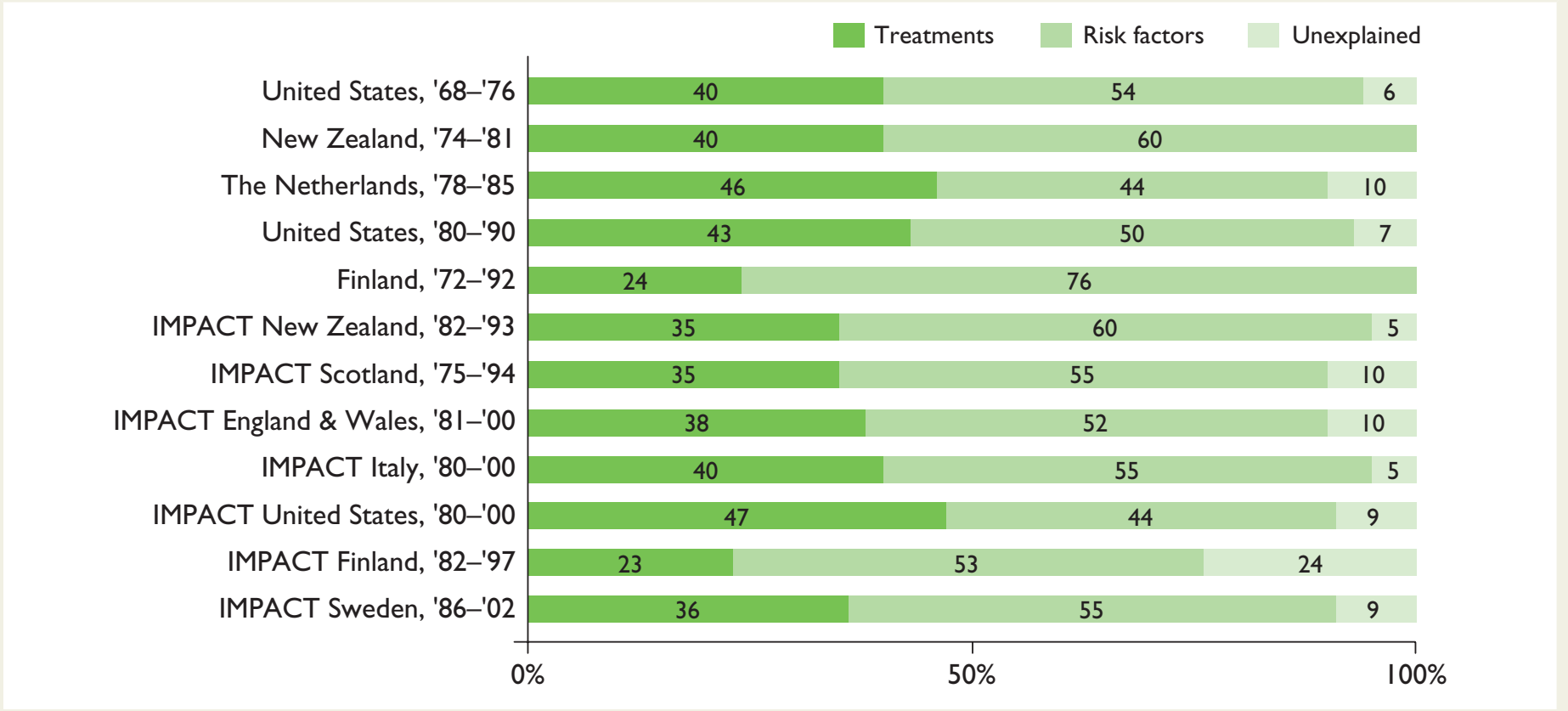


Figure 1 Percentage of the decrease in deaths from coronary heart disease attributed to treatments and risk factor changes in different populations (adapted from Di Chiara *et al.*[31])

Cost saving, improvement of the quality and lenght of people's lives, prevention of other conditions (cancer, pulmunary diseases, type 2 diabetes)

MONICA - IMPACT

Who should benefit from it ?

- RISCHIO = probabilità di sviluppare CVD entro un certo periodo di tempo
- Trattare la **persona** e non il fattore di rischio !
- Effetto **esponenziale** dalla somma di più F.R.C.
- Non esiste un cut-off oltre il quale iniziare la terapia, ma si tratta di un ***continuum***
- I soggetti a più **alto rischio** sono quelli che ottengono il maggior vantaggio dalla correzione
- Mancato riconoscimento del rischio ➜
  - inadeguato trattamento negli Alto Rischio
  - abuso di farmaci nei Basso Rischio

Who should benefit from it ?

- "**Rischio cardiovascolare globale**": il CVD risk é il risultato dell'interazione di **multipli F.R.**
- Utilità di "**carte del rischio**" (**SCORE**) per il *decision making* ed evitare sotto- o sovra-th
- **Alto rischio** ➜ trattamento immediato per **tutti F.R.**
- **Giovani**: meglio il **rischio relativo** o il "**risk age**"
- **Donne**: rischio dilazionato di 10 aa, non evitato
- **Flessibilità**: se l'ideale non si può ottenere su un F.R., bisogna adottare strategia aggressiva sugli altri

il progetto cuore

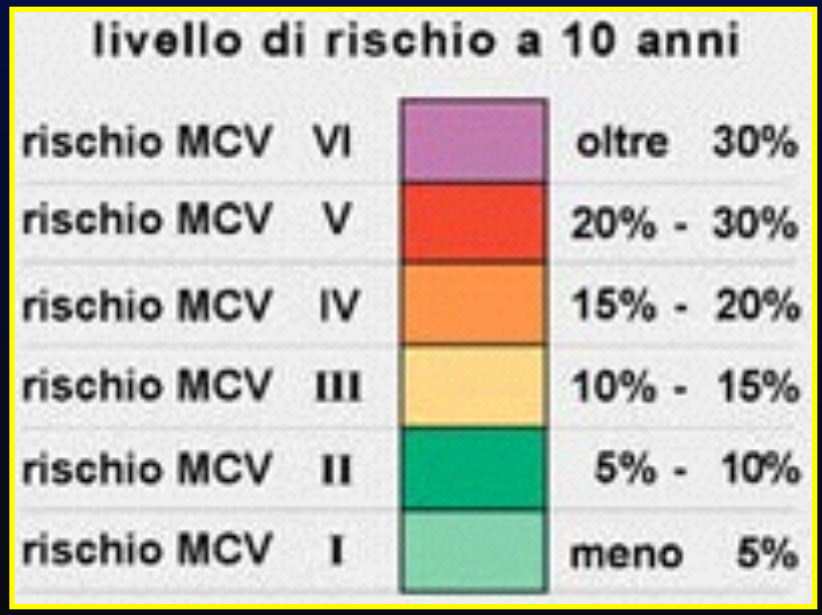
ISTITUTO SUPERIORE DI SANITÀ

17 coorti arruolate in Italia tra il 1980 e il 2002 (Monica, Pamela, Matiss, Atena)

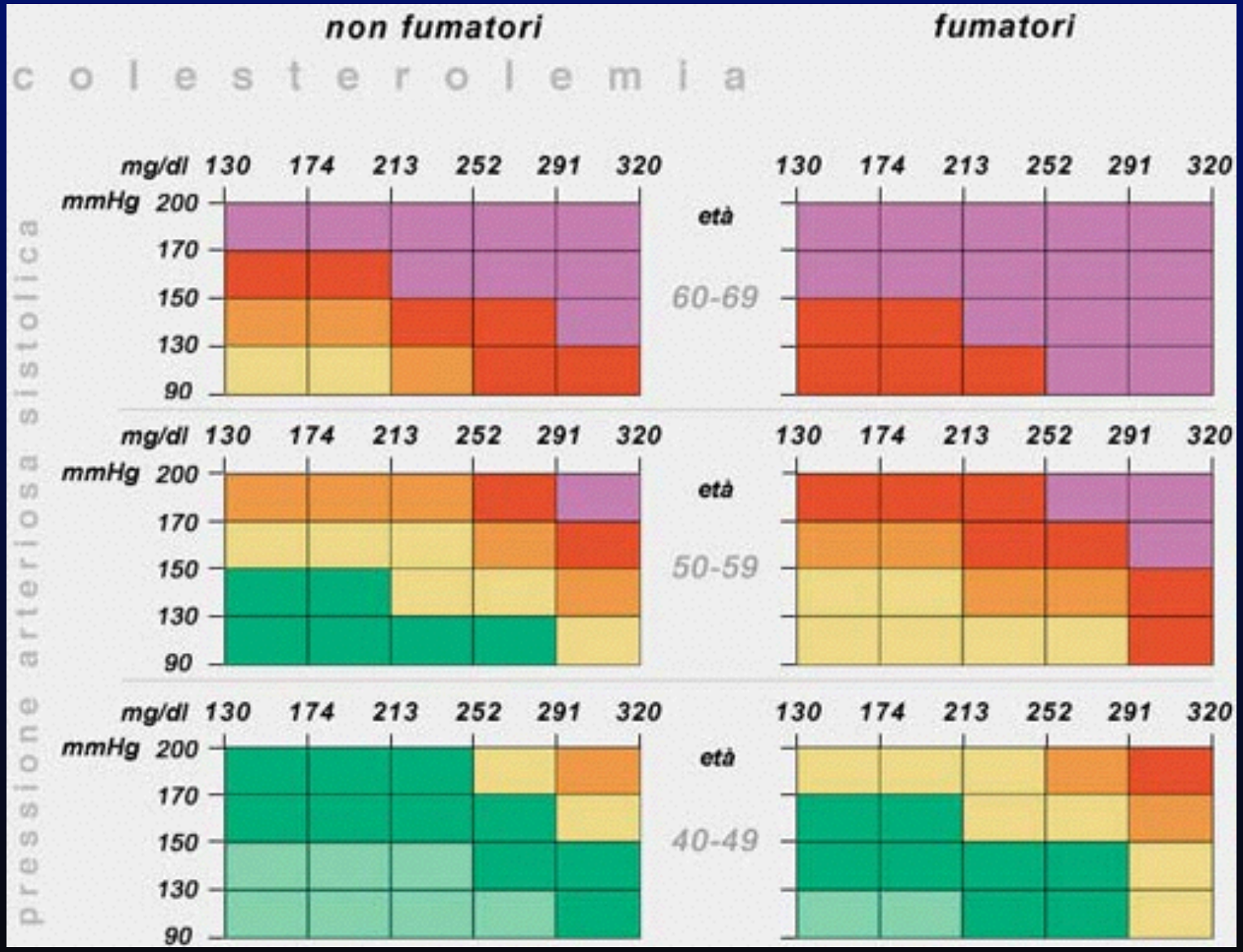
CARTE del RISCHIO C.V.

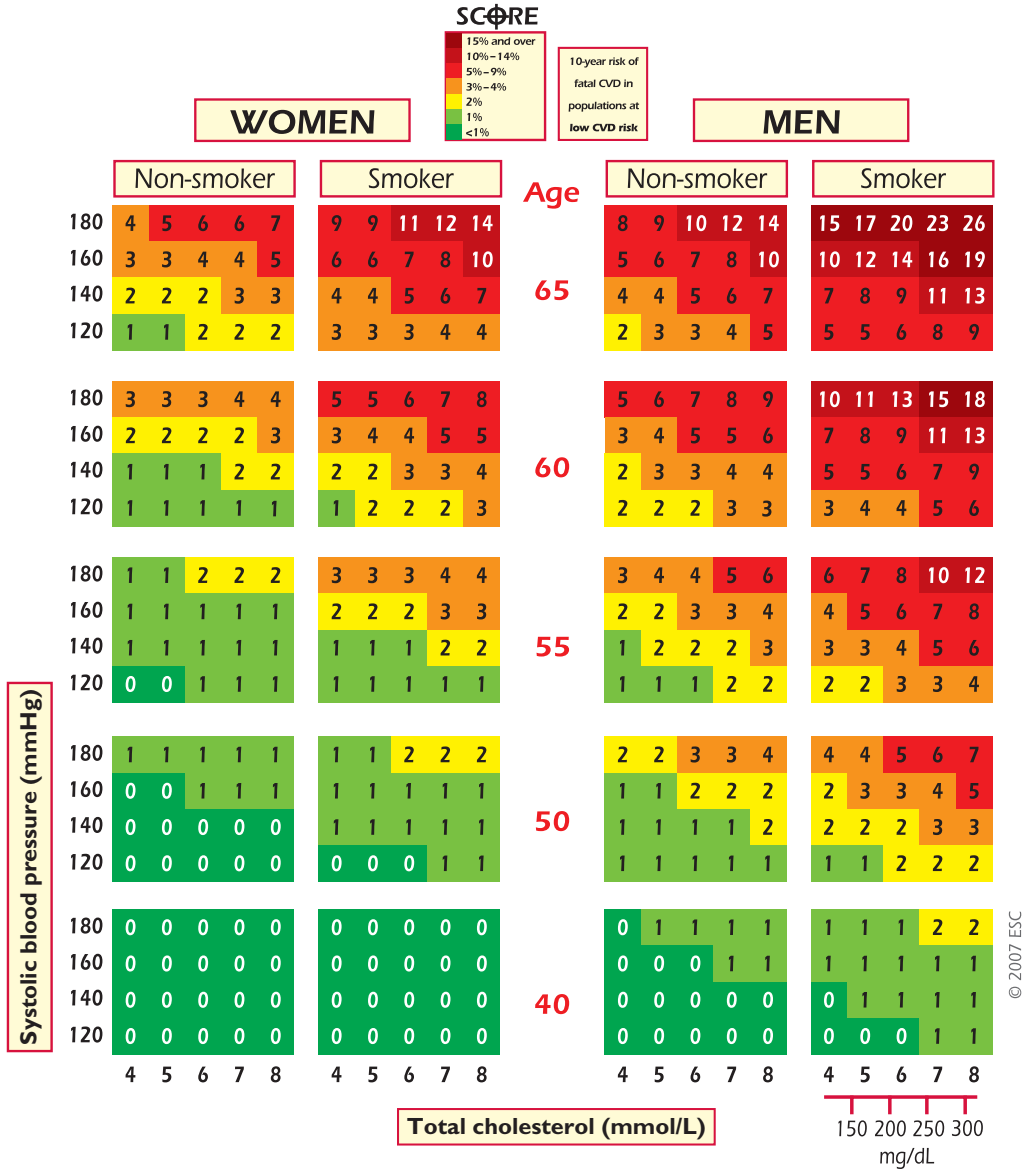
uomini
- diabetici
- non diabetici

donne
- diabetiche
- non diabetiche



UOMINI DIABETICI





Low CVD countries are Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom.

Figure 4 SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in countries at low CVD risk based on the following risk factors: age, sex, smoking, systolic blood pressure, and total cholesterol. Note that the risk of total (fatal + non-fatal) CVD events will be approximately three times higher than the figures given.

HeartScore

Paesi a Basso Rischio

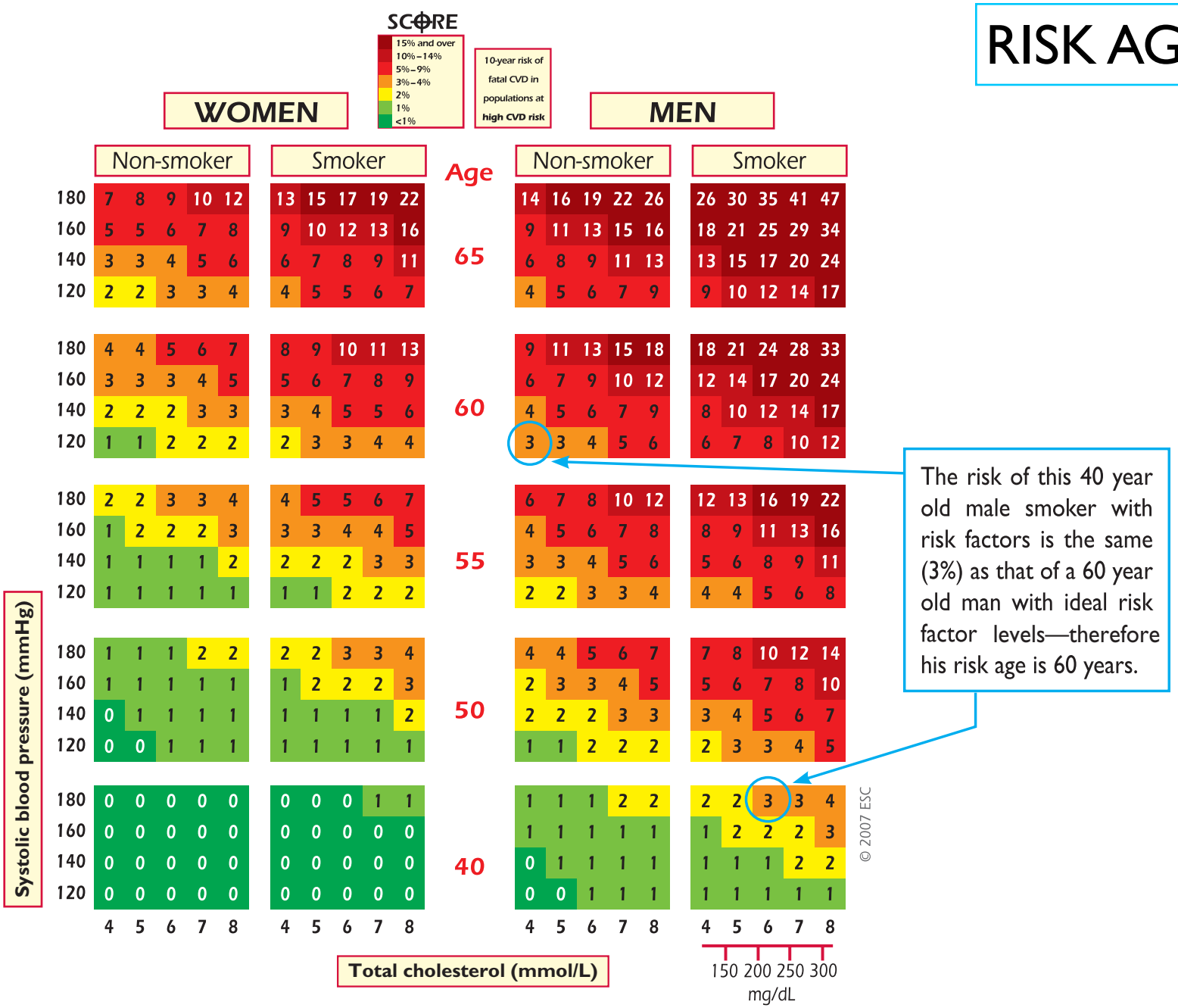


Figure 6 Illustration of the risk–age concept.

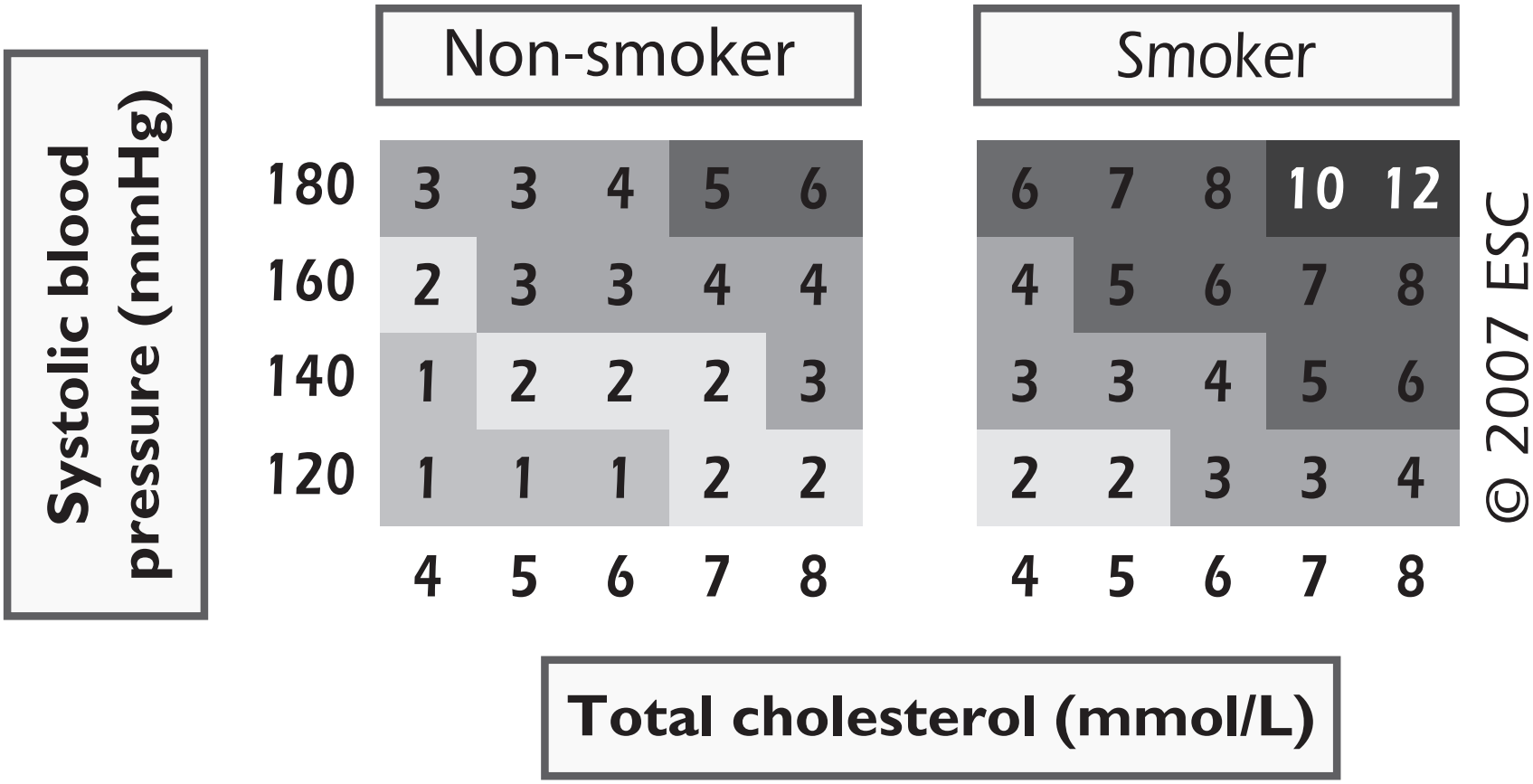


Figure 5 Relative risk chart for 10-year mortality. Conversion of cholesterol mmol/L → mg/dL: 8 = 310, 7 = 270, 6 = 230, 5 = 190, 4 = 155.

LIMITI degli ALGORITMI

- In popolazioni differenti i vari parametri possono avere ruolo e peso diversi (genetica?)
- Le carte si fermano a 69 anni
- Non considerati:
  - Pressione diastolica
  - C-LDL
  - Sovrappeso / obesità
  - Diabete
  - Sedentarietà
  - Famigliarità
  - Malattia renale (GFR < 60 ml/min/1.73m^2)
  - Placche carotidee
  - Stato sociale

VERY HIGH RISK

- CVD documentata, SCA, STEMI, rivascolarizzazione - stroke, arteriopatia periferica
- DIABETE (tipo 1 o 2) con 1 o più FRC e/o danno d'organo (microalbuminuria)
- IRC SEVERA : GFR < 30 ml/min/1.73m^2
- SCORE ≥ 10%

HIGH RISK

- Singolo F.R. marcatamente elevato *(es. Dislipidemia famigliare, Ipertensione severa)*
- DIABETE senza FRC né danno d'organo
- IRC moderata: GFR 30-59 ml/min/1.73m^2
- SCORE ≥ 5% e < 10%

MODERATE RISK

- SCORE ≥ 1% e < 5%

LOW RISK

- SCORE < 1%

Recommendations regarding risk estimation

Recommendations	Class[a]	Level[b]	GRADE	Ref[C]
Total risk estimation using multiple risk factors (such as SCORE) is recommended for asymptomatic adults without evidence of CVD.	I	C	**Strong**	36
High-risk individuals can be detected on the basis of established CVD, diabetes mellitus, moderate to severe renal disease, very high levels of individual risk factors, or a high SCORE risk, and are a high priority for intensive advice about all risk factors.	I	C	**Strong**	36,37

CVD = cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

ALTO RISCHIO:

- CVD nota
- Diabete
- Malattia renale moderato/severa
- Livelli molto alti di F.R. individuali
- Alto SCORE risk

Dubbio

Un Paziente in terapia con TKIs è da considerarsi "di default" ad alto rischio ?

Table 4 Guideline recommendations vs. achievements in patients with established coronary heart disease in EUROSPIRE III (2006-2007)

Guideline recommendations	Proportions at goal
Smoking cessation among smokers	48
Regular physical activity	34
BMI <25 kg/m^2	18
Waist circumference	
<94 cm (men)	25
<80 cm (women)	12
Blood pressure <140/90 mmHg	50
Total cholesterol <4.5 mmol/L (175 mg/dL)	49
LDL cholesterol <2.5 mmol/L (100 mg/dL)	55
Among patients with type 2 diabetes:	
Fasting glycaemia <7.0 mmol/L (125 mg/dL)	27
HbA_{1c} <6.5%	35

European Guidelines on cardiovascular disease prevention in clinical practice
European Heart Journal (2012) 33. 1635-1701

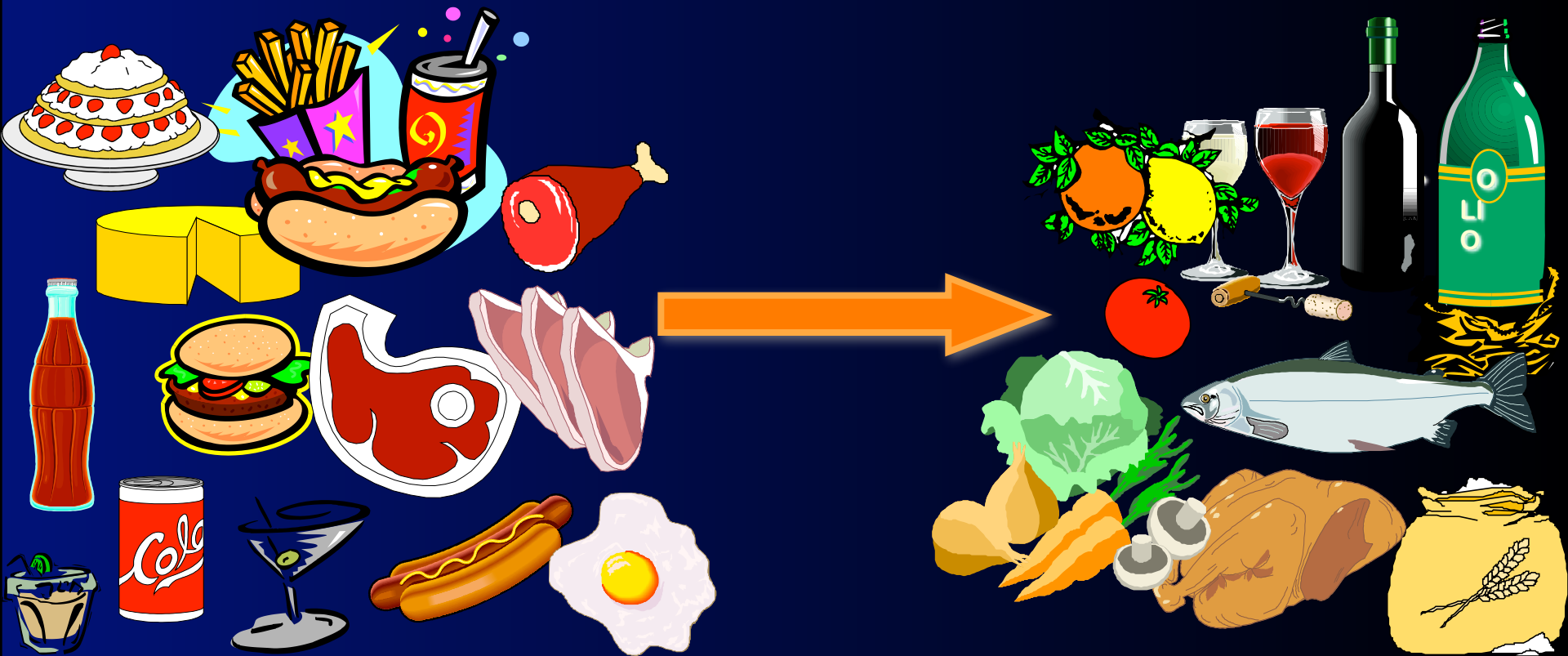
Rischio CV totale (SCORE) %	Livelli di Col-LDL				
	<70 mg/dL <1.8 mmol/L	70-100 mg/dL 1.8-2.5 mmol/L	100-155 mg/dL 2.5-4.0 mmol/L	155-190 mg/dL 4.0-4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	Nessun intervento	Nessun intervento	Intervento sullo stile di vita	Intervento sullo stile di vita	Intervento sullo stile di vita; se insufficiente considerare farmacoterapia
≥1 a <5	Intervento sullo stile di vita	Intervento sullo stile di vita	Intervento sullo stile di vita; se insufficiente considerare farmacoterapia	Intervento sullo stile di vita; se insufficiente considerare farmacoterapia	Intervento sullo stile di vita; se insufficiente considerare farmacoterapia
>5 a <10, o alto rischio	Intervento sullo stile di vita; considerare farmacoterapia*	Intervento sullo stile di vita; considerare farmacoterapia*	Intervento sullo stile di vita e immediata farmacoterapia	Intervento sullo stile di vita e immediata farmacoterapia	Intervento sullo stile di vita e immediata farmacoterapia
≥10, o rischio molto alto	Intervento sullo stile di vita; considerare farmacoterapia*	Intervento sullo stile di vita e immediata farmacoterapia*	Intervento sullo stile di vita e immediata farmacoterapia	Intervento sullo stile di vita e immediata farmacoterapia	Intervento sullo stile di vita e immediata farmacoterapia

*In pazienti con infarto del miocardio, la terapia con statine dovrebbe essere considerata indipendentemente dai livelli di Col-LDL
CV = Cardiovascolare
Col-LDL= colesterolo a lipoproteine a bassa densità.

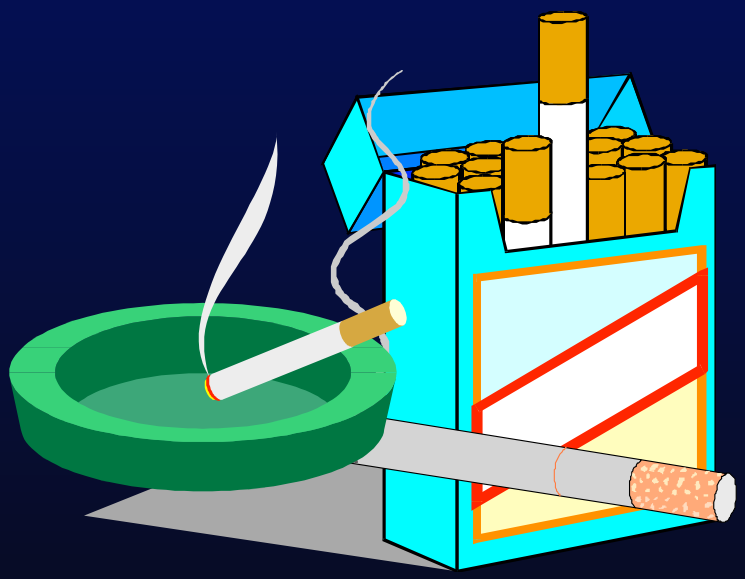
ALIMENTAZIONE CORRETTA

RIDUZIONE DELL'APPORTO DI ZUCCHERI SEMPLICI,
GRASSI SATURI E COLESTEROLO

DIETA MEDITERRANEA !



STILE di VITA



POSITIVELY
NO SMOKING

Considerare anche il FUMO PASSIVO !

STILE di VITA

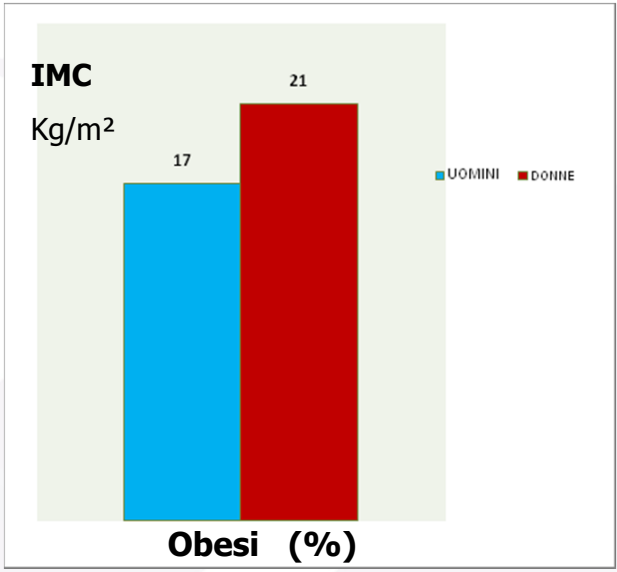
TIPO A

TIPO B

OBESITY

Which index of obesity is the best predictor of CV risk?

- Both overweight (IMC 25-29.9 Kg/m²) and obesity (IMC≥30 Kg/m²) are associated with a risk of death in CVD
- There is a positive linear association of IMC with all-cause mortality
- All cause mortality is lowest with a IMC of 20-25 Kg/m²
- Further weight reduction cannot be considered protective against CVD



Health Examination Survey 1998-2002

European Guidelines on cardiovascular disease prevention in clinical practice; European Heart Journal (2012) 33. 1635-1701

STILE di VITA

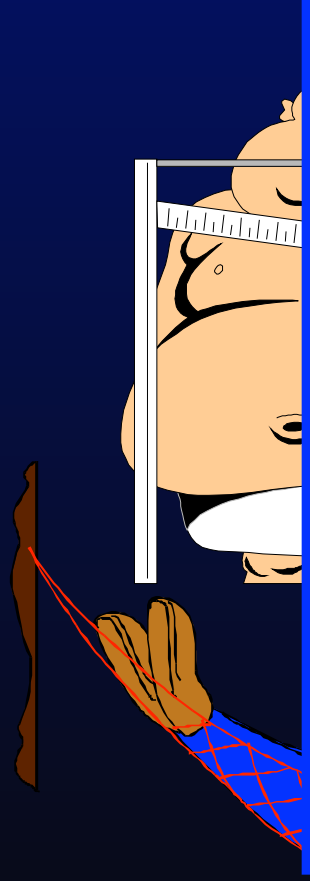
B.M.I. < 25 Kg/m²

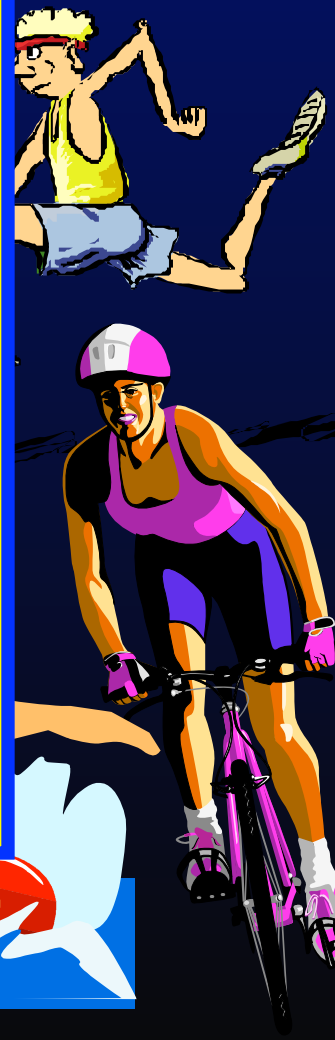
(Body Mass Index)

CIRC. ADDOME:

♂ < 102 (94) cm

♀< 88 (80) cm





Recommendations regarding physical activity

Recommendations	Class[a]	Level[b]	GRADE	Ref[C]
Healthy adults of all ages should spend 2.5–5 h a week on physical activity or aerobic exercise training of at least moderate intensity, or 1–2.5 h a week on vigorous intense exercise. Sedentary subjects should be strongly encouraged to start light-intensity exercise programmes.	I	A	Strong	305–308
Physical activity/aerobic exercise training should be performed in multiple bouts each lasting ≥10 min and evenly spread throughout the week, i.e. on 4–5 days a week.	IIa	A	Strong	305–308
Patients with previous acute myocardial infarction, CABG, PCI, stable angina pectoris, or stable chronic heart failure should undergo moderate-to-vigorous intensity aerobic exercise training ≥3 times a week and 30 min per session. Sedentary patients should be strongly encouraged to start light-intensity exercise programmes after adequate exercise-related risk stratification.	I	A	Strong	309, 310

BMC Cancer

BioMed Central

Research article

Open Access

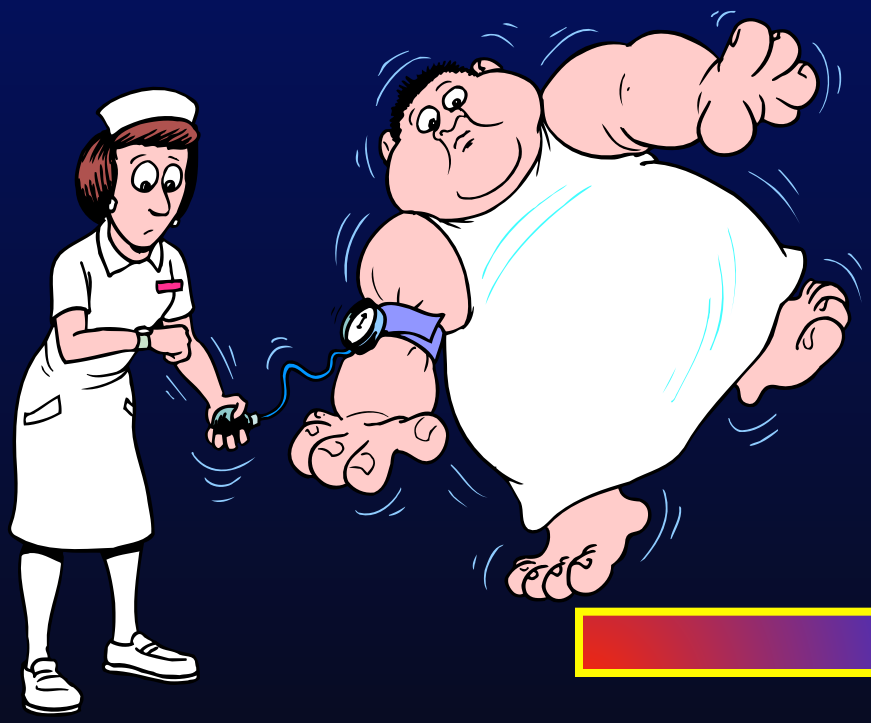
Population attributable risk of breast cancer in white women associated with immediately modifiable risk factors

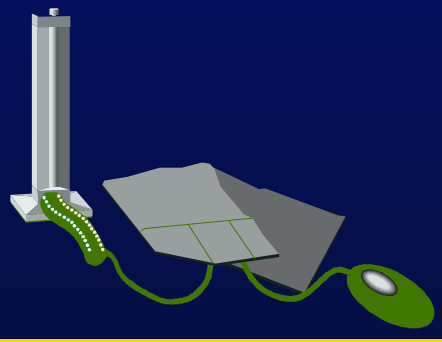
Christina A Clarke*, David M Purdie and Sally L Glaser

Physical inactivity

White women aged 40–79 years reporting no vigorous/moderate physical activity in the last month ranged from 16.1 to 41.0% by county (Table 2). Using an RR estimate of 1.3[6], PAR estimates for physical inactivity ranged between 0.0% and 6.1% for county groups (Table 2). We estimated that statewide, 7.5% of breast cancer cases, or 1,422 cases per year, were attributable to a sedentary lifestyle. Considering ranges of RR estimates from 1.2 to 1.4 and population prevalences from 15% to 45%, we estimated a corresponding range of PARs of 2%–15% (Figure 3).

IPERTENSIONE

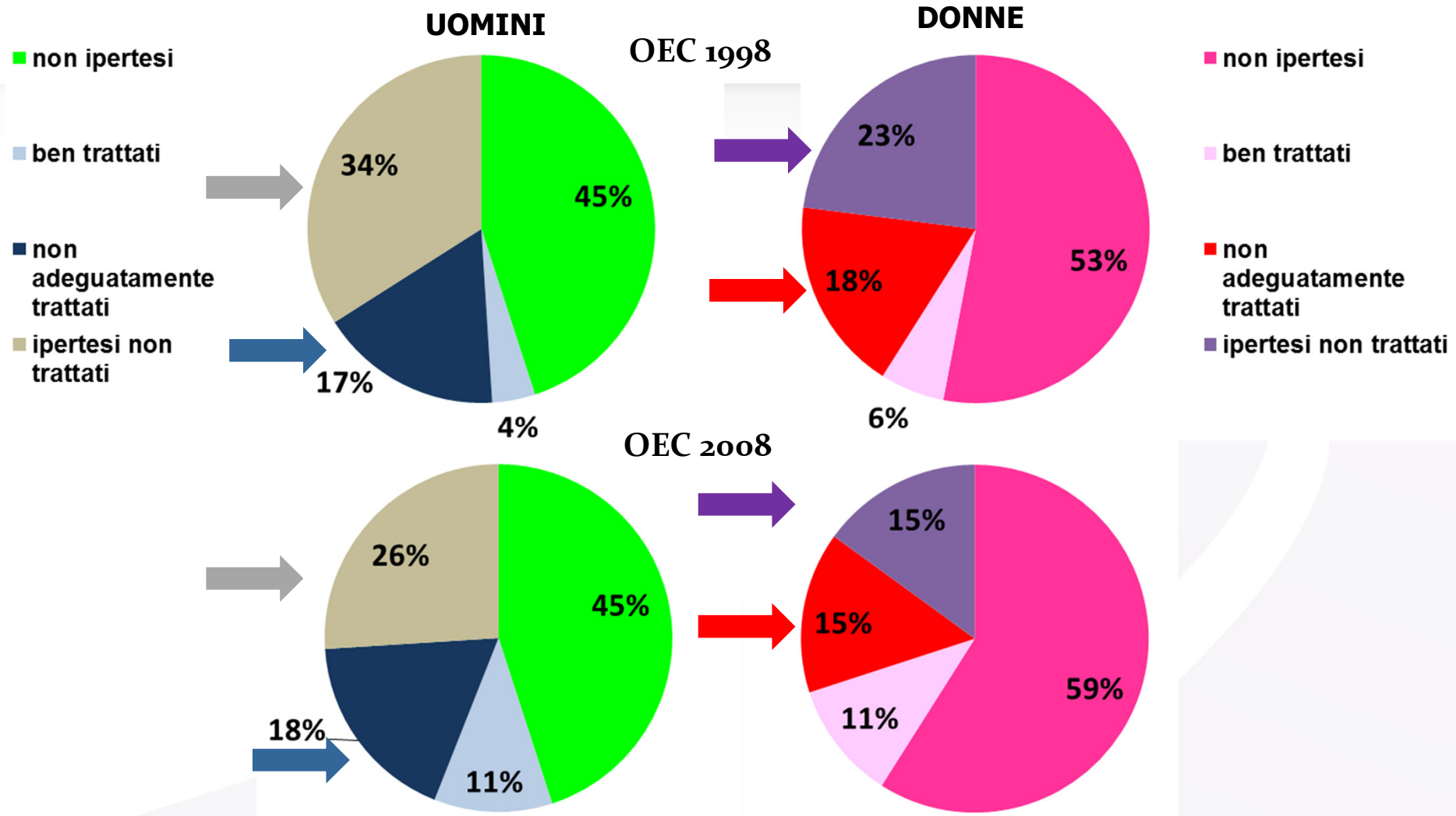




< 140/90 mmHg
(Ideale:< 130/80 mmHg)

Dieta + Farmaci anti ipertensivi

PREVALENCE OF HYPERTENSION IN ITALY



Non iperteso: PAS<140 mmHg E PAD<90 mmHg E senza trattamento

Ben trattato: PAS<140 mmHg E PAD<90 mmHg

Non adeguatamente trattato: PAS≥140 mmHg O PAD 90≥ mmHg

Ipertesi non trattati: PAS≥140 mmHg O PAD 90≥ mmHg E senza trattamento

Health Examination Survey 1998-2002 e 2008-2012

Table 13 Definitions and classification of blood pressure levels[a]

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

BP = blood pressure.

[a]BP levels in untreated individuals.

Table 14 Blood pressure thresholds for definition of hypertension with different types of blood pressure measurement

	SBP (mmHg)	DBP (mmHg)
Office or clinic	140	90
24-hour	125–130	80
Day	130–135	85
Night	120	70
Home	130–135	85

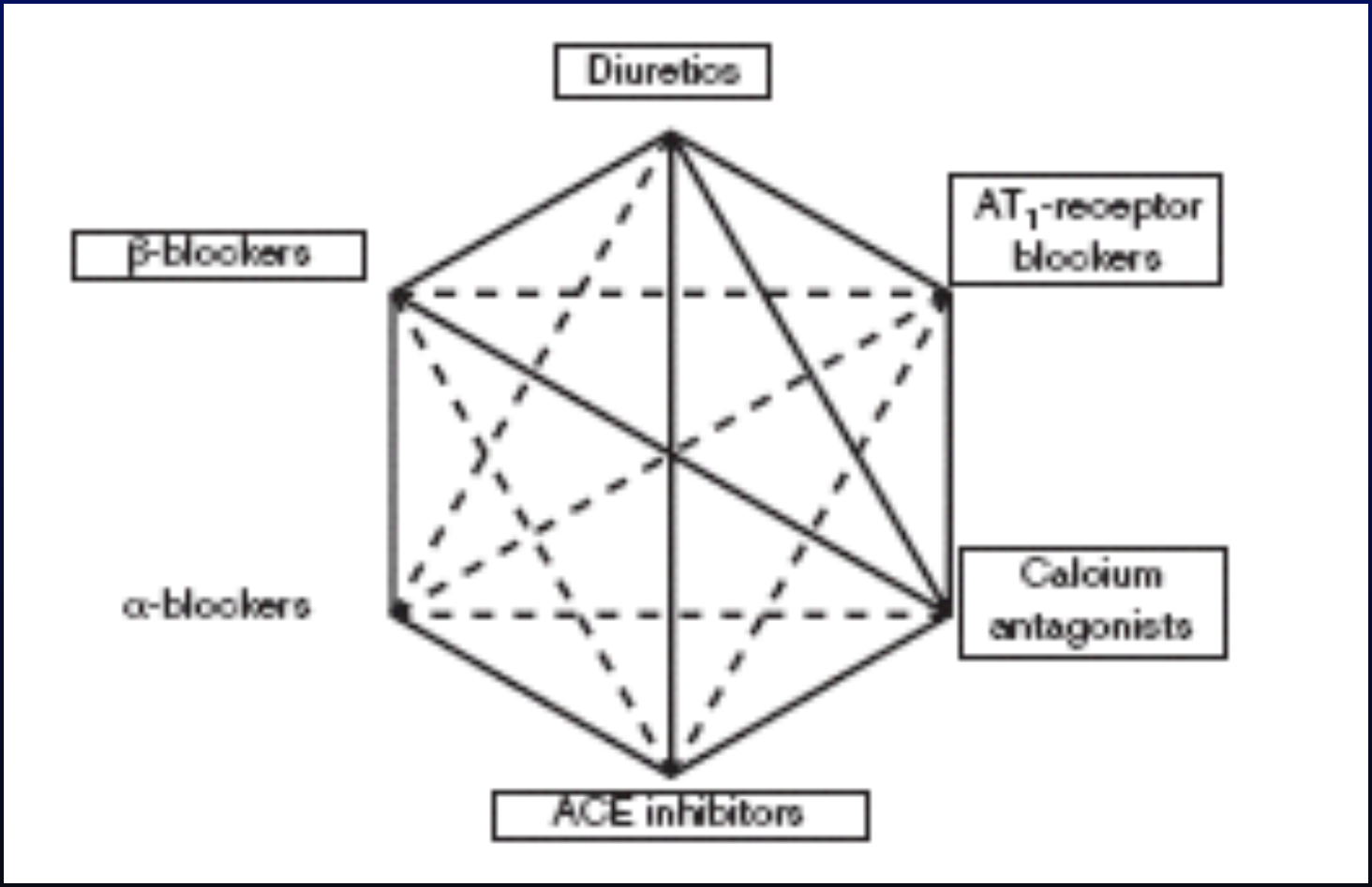
BP = blood pressure; DPB = diastolic blood pressure; SBP = systolic blood pressure.

Modifiche stile di vita e controllo pressorio

MODIFICHE STILE di VITA	RIDUZIONE di PAS (RANGE)
Riduzione peso	5 –20 mmHg / 10 kg
Dieta DASH*	8 – 14 mmHg
Dieta iposodica	2 – 8 mmHg
Attività fisica	4 – 9 mmHg
Riduzione alcool	2 – 4 mmHg

**Dietary Approaches to Stop Hypertensione*

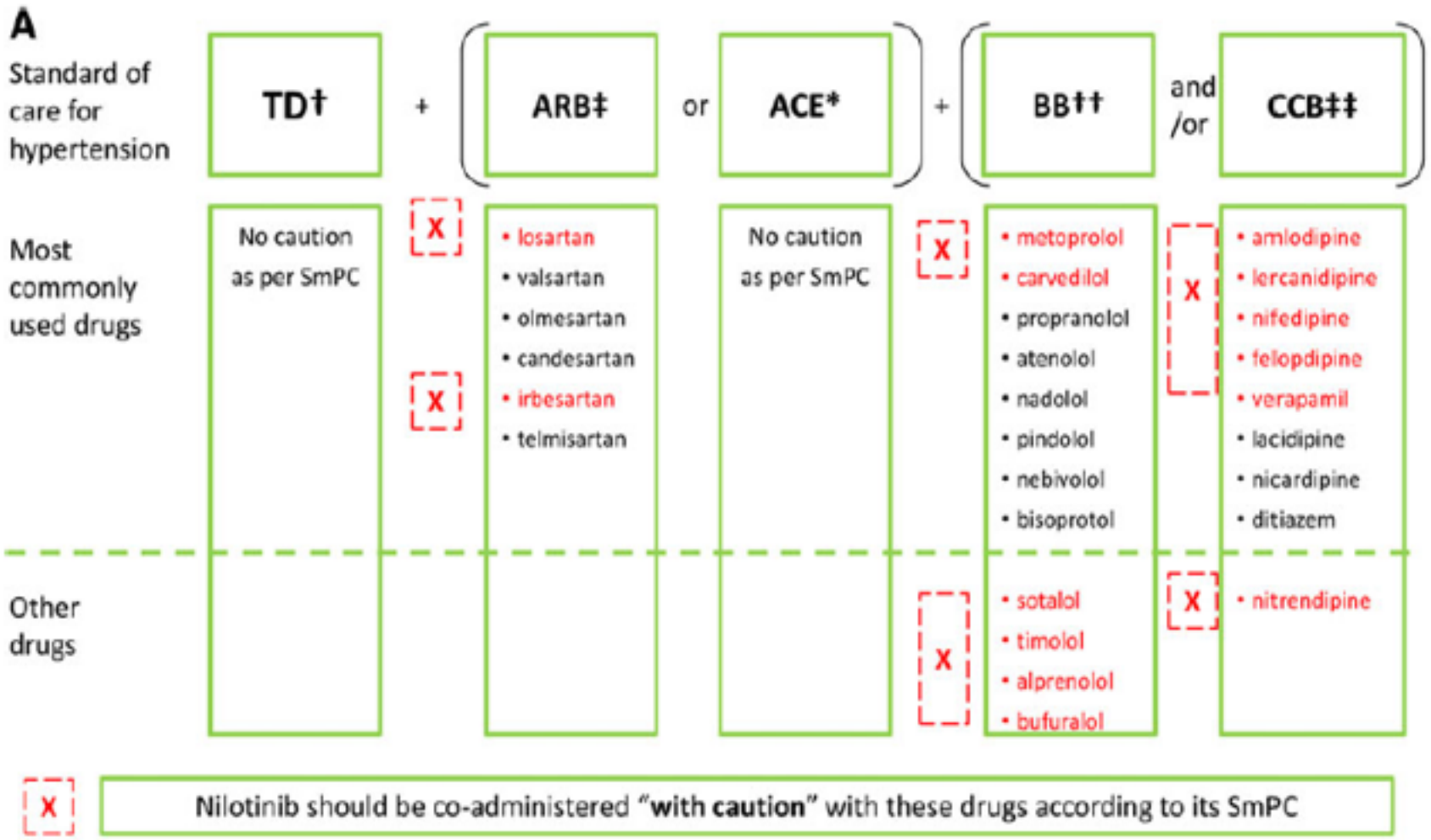
FARMACI ANTIIPERTENSIVI



LINEE GUIDA ESC-ESH

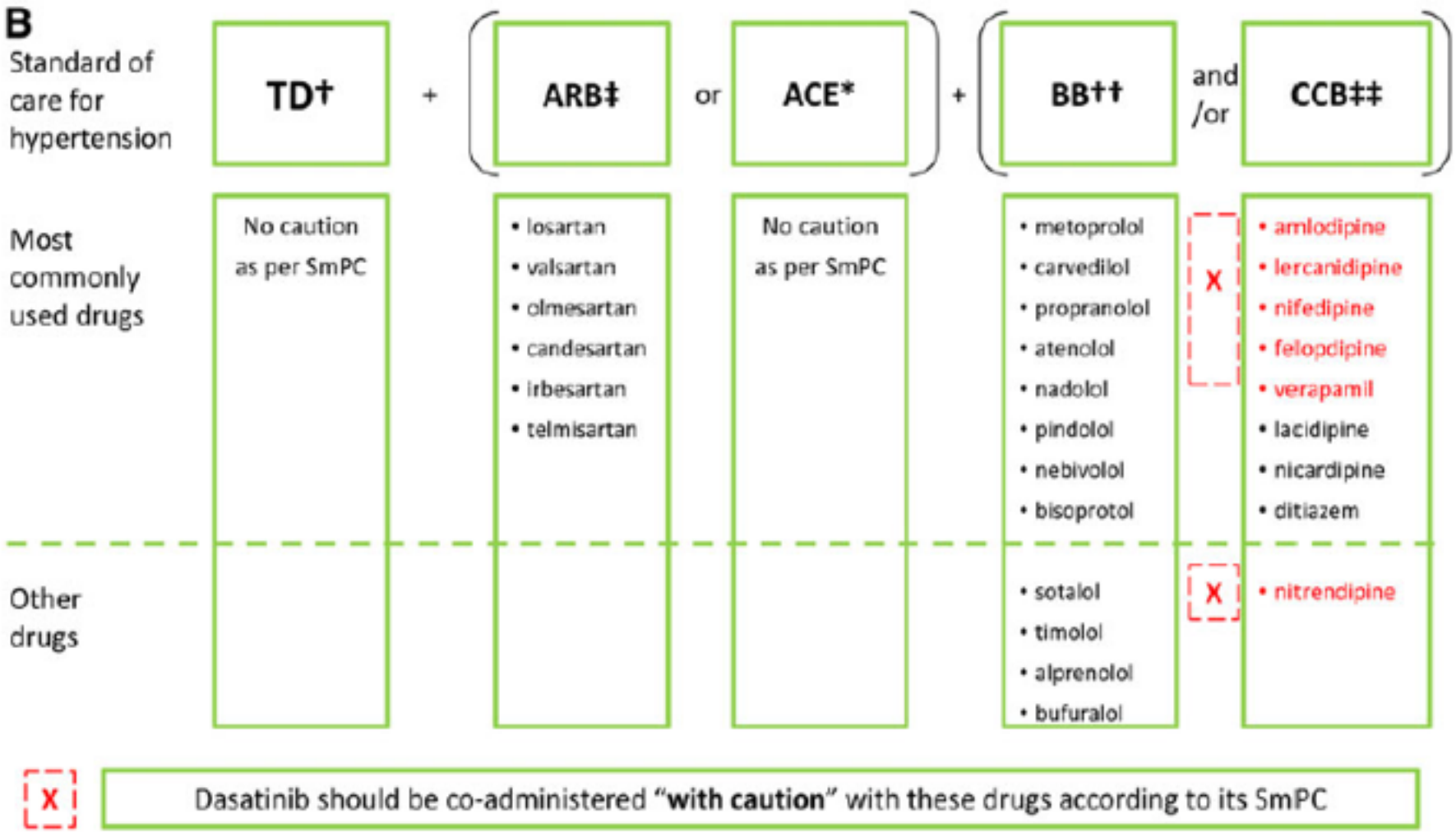
	NORMALE	NORMALE ALTA	Grado I	Grado II	Grado III
	120-129 80-84	130-139 85-89	140-159 90-99	160-179 100-109	> 180 > 110
NO FRC	Nessun trattam.	Nessun trattam.	Stile vita … + farmaci	Stile vita … + farmaci	Stile vita + farmaci
1-2 FRC	Stile vita	Stile vita	Stile vita … + farmaci	Stile vita … + farmaci	Stile vita + farmaci
3 o > FRC	Stile vita	Stile vita	Stile vita + farmaci	Stile vita + farmaci	Stile vita + farmaci
CCA	Stile vita + farmaci	Stile vita + farmaci	Stile vita + farmaci	Stile vita + farmaci	Stile vita + farmaci

Ipertensione e TKIs



E. Abruzzese, M. Breccia, R. Latagliata, BioDrugs 2013

Ipertensione e TKIs



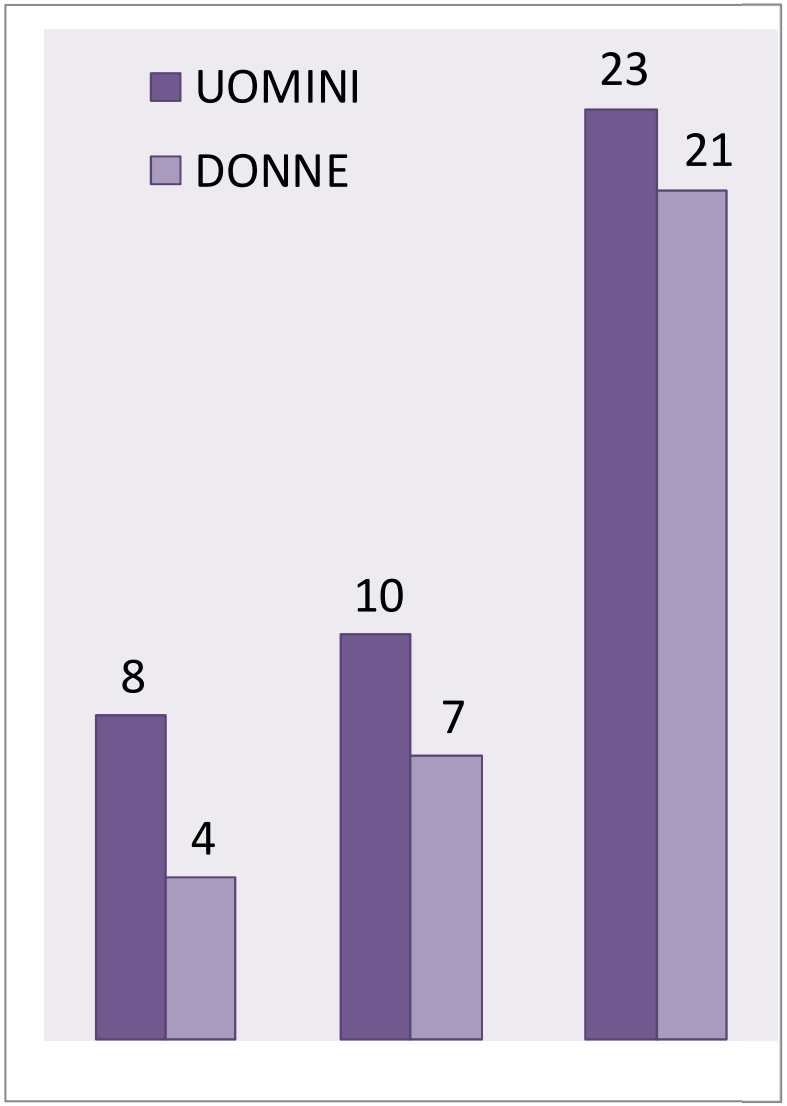
E. Abruzzese, M. Breccia, R. Latagliata, BioDrugs 2013

Recommendations on diabetes mellitus

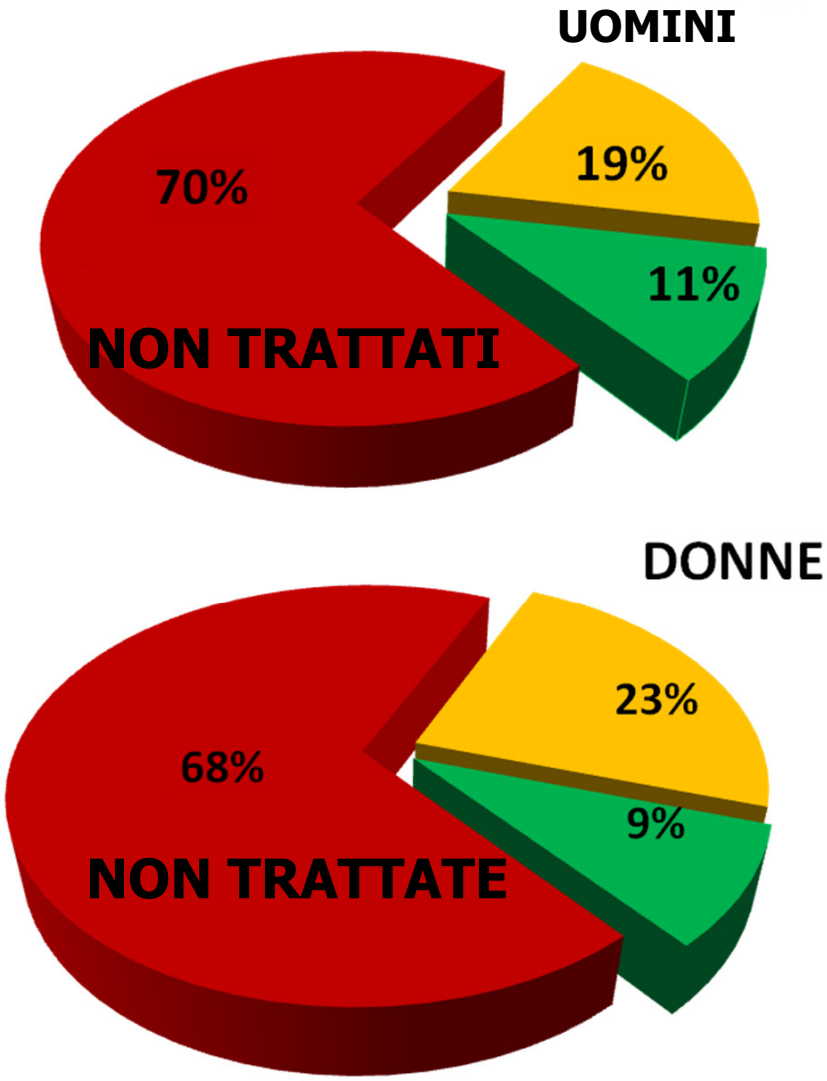
DIABETE

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
The target HbA_{1c} for the prevention of CVD in diabetes of <7.0% (<53 mmol/mol) is recommended.	I	A	Strong	434, 435
Statins are recommended to reduce cardiovascular risk in diabetes.	I	A	Strong	166, 436
Hypoglycaemia and excessive weight gain must be avoided and individual approaches (both targets and drug choices) may be necessary in patients with complex disease.	I	B	Strong	435, 437, 438
Metformin should be used as first-line therapy if tolerated and not contraindicated	IIa	B	Strong	439
Further reductions in HbA_{1c} to a target of <6.5% (<48 mmol/mol) (the lowest possible safely reached HbA_{1c}) may be useful at diagnosis. For patients with a long duration of diabetes this target may reduce risk of microvascular outcomes.	IIb	B	Weak	435
BP targets in diabetes are recommend to be <140/80 mmHg.	I	A	Strong	440, 441
Target LDL cholesterol is <2.5 mmol/L, for patients without atherosclerotic disease total cholesterol may be <4.5 mmol/L, with a lower LDL cholesterol target of <1.8 mmol/L (using higher doses of statins) for diabetic patients at very high CVD risk.	IIb	B	Weak	442
Antiplatelet therapy with aspirin is not recommended for people with diabetes who do not have clinical evidence of atherosclerotic disease.	III	A	Strong	443

Prevalence of diabetes in Italy



Health Examination Survey 1998-2002



TARGET

- **HbA1c < 7.0%** (< 6.5% se lunga durata)
- **PAO** < 140/90 mmHg (meglio **<130/80**)
- **CHOL**:
  - **LDL < 115 mg/dl** *(Chol Tot < 190 mg/dl)*
  - Alto rischio: **LDL < 100 mg/dl**
  - Rischio molto alto: **LDL < 70 mg/dl**
  - Basse HDL ed ipertrigl sono F.R. indipendenti

Problema: il target

- Mancato raggiungimento del target terapeutico in un'elevata quota di pazienti a rischio cardiovascolare elevato/moderato
- Scarsa consapevolezza della correlazione tra riduzione del rischio cardiovascolare e obiettivi terapeutici suggeriti dalle Linee Guida
- Mancato monitoraggio dell'efficacia del trattamento ipocolesterolemizzante
- Inadeguatezza dei farmaci ("dose tritation")


indeland

LA DIAGNOSI DI CARDIOTOSSICITA'

P.O. MOLINETTE

Evento residenziale

TERAPIE ONCOLOGICHE E

Diagnostica della cardiotossicità

ORARIO

Dalle 9.00 alle 17.00

SEDE DEL CORSO

Torino, Via Rosmini 4/A
terzo piano

Evento organizzato con il pat
A.R.C.A.

Corso accreditato s
Sistema ECM Regione Pie
COD. 20492 - Crediti calc

AREA TEMATICA

Oncologica

FINALITA'

Acquisire conoscenze e competenze

approfondimenti sulla tossicità cardiaca nel paziente oncologico

ARTICOLAZIONE

Il Corso si articola in formula mista

Mauro GIORGI
S.C. CARDIOLOGIA 2 - OSP. MOLINETTE
CITTA' della SALUTE e della SCIENZA di TORINO

PROGRAMMA

1° giorno

9.00-9.30 Le dimensioni del problema e il modello di rete (O. Bertetto)
9.30-11.00 Il rischio di tossicità riguardo a:
- terapie oncologiche (M. Mistrangelo)
- terapie ematologiche (P. Pregno)
- trattamenti radianti (M. Levis)

11.00-12.30 Meccanismi di cardiotossicità: Disfunzione ventricolare sinistra, Ischemia

15.30-16.00 Cardioprotezione e terapia cardiologica (P. Lusardi)
16.00-17.00 Management della cardiotossicità: il ruolo del cardiologo e dell'oncologo (A. Fava, M. Mistrangelo)

2° giorno

9.00-13.00 Suddivisione dei partecipanti in gruppi di lavoro con gestione casi clinici supportati da un leader (M. Giorgi, A. Fava, P. Lusardi, E. Coletti Moia, A. Bonzano, A. Milan, I.

esi delle proposte e con raccomandazioni finali

16.30-17.00 Valutazione

DIAGNOSI

La cardiotox può interessare tutte le strutture cardiache
(miocardio, pericardio, coronarie, tessuto di conduzione, valvole)

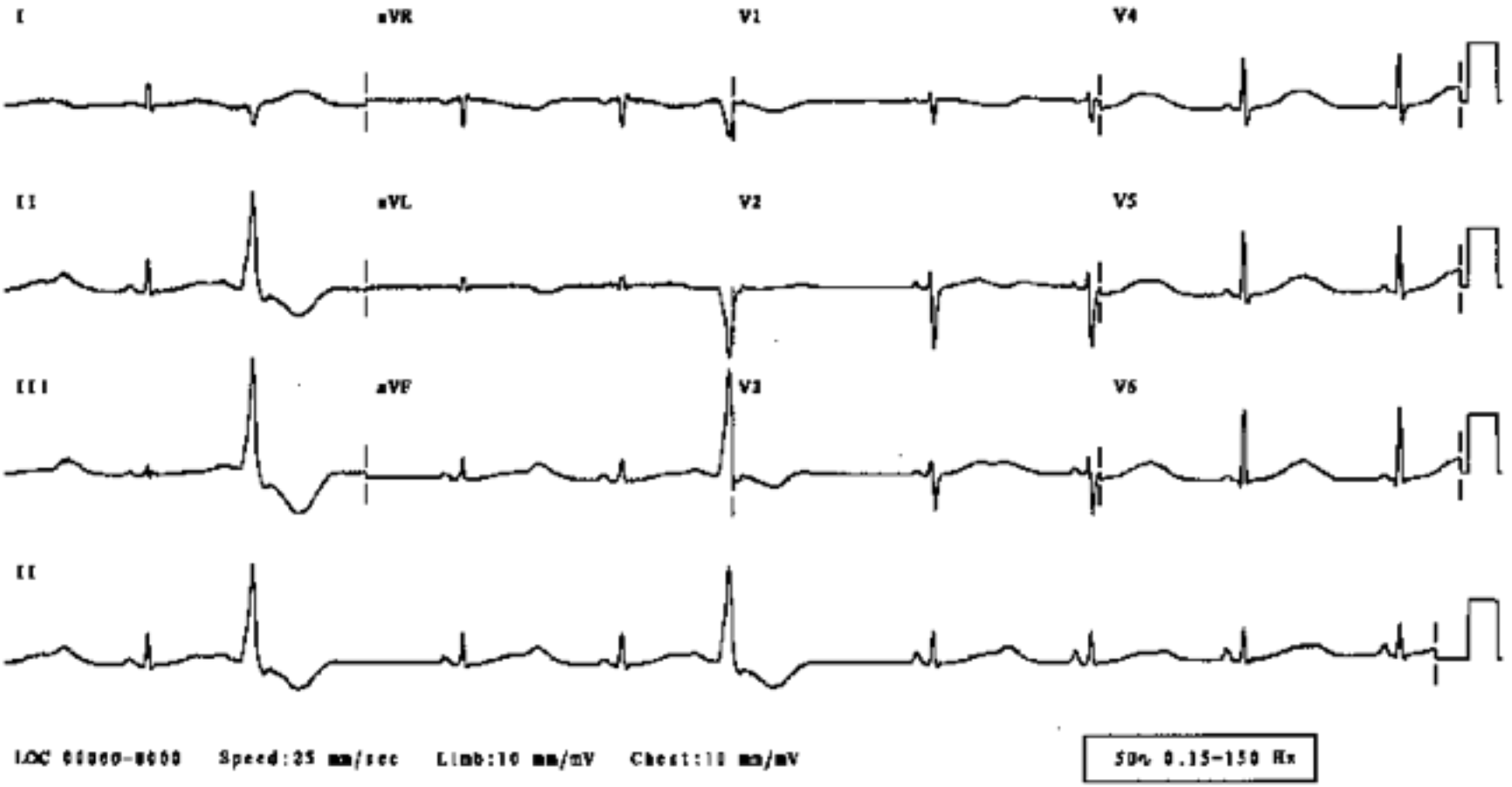
- ECG basale
- ECG HOLTER
- TEST ERGOMETRICO
- SCINTIGRAFIA MIOCARDICA BASALE e SFORZO
- CORONAROGRAFIA
- RMN / MRI
- ECOCARDIOGRAFIA
- MARKERS BIOCHIMICI (TnI – BNP)
- (BIOPSIA MIOCARDICA)

ECG – ECG HOLTER

- **TACHICARDIA SINUSALE**: importante segno di allarme, se persistente in Pt altrimenti stabile
- **ARITMIE IPERCINETICHE** : CPSV, CPV, TPSV, FA, TV, TdP
- **ARITMIE IPOCINETICHE**: bradic., BBdx-s, BAV I - III
- **ALLUNGAMENTO del QTc**
- **RIDUZIONE VOLTAGGI** : pericardite
- SEGNI di **IPERTROFIA – SOVRACCARICO**
- SEGNI di **ISCHEMIA – NECROSI**: sottoST, onde Q – Tneg

➢ VPN ≈ 95 % → se normale, esclusione di scompenso

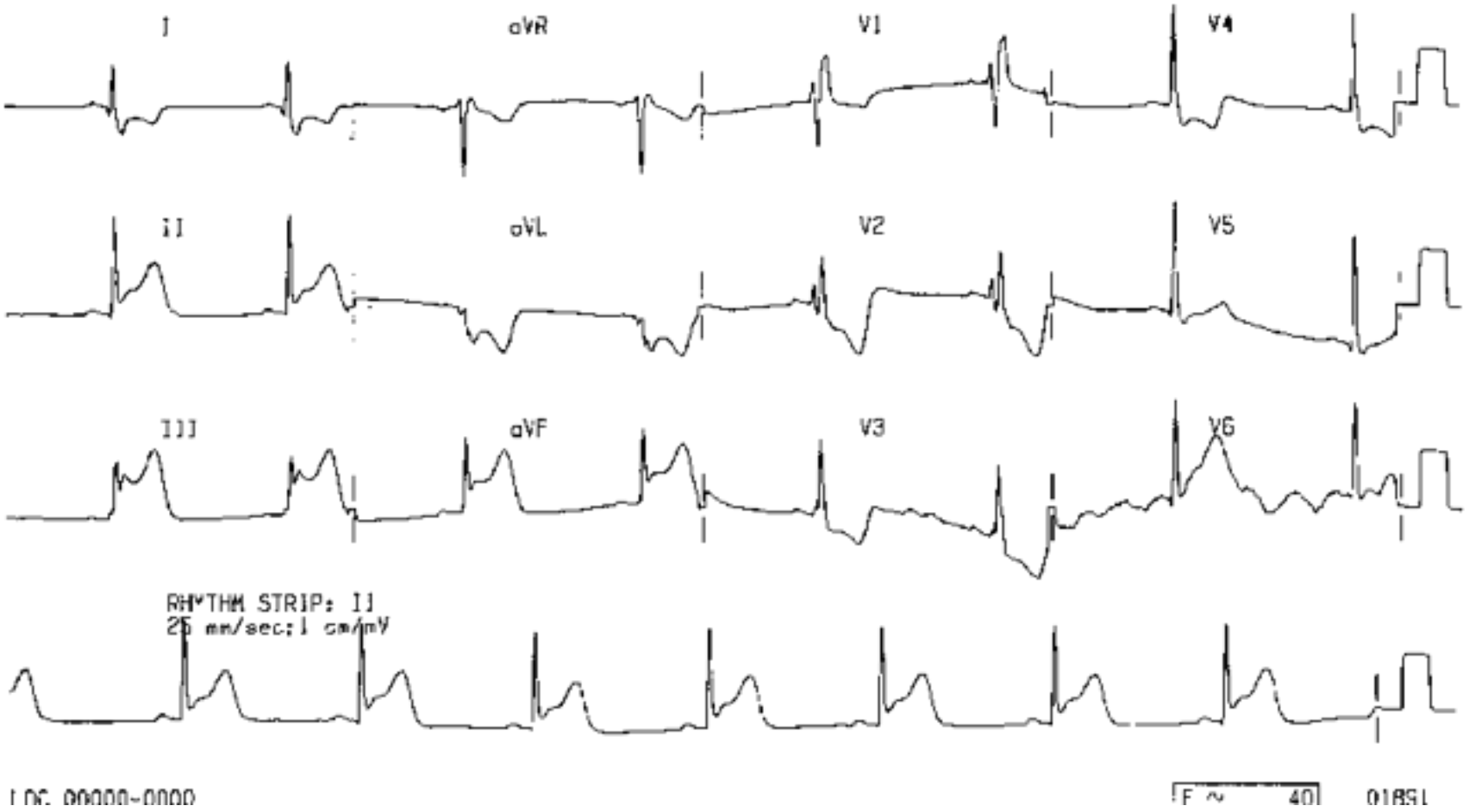
ALLUNGAMENTO QTc



$$QTc\ (Bazett) = QT / RR^{1/2}$$

v.n. < 0.44 sec

ONDA di LESIONE

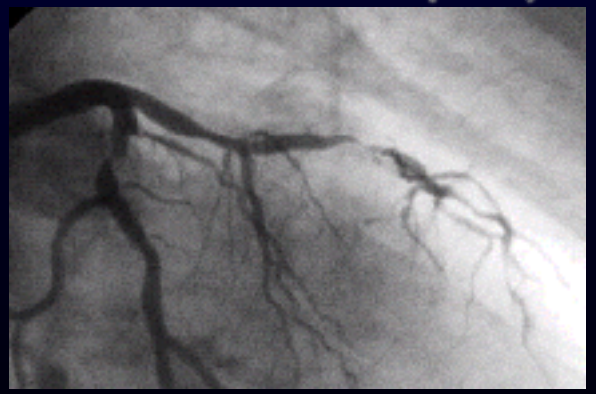


DIAGNOSI di SINDROME CORONARICA

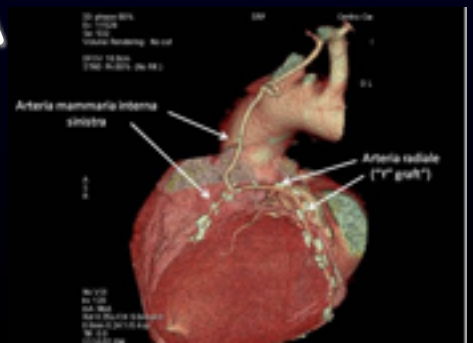
1. TEST ERGOMETRICO

2. ECOSTRESS (dpm – dobu – sforzo)
3. SCINTIGRAFIA MIOCARDICA (dpm-Tc / sforzo-Tl201)

4. CORONAROGRAFIA (anche coronarite da RX-terapia)
5. TEST ERGONOVINA (spasmo!)



6. TC CORONARICA

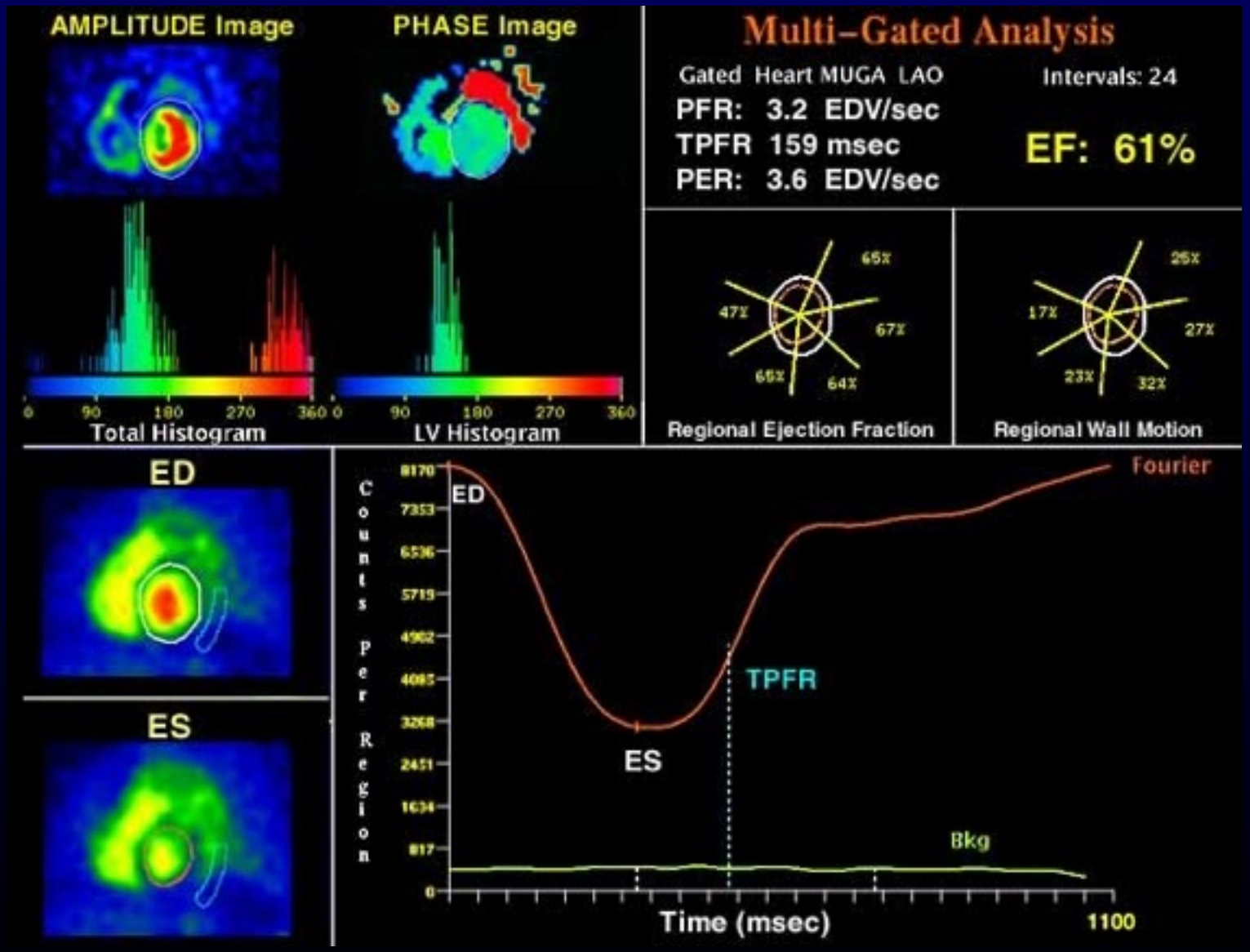


SCINTIGRAFIA MIOCARDICA

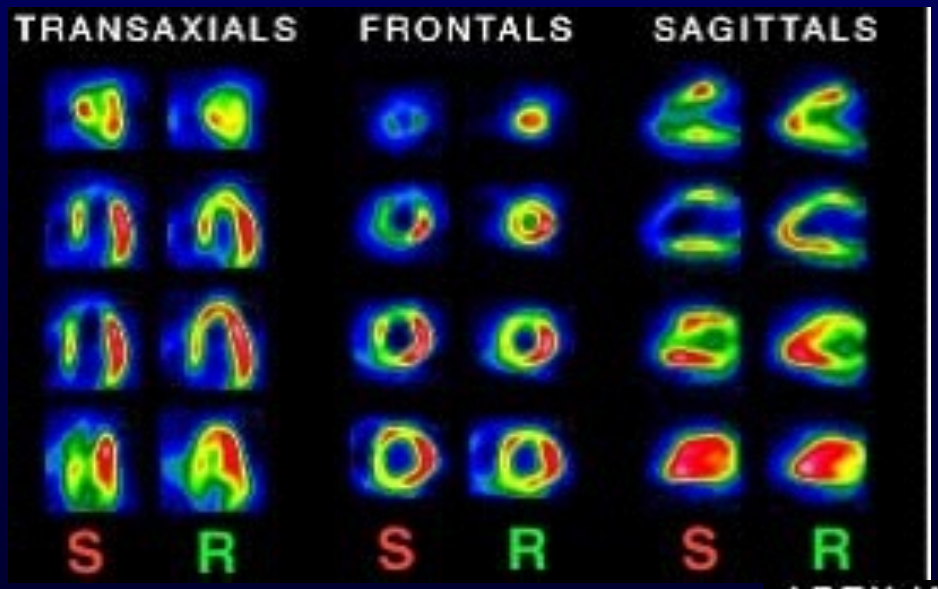
- **ANGIOCARDIOSc. RADIOSIOTOPICA**: volumetria – valutazione dell'EF (più "pessimistica" dell'ECHO)*
- **DA SFORZO (Tl 201) o STRESS DIPIRIDAMOLO (Tc)**: diagnosi di cardiopatia ischemica
- **AC ANTI-MIOSINA (Indio^{111})**: utile a scopo "speculativo", in Molinette abbandonata per difficoltà pratiche e tempi lunghi

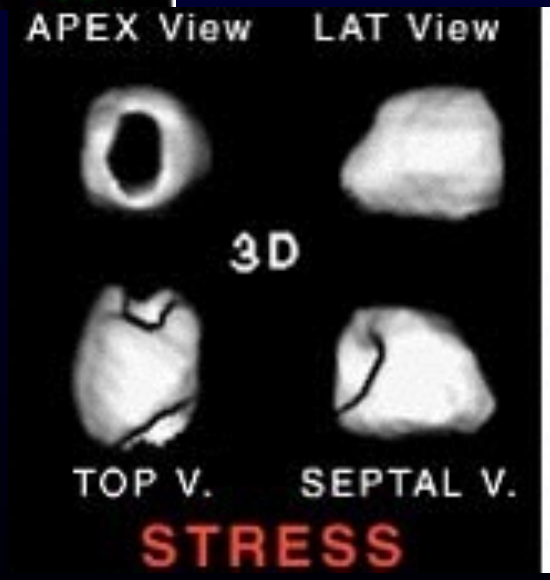
N.B.: meglio evitare la somministrazione di radioisotopi per la valutazione dell'EF

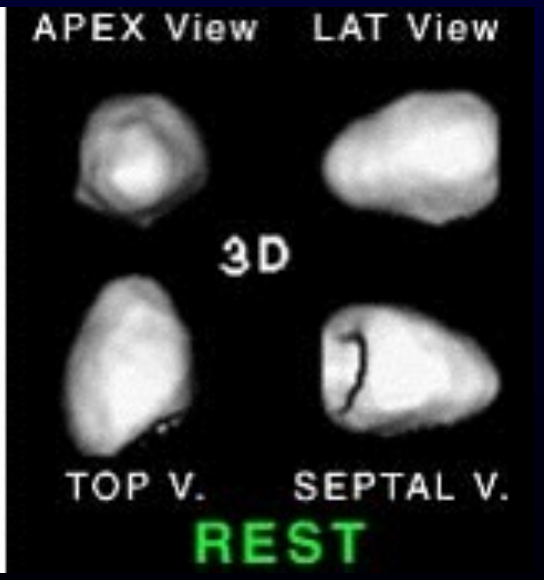
ANGIOCARDIOSCINTIGRAFIA

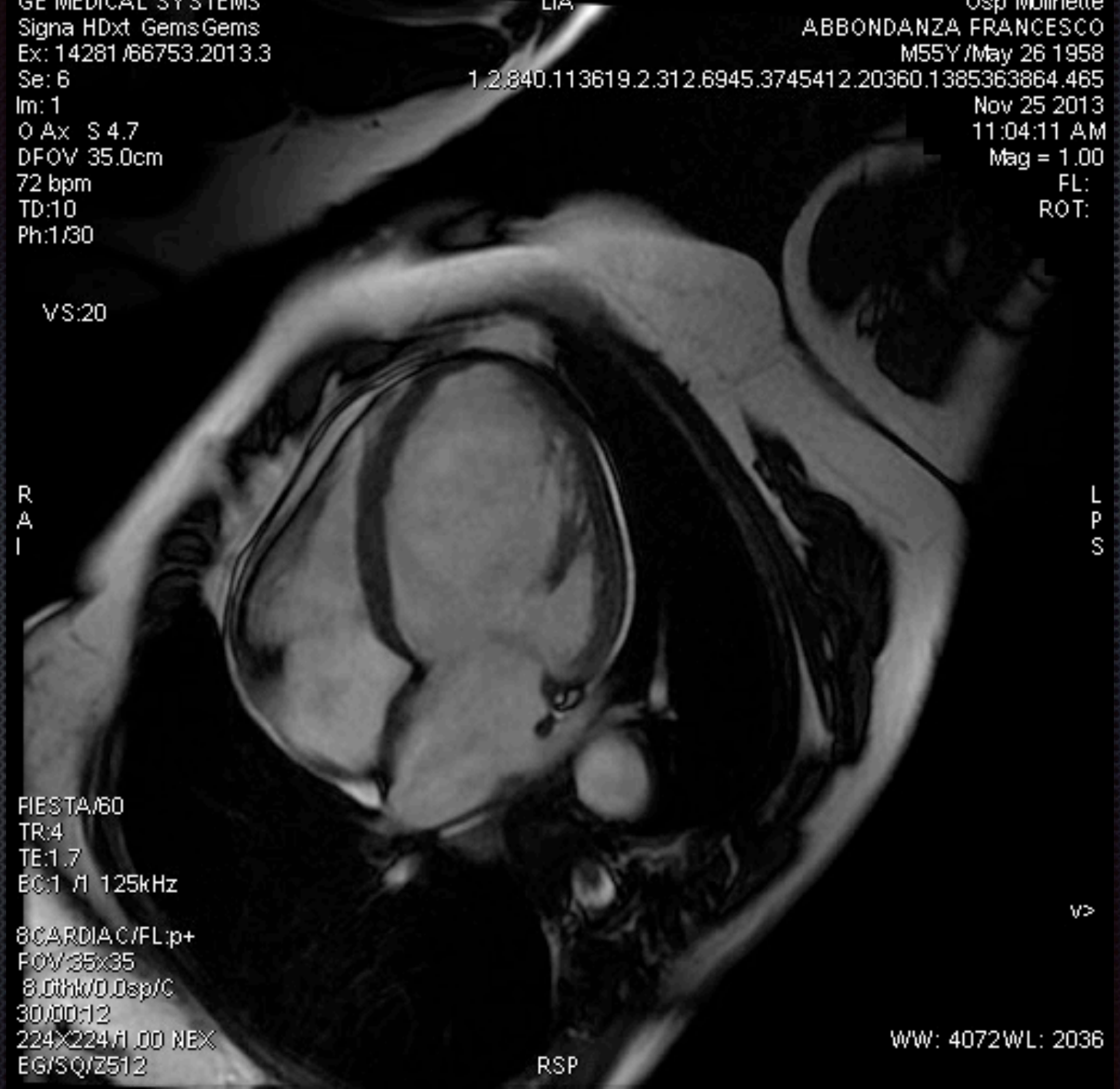


SCINTIGRAFIA STRESS








GE MEDICAL SYSTEMS
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Im: 1
O Ax S 4.7
DFOV 35.0cm
72 bpm
TD:10
Ph:1/30
VS:20
LIA
Osp Molinette
ABBONDANZA FRANCESCO
M55Y/May 26 1958
1.2.840.113619.2.312.6945.3745412.20360.1385363864.465
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11:04:11 AM
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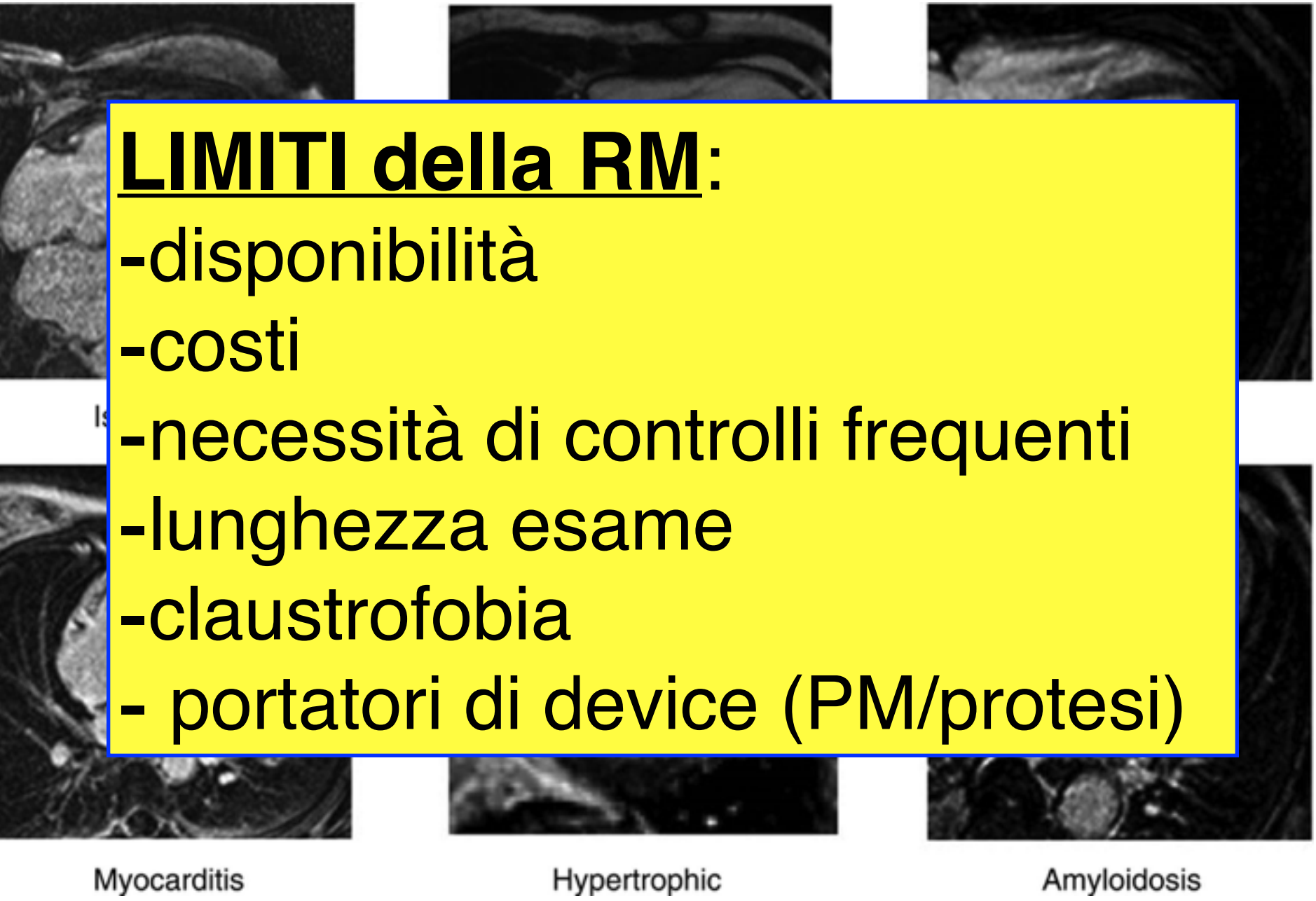


<u>LIMITI della RM</u>:

-disponibilità

-costi

-necessità di controlli frequenti

-lunghezza esame

-claustrofobia

- portatori di device (PM/protesi)

Myocarditis

Hypertrophic

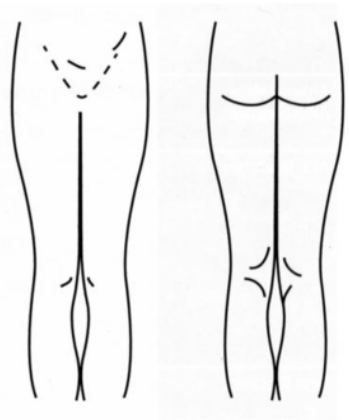
Amyloidosis

Edinburgh Claudication Questionnaire

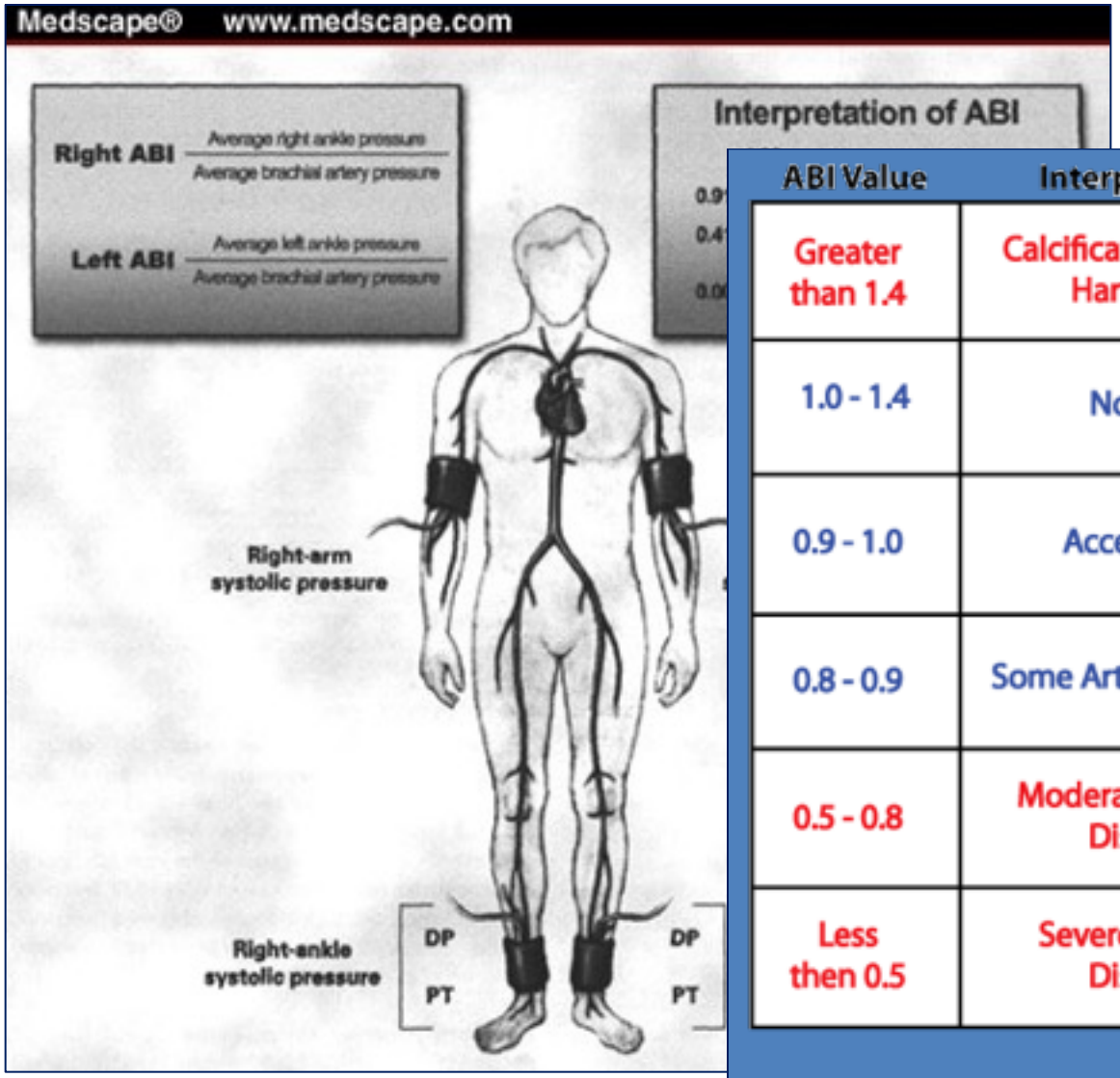
The Edinburgh Claudication Questionnaire:
CAD/PVD

* A positive questionnaire diagnosis of claudication is made only if the ***"correct"*** answer is given to ***all questions***

Questions	Correct Answer
1. Do you get pain or discomfort in your legs(s) when you walk? ○ Yes ○ No ○ Unable to walk • If you answered "yes" to question 1, please answer the following questions	Yes
2. Does the pain ever begin when you are standing or sitting still?	No
3. Do you get it when you walk uphill or in a hurry?	Yes
4. Do you get it when you walk at an ordinary pace on the level?	Yes
5. What happens if you stand still? • Usually continues for more than 10 minutes? • Usually disappears in 10 minutes or less?	 No Yes
6. Where do you get this pain or discomfort? • Mark the places with an "X" on the diagram	



Ankle-Brachial Index



ABI Value	Interpretation	Recommendation
Greater than 1.4	Calcification / Vessel Hardening	Refer to vascular specialist
1.0 - 1.4	Normal	None
0.9 - 1.0	Acceptable	
0.8 - 0.9	Some Arterial Disease	Treat risk factors
0.5 - 0.8	Moderate Arterial Disease	Refer to vascular specialist
Less then 0.5	Severe Arterial Disease	Refer to vascular specialist

MARKERS BIOCHIMICI

- I tradizionali markers enzimatici di danno cardiaco (**CK-MB, CK-MB massa, Mioglobina**) hanno dimostrato uno scarso VPP e non si sono dimostrati utili nel predire la CTX

- Nuovi markers biochimici:
  - **BNP**
  - **Troponina**

PEPTIDI NATRIURETICI

- NT-proBNP , α-ANP e BNP
- L'aumento di pressione t.d. stimola i recettori di stiramento atriali:
  - effetto natriuretico
  - effetto vasodilatatorio
- Il rilascio aumenta molto nello scompenso
- Alto valore prognostico (95%)
- Livelli normali-bassi in pts non trattati → scarsa probabilita' di CHF → no ulteriori indagini
- Livelli alti → prob. disfunz. diastolica
- Altre cause : ipertensione, valvulopatie, ischemia, embolia polmonare, IVS

NT – proBNP

- Frammento amino-terminale del BNP
- Screening in PTs asintomatici (→ ACE-i)
- Sintomatologia (dispnea) di natura incerta
- Stratificazione prognostica:
  - BNP < 350 → buona prognosi
  - BNP > 350 → alta riammissione in H a 6 mesi
  - BNP > 750 → 100% re-ospedalizzazione
- Titolazione della terapia, es. Bisoprololo:
  - Responders = BNP ↓ , EF ↑
  - Non responders = BNP ↑, EF ↓

➢ Problema: ampia zona grigia (350-750)

BNP come indicatore di CTX

- Disomogenità degli studi, bassa numerosità delle casistiche, dati incompleti, metodi di misura disponibili in commercio solo in 8 studi (solo 3 auto)
- Mancanza di univocità delle conclusioni
- Possibile effetto inibitorio della doxo su espressione genica del BNP (effetto paradosso di ↓)
- A = ↑ persistente (33%), B = ↑ transitorio (36%), C = nessun ↑ (31%): solo A peggiora EF a 1 aa f.u.

➢ Al momento NON raccomandato l'uso routinario

➢ Necessità di ulteriori studi

TROPONINA (I – T)

- Omogeneità del livello decisionale (Coeff.Var. 10%)
- Positività nel **30-34%** dei PTs sottoposti a C.T.
- **TnI**: specificità = 100%, V.P.P. = 100%, V.P.N. = 99%
- TnT, CK-MBm: sensibilità = 90%, V.P.N. = 97.6%
- Velocità di positivizzazione: CK-MB, Myo, TnT (IMA)
- Tn+ predice disfunzione cardiaca **< 3 mesi**
- Il valore di Tn predice **grado** e **severità** di disfunzione
- Persistenza di **Tn+ > 1 mese → 85% MACE in 1 aa**
- Tn- identifica i PTs a più basso rischio di CTX

TROPONINA (I – T)

- CUT OFF:
  - TnI > 0.08
  - TnT > 0.03
- **PROTOCOLLO**: pre, post, 24 – 48 – 72 h, 1 mese

➢ Determinazione di CTX in **tempi molto precoci**

➢ Alla fine di C.T. permette di identificare i PTs ad **alto rischio** di CTX → stretto controllo funzione cardiaca

➢ **Rapporto costo-beneficio**: esclusione dei PTs a basso rischio dal monitoraggio cardiaco a lungo termine

➢ Possibile **cardioprotezione** in sogg asintomatici (CTX subclinica)

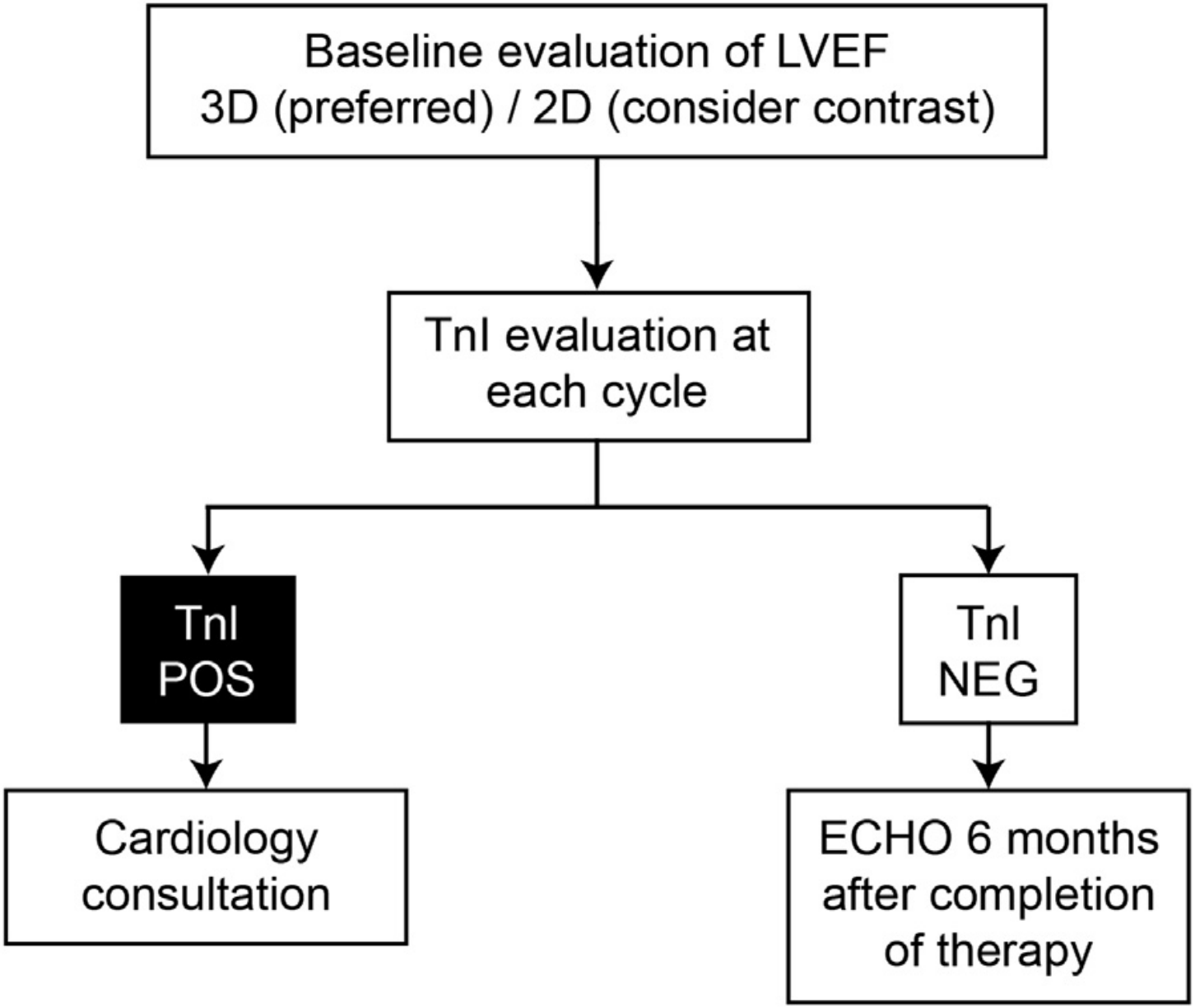
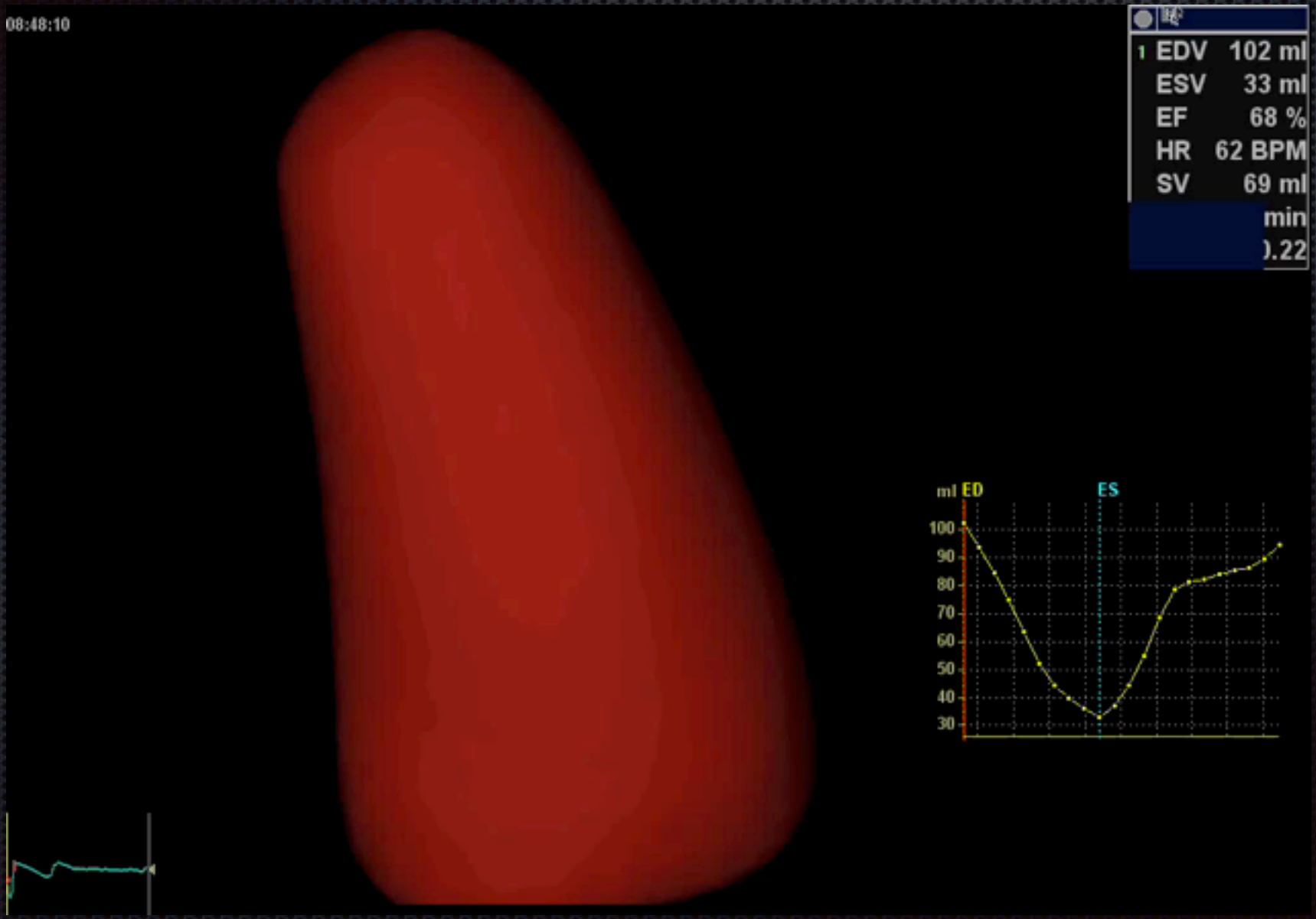


Figure 17 Early detection of subclinical LV dysfunction using biomarkers.

ECOCARDIOGRAFIA



clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii155–vii166, 2012
doi:10.1093/annonc/mds293

Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines†

G. Curigliano[1], D. Cardinale[2], T. Suter[3], G. Plataniotis[4], E. de Azambuja[5], M. T. Sandri[6], C. Criscitiello[1], A. Goldhirsch[1], C. Cipolla[2] & F. Roila[7], on behalf of the ESMO Guidelines Working Group*

La cardiotossicità è caratterizzata da almeno uno tra:

-sintomi di scompenso cardiaco

-segni clinici di scompenso cardiaco (es. T3 o tachicardia)

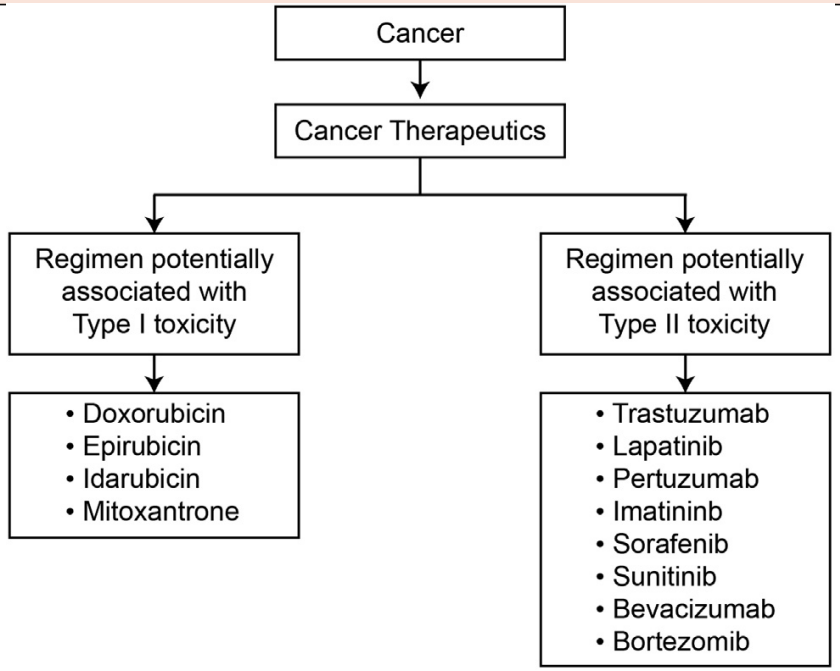
-Riduzione di EF di almeno 5% sotto i 55% con sintomi o segni di scompenso

-Riduzione del 10% sotto i 55% senza segni o sintomi associati

CARDIOTOSSICITA'

Table 1 Characteristics of type I and II CTRCD

	Type I	Type II
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course and typical response to antiremodeling therapy (β-blockers, ACE inhibitors)	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2–4 months after interruption (reversible)
Dose effects	Cumulative, dose related	Not dose related
Effect of rechallenge	High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death	Increasing evidence for the relative safety of rechallenge (additional data needed)
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities (though not thoroughly studied)



TIPO I

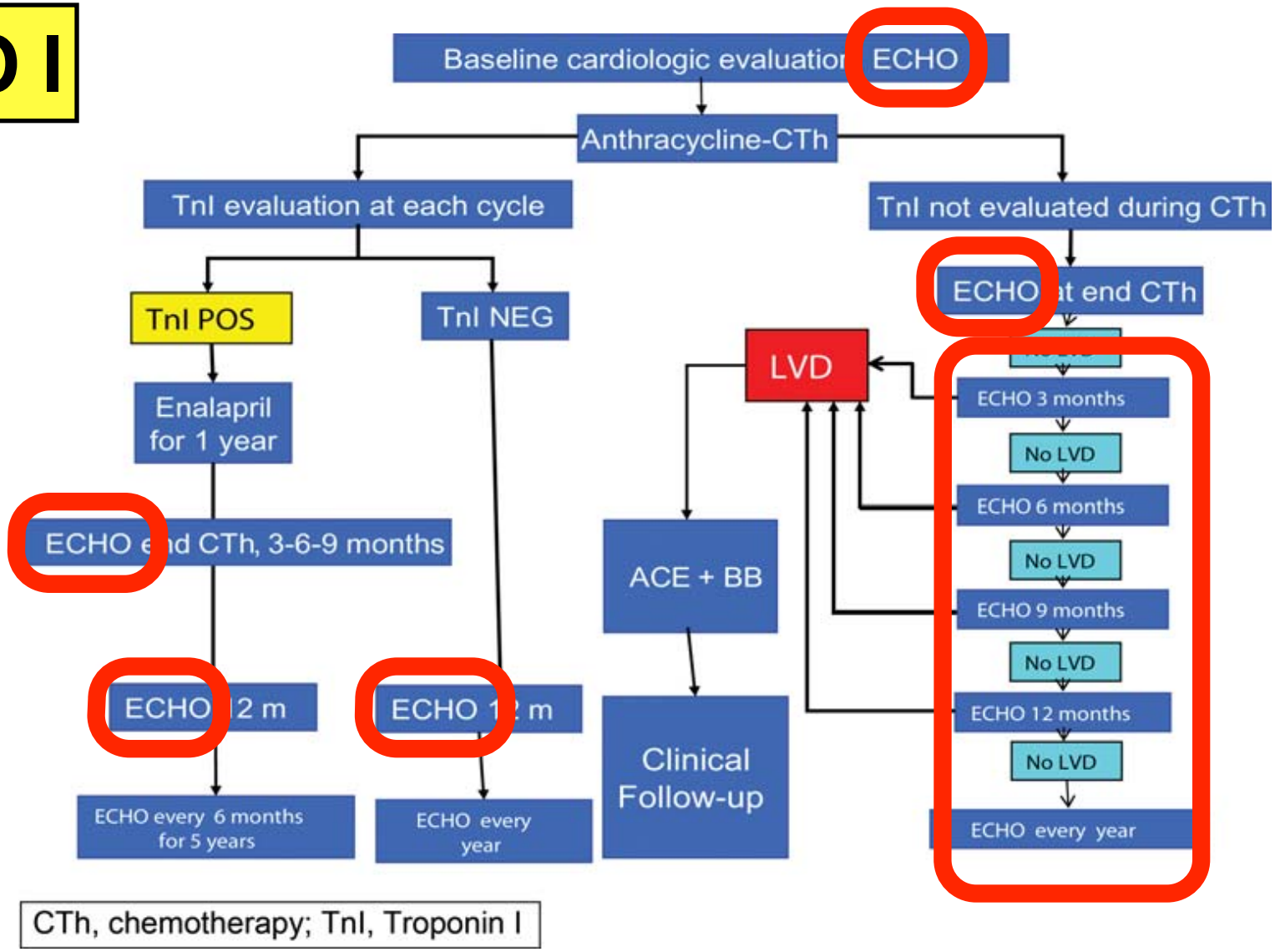


Figure 1. Algorithm for the management of cardiotoxicity in patients receiving anthracyclines.

TIPO II

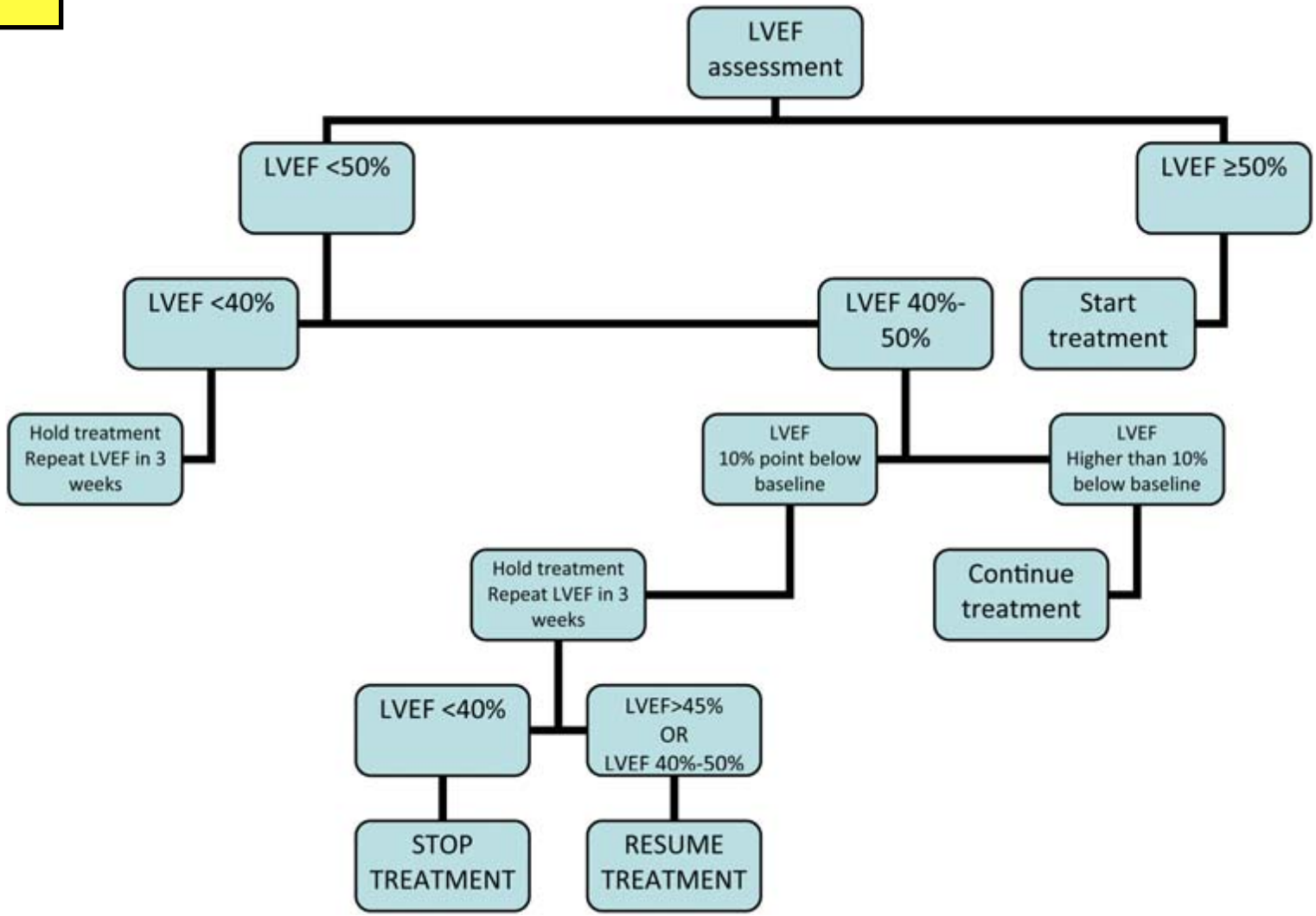
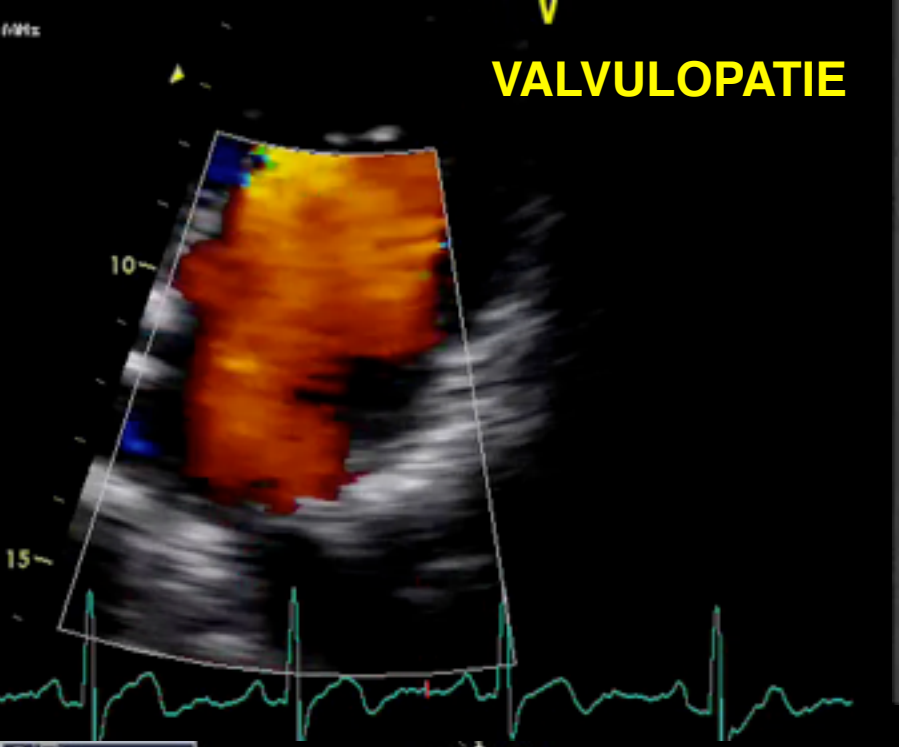
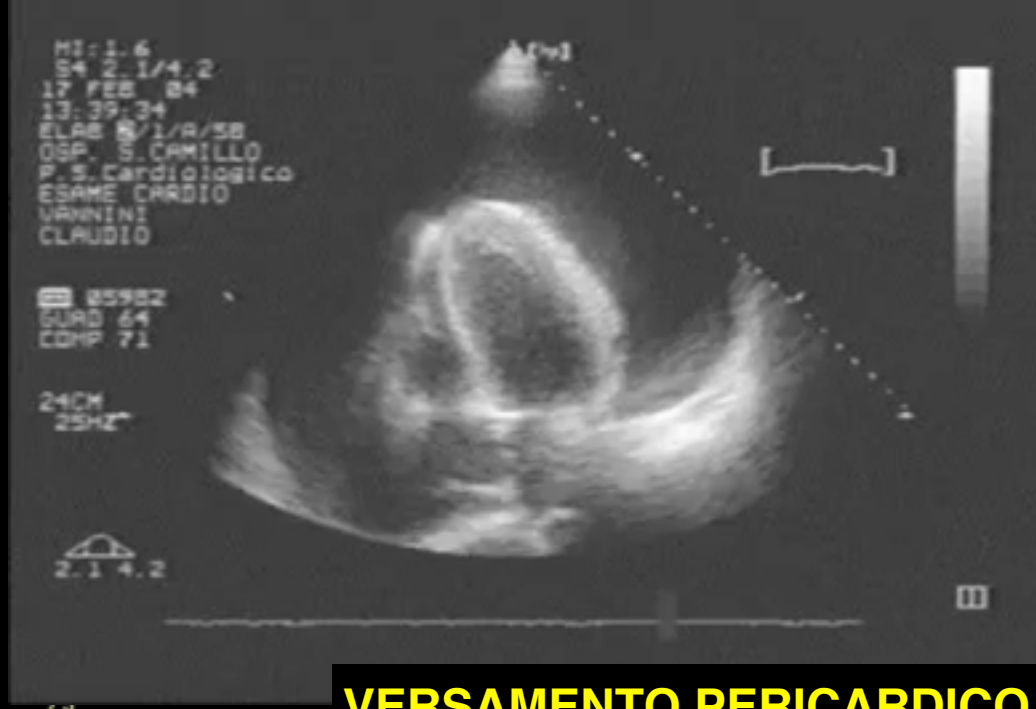


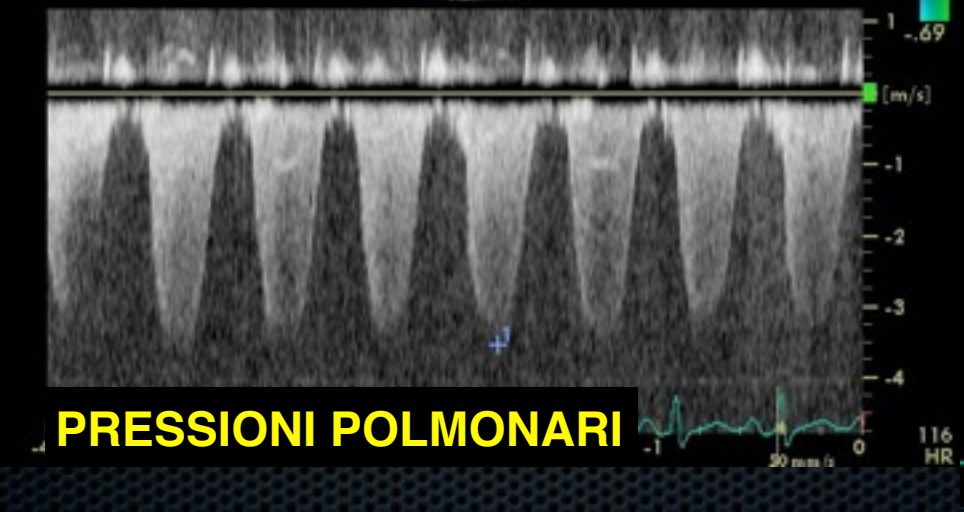
Figure 2. Algorithm for continuation and discontinuation of trastuzumab based on LVEF assessments.

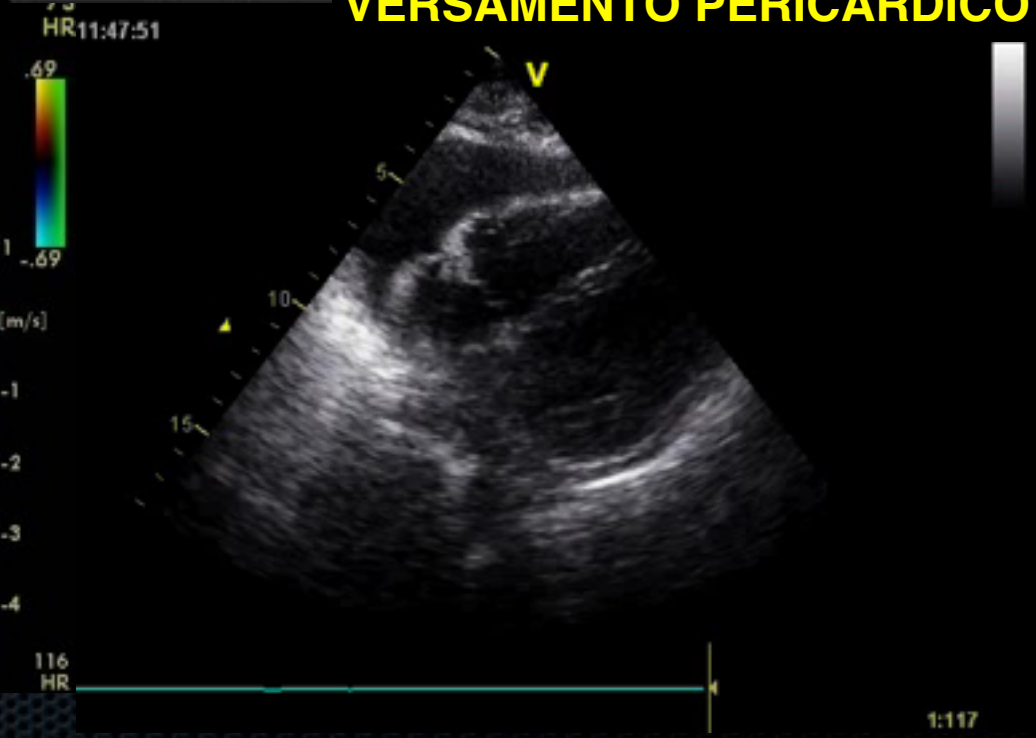
ECOCARDIOGRAFIA

- Volumetrie, geometria, spessore, massa
- Funzione sistolica (EF) e cinesi segmentaria
- Funzione diastolica
- Versamento pericardico
- Doppler: valvulopatia associata (IM)
- Stima accurata delle pressioni polmonari
- Parametri emodinamici quantitativi: portata, stroke volume, gradienti
- Nuove tecnologie: TDI, strain, 3D, perfusione

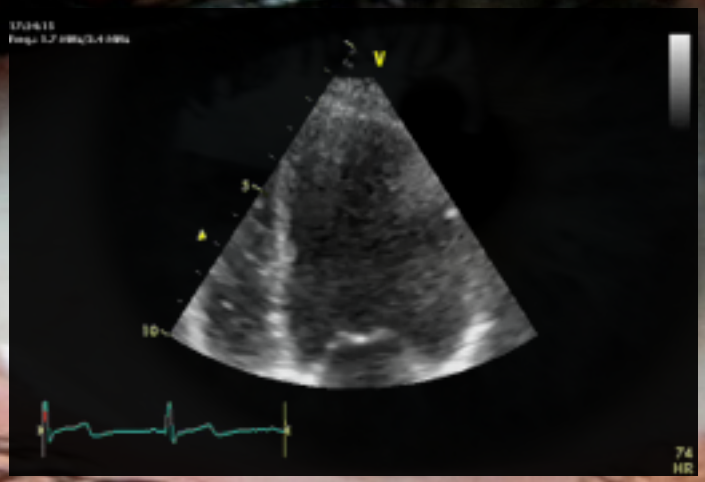

VALVULOPATIE
10
15
1 v 3.56 m/s
p 50.61 mmHg
Frq 9.12 kHz


MI:1.6
TIS 2.1/4.2
17 FEB 04
13:39:34
ELAB 1/A/SB
OSP. S.CAMILLO
P.S.Cardiologico
ESAME CARDIO
VANNINI
CLAUDIO
85952
GUAD 64
COMP 71
24CM
25HZ
2.1 4.2


PRESSIONI POLMONARI
[m/s]
1
-1
-2
-3
-4
0
30 mm/s


VERSAMENTO PERICARDICO
HR11:47:51
.69
-.69
116
HR
1:117

LIMITI dell'ECOCARDIOGRAFIA



Valutazione ecocardiografica dei volumi, dell'EF e della cinesi segmentaria: un campo minato!

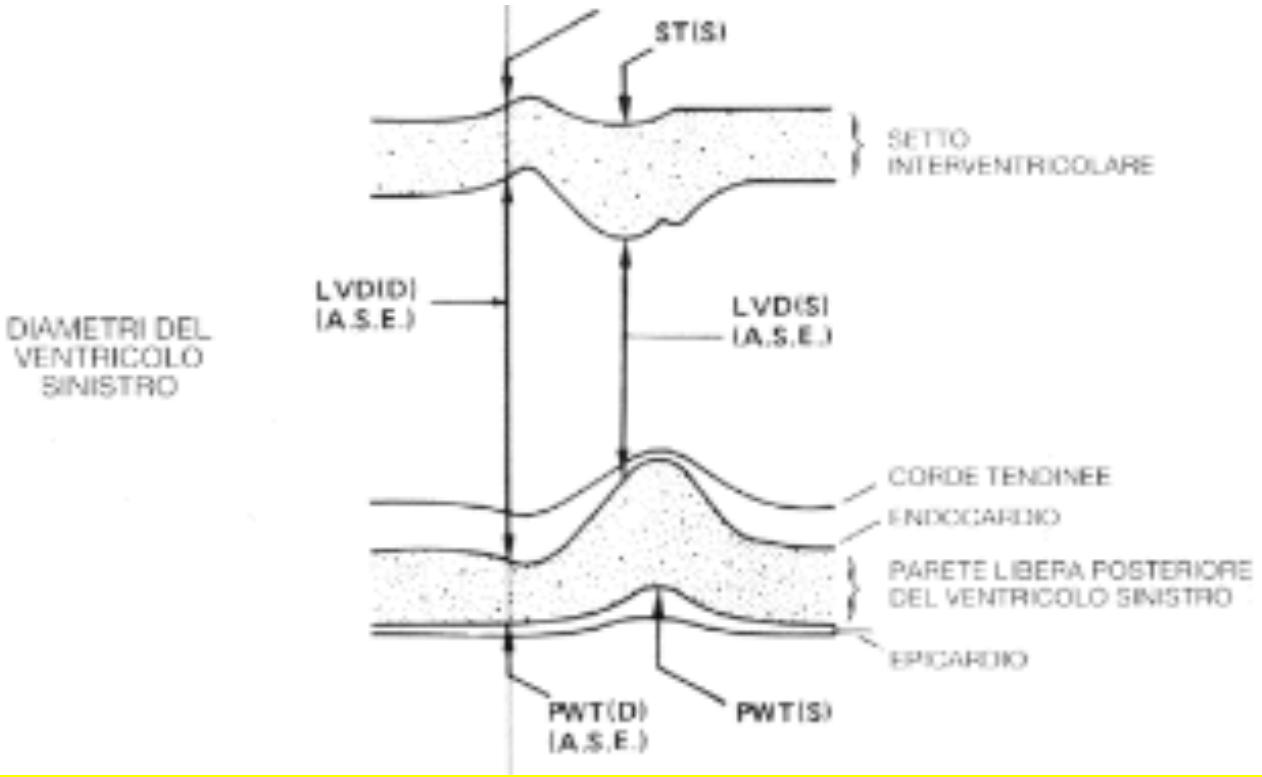
- Negli adulti il quesito **più comune** delle richieste di esami echo riguarda la valutazione delle dimensioni e della funzione ventricolare
- M-mode e 2D: **assunzioni geometriche** rilevanti
- Ampia **variabilità** inter- ed intra-osservatore
- Ancora diffusa valutazione "**oculometrica**" della funzione globale e regionale
- Pur esistendo metodi più precisi ("Simpson rule biplano"), non sono applicati ("**time consuming**")

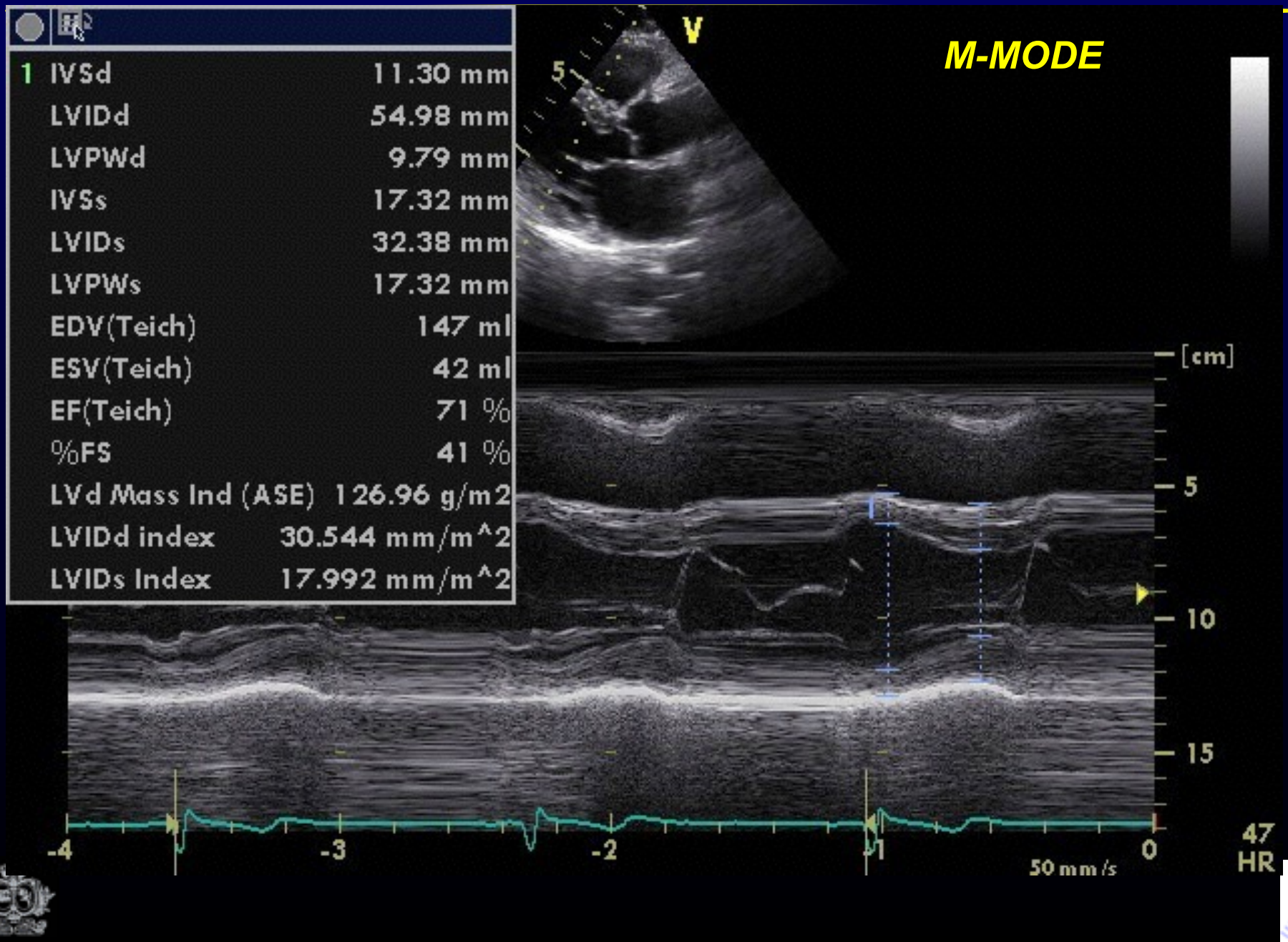
EF e PITFALLS

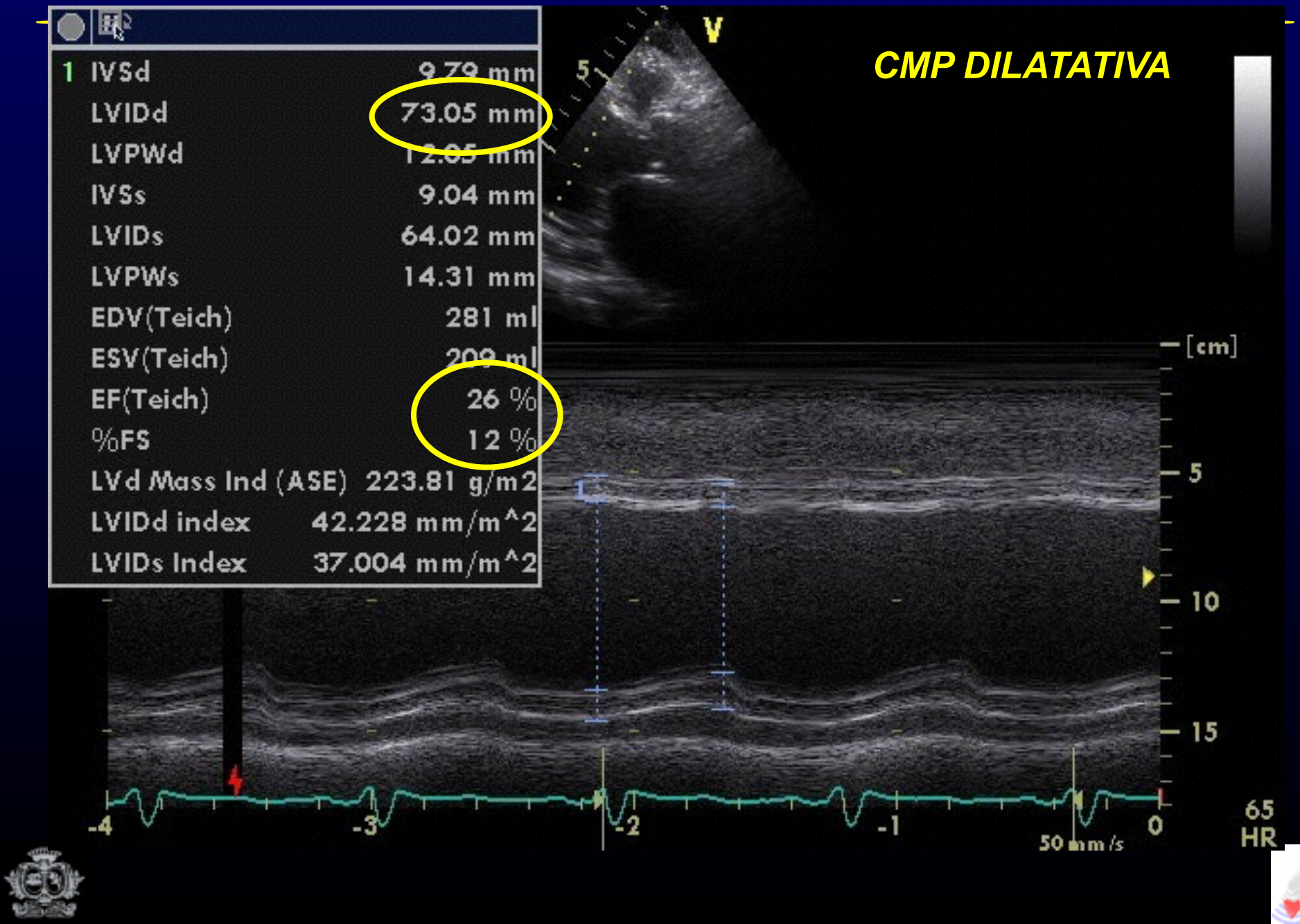
- Ogni Pt è caratterizzato da condizioni funzionali ed emodinamiche diverse
- L'EF non riflette accuratamente lo stato contrattile del miocardio, essendo influenzata dalle **condizioni di carico** (⟶ annotare FC e PAO durante gli esami)
- **L'EF non sempre riflette la portata cardiaca**, che può:
  - essere conservata in Pts con bassa EF, ma VS di volumetria aumentata
  - essere ridotta in Pts con EF normale, ma piccola volumetria ventricolare / ipertrofia o insufficienza mitralica severa o compromissione della funzione diastolica

MISURE VS M-MODE TEICHOLZ

margine interno - margine interno
interfaccia sangue - muscolo
inizio QRS



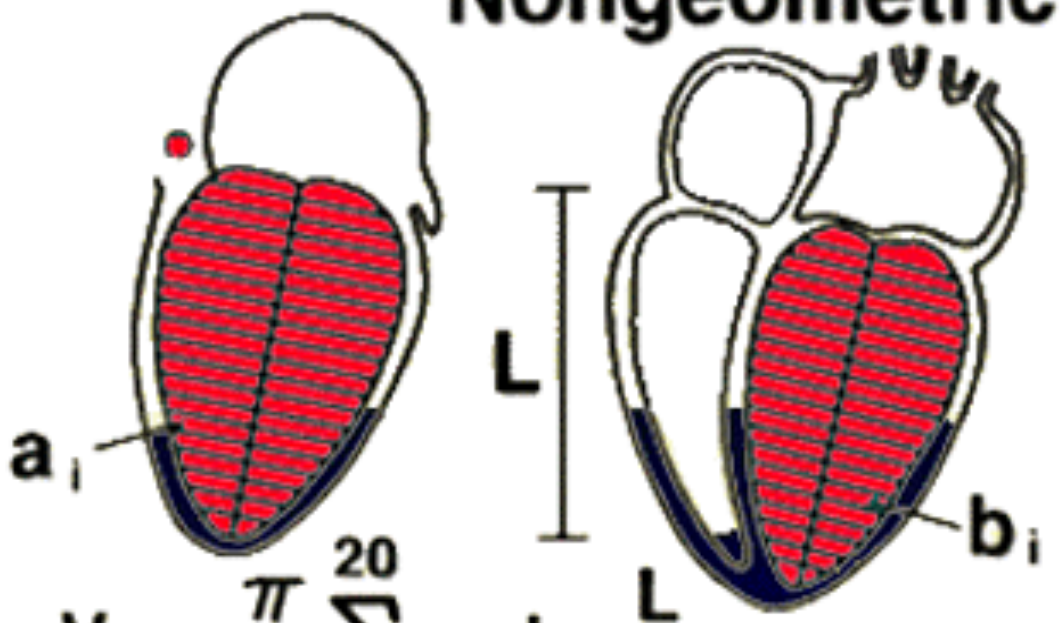

M-MODE
1 IVSd 11.30 mm
LVIDd 54.98 mm
LVPWd 9.79 mm
IVSs 17.32 mm
LVIDs 32.38 mm
LVPWs 17.32 mm
EDV(Teich) 147 ml
ESV(Teich) 42 ml
EF(Teich) 71 %
%FS 41 %
LVd Mass Ind (ASE) 126.96 g/m2
LVIDd index 30.544 mm/m^2
LVIDs Index 17.992 mm/m^2
[cm]
5
10
15
-4
-3
-2
-1
0
50 mm/s
47
HR


CMP DILATATIVA
1 IVSd 9.79 mm
LVIDd 73.05 mm
LVPWd 12.05 mm
IVSs 9.04 mm
LVIDs 64.02 mm
LVPWs 14.31 mm
EDV(Teich) 281 ml
ESV(Teich) 209 ml
EF(Teich) 26 %
%FS 12 %
LVd Mass Ind (ASE) 223.81 g/m2
LVIDd index 42.228 mm/m^2
LVIDs Index 37.004 mm/m^2
[cm]
5
10
15
-4
-3
-2
-1
0
50 mm/s
65
HR

m-MODE: TEICHOLZ

Left Ventricular Volumes

Nongeometric Models



$$V = \frac{\pi}{4} \sum_{i=1}^{20} a_i b_i \frac{L}{20}$$

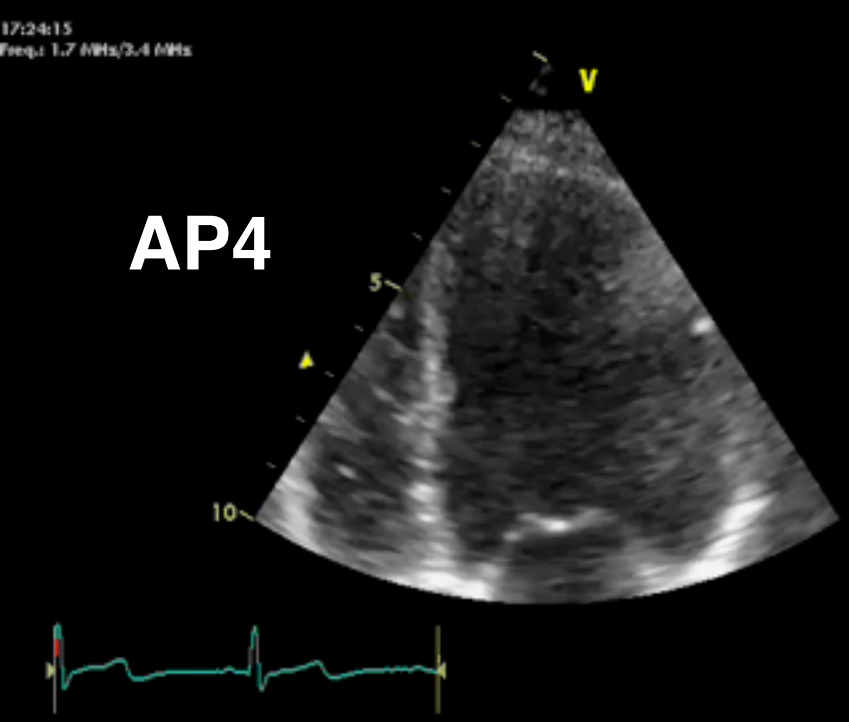
Method of discs (modified Simpson's rule)

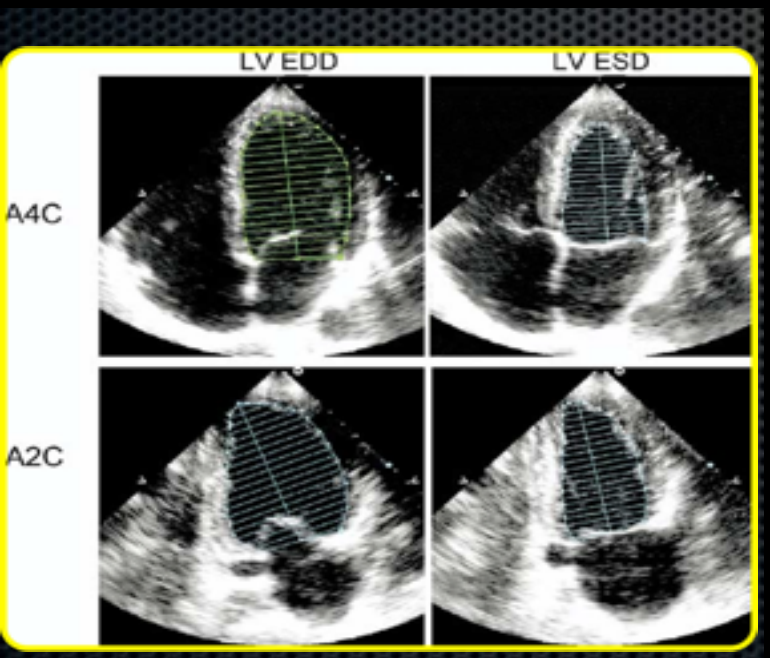
$$V = 0.85 \frac{(A)^2}{L}$$

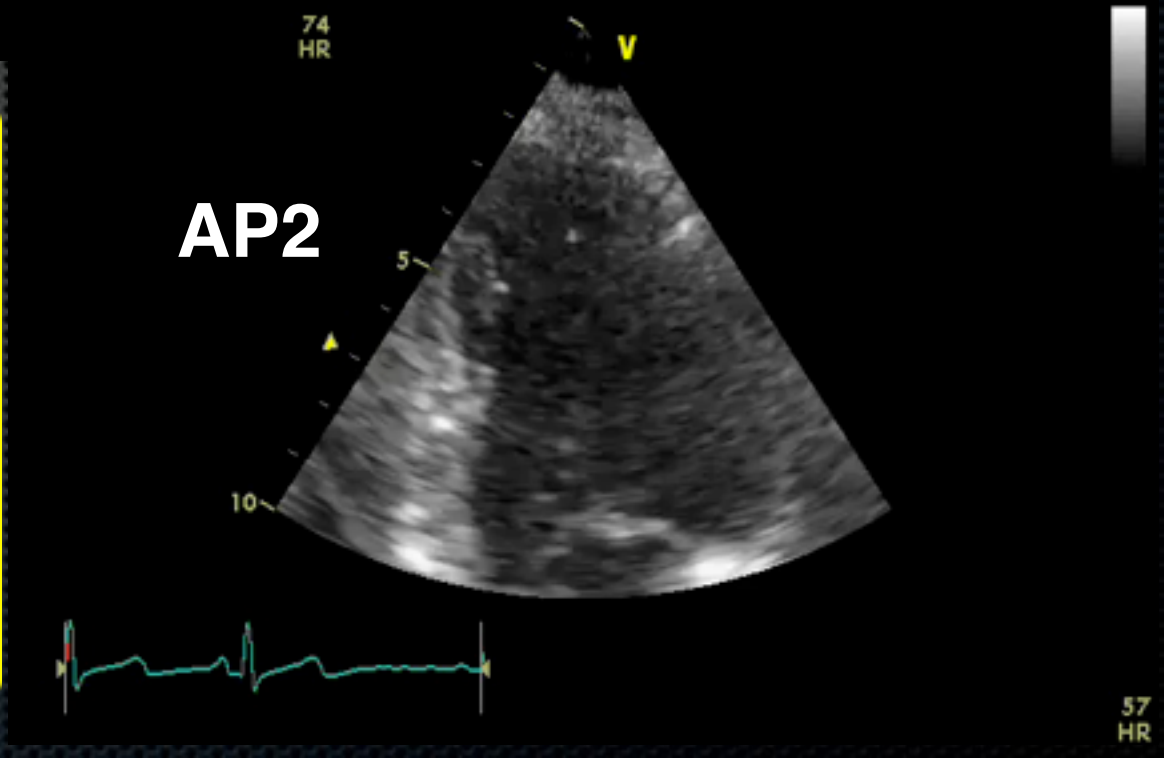
Single plane area length

JASE 2:358

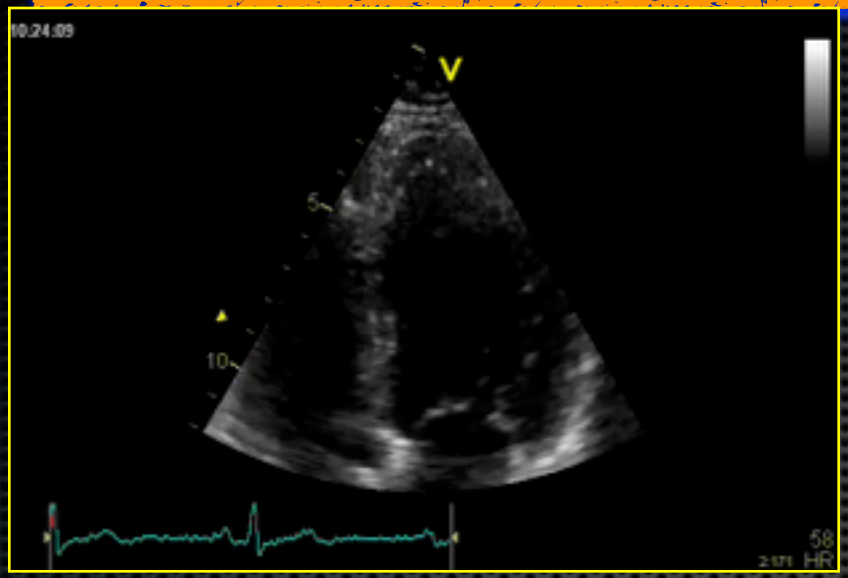
2D BIPLANO: SIMPSON RULE - ∑ DISCHI

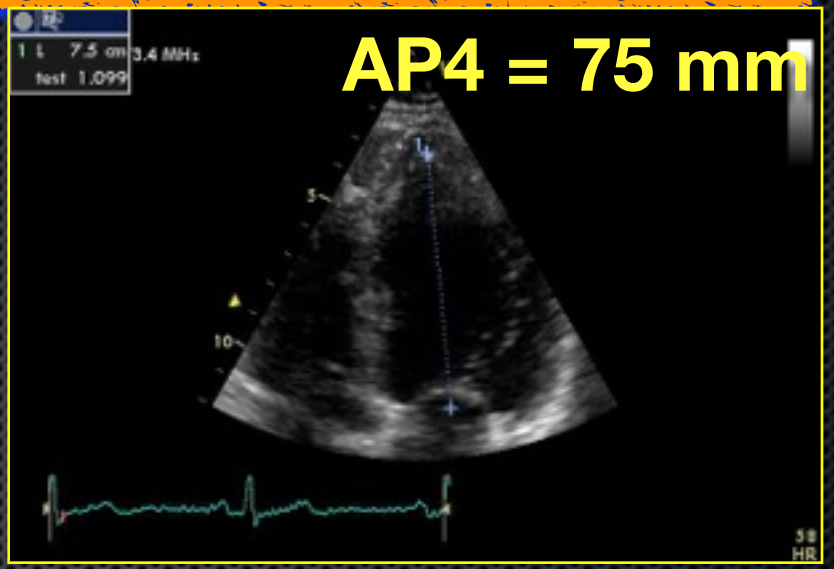


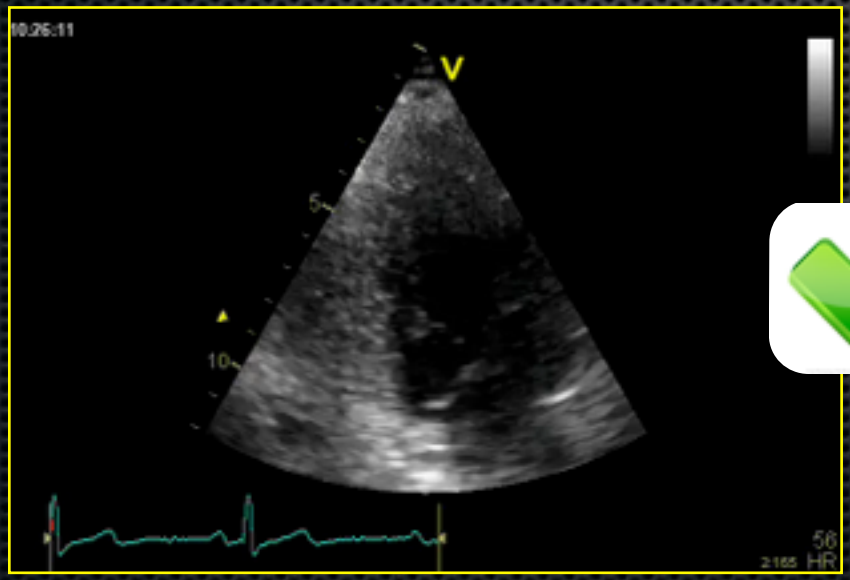


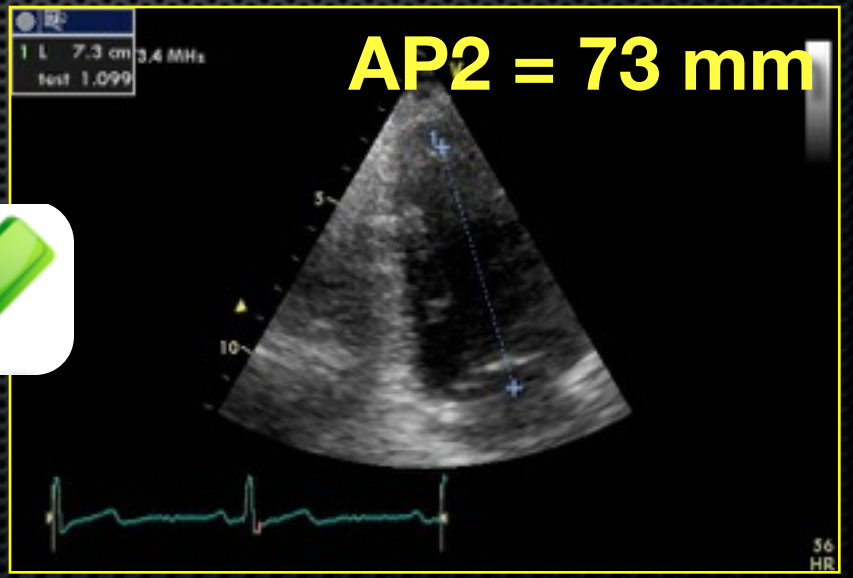


FORESHORTENING

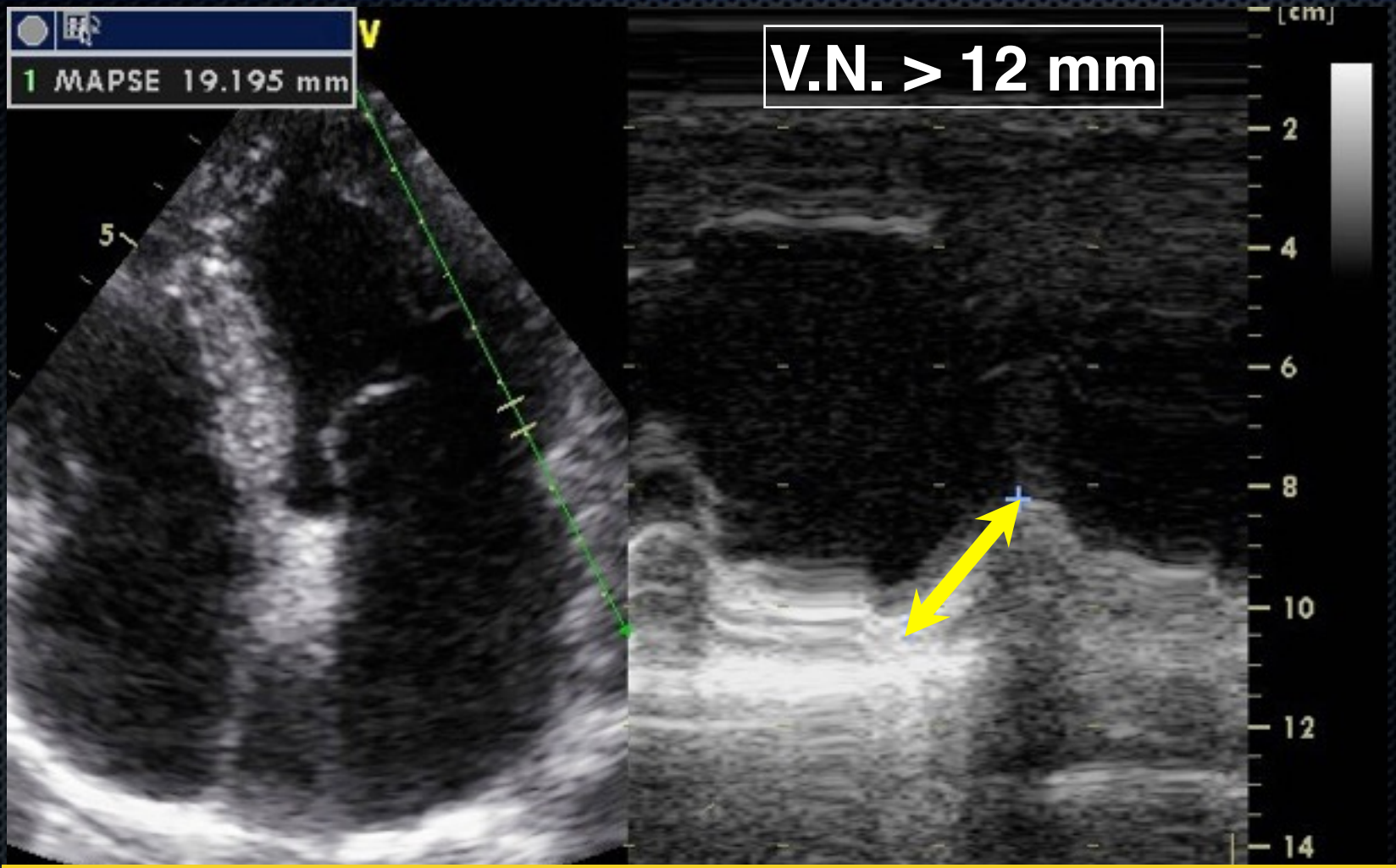






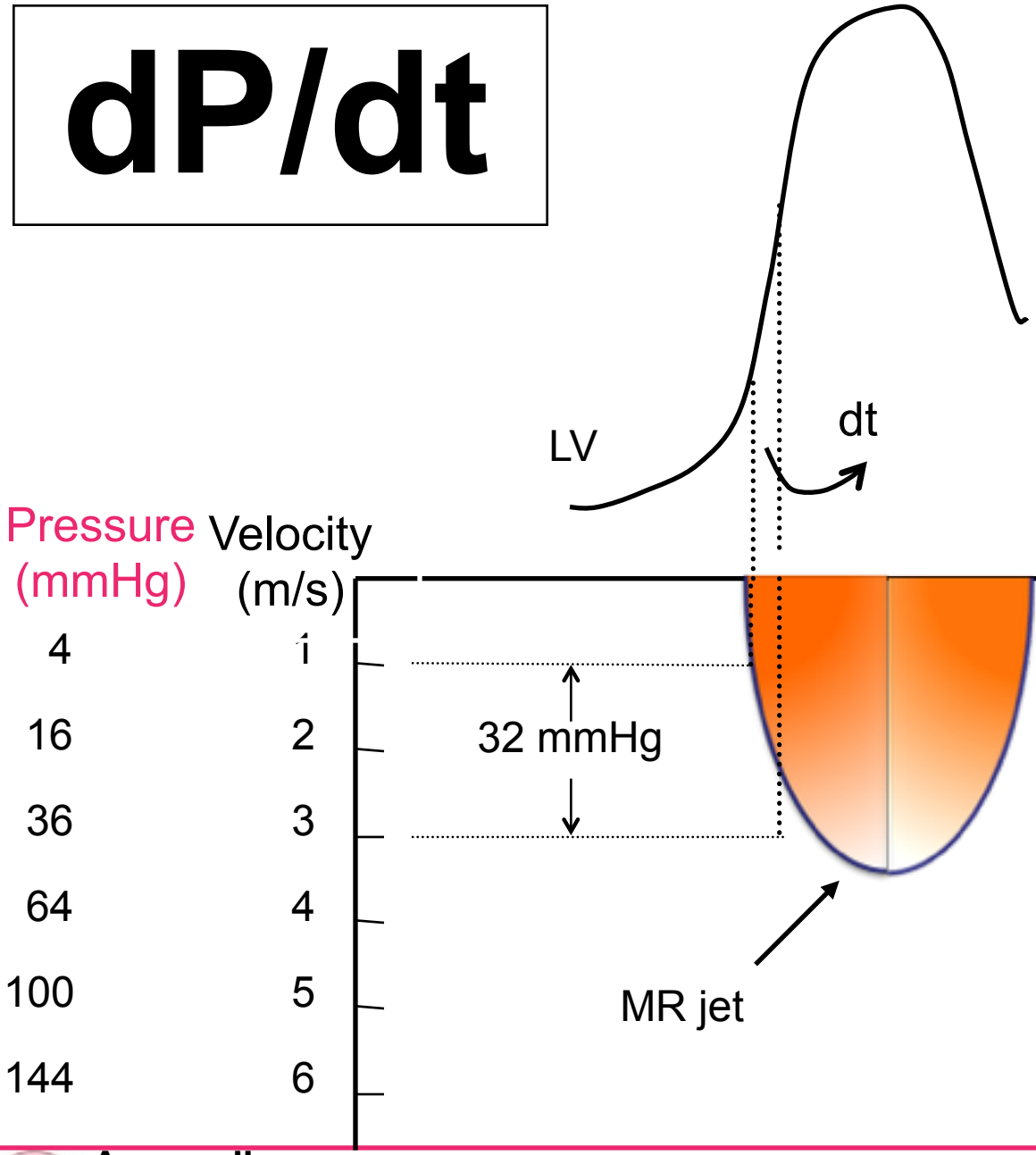


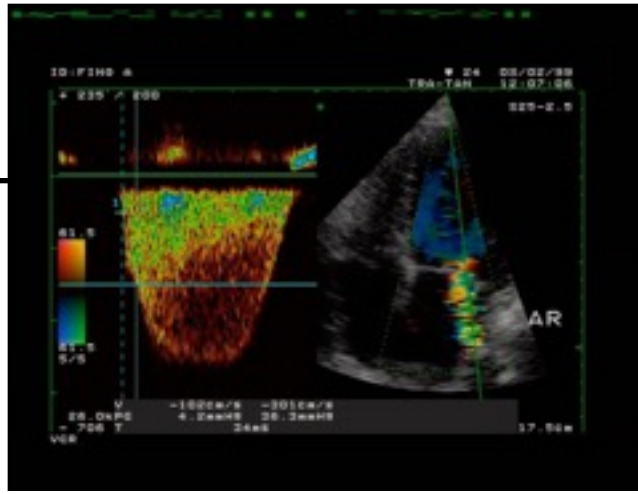
MAPSE



MAPSE = “**M**itral **A**nnular **P**lane **S**ystolic **E**xcursion"

dP/dt

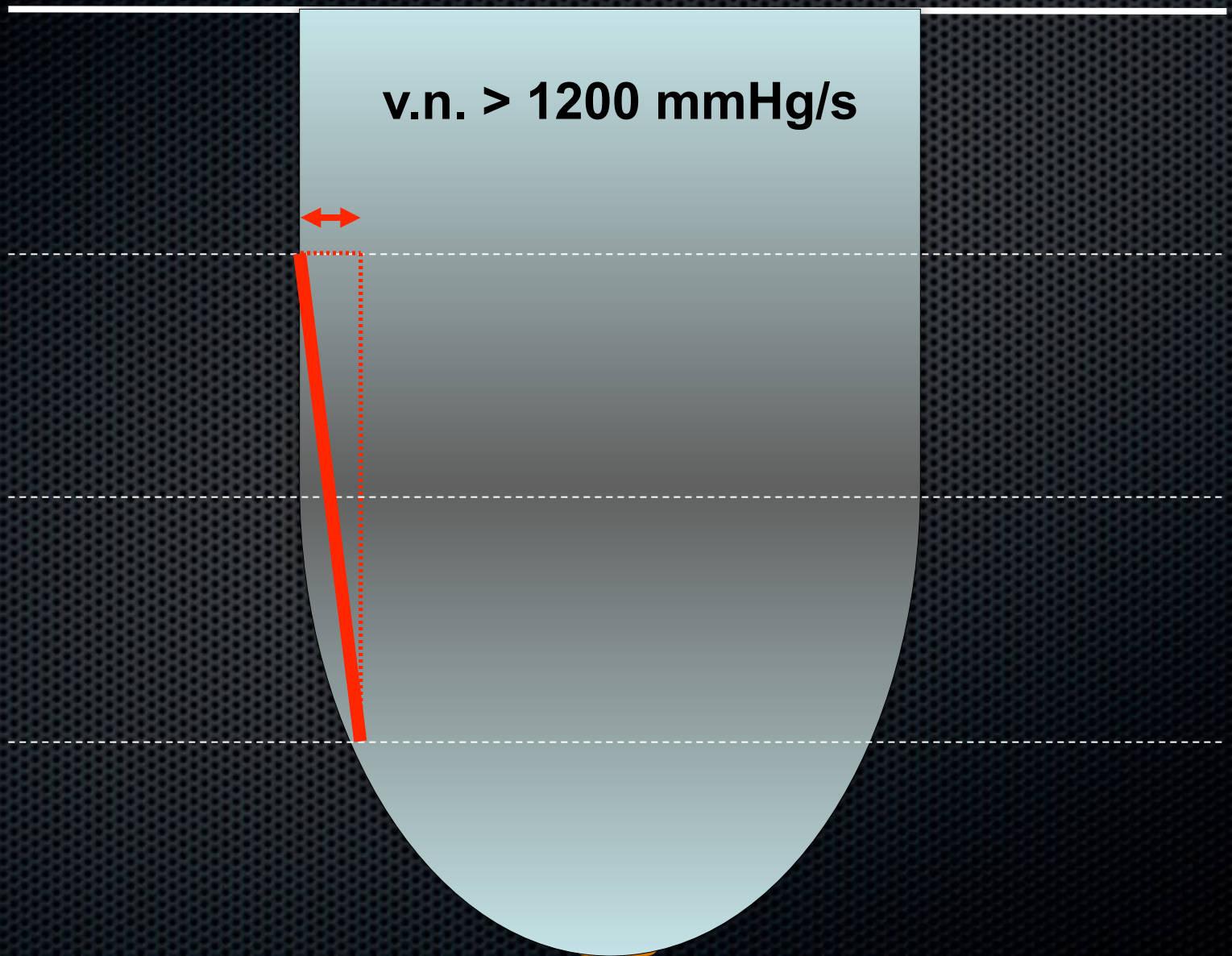




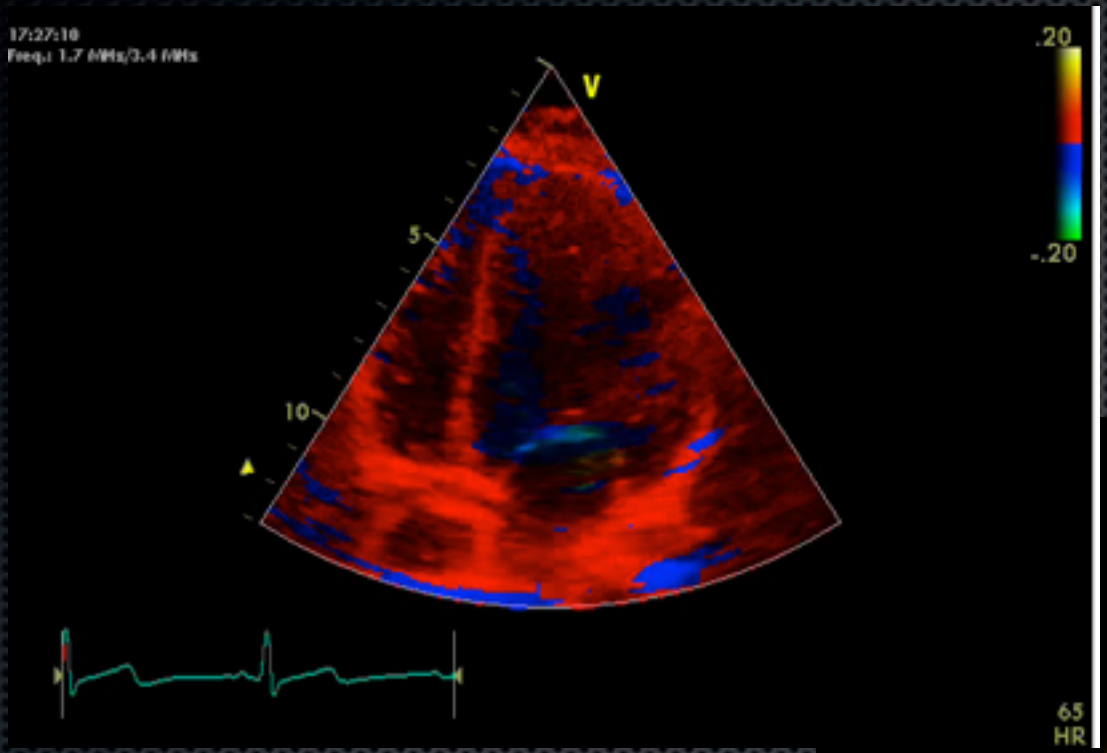
dP/dt = 32 mmHg / time (sec)

(n.v. >1200 mmHg/sec)

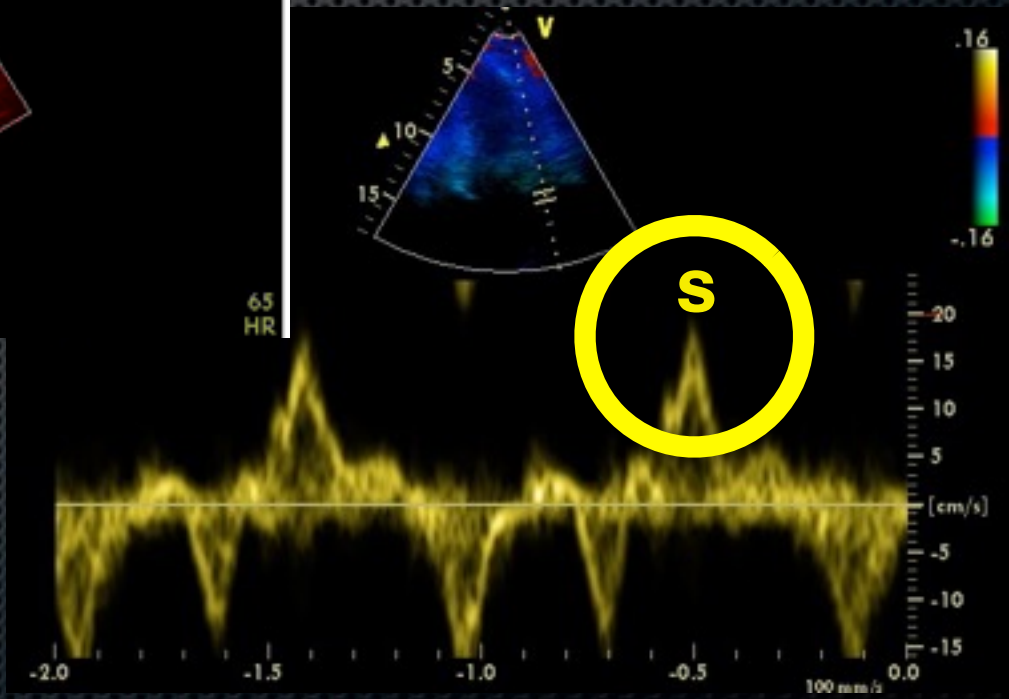
Dp / dt



DOPPLER TISSUTALE

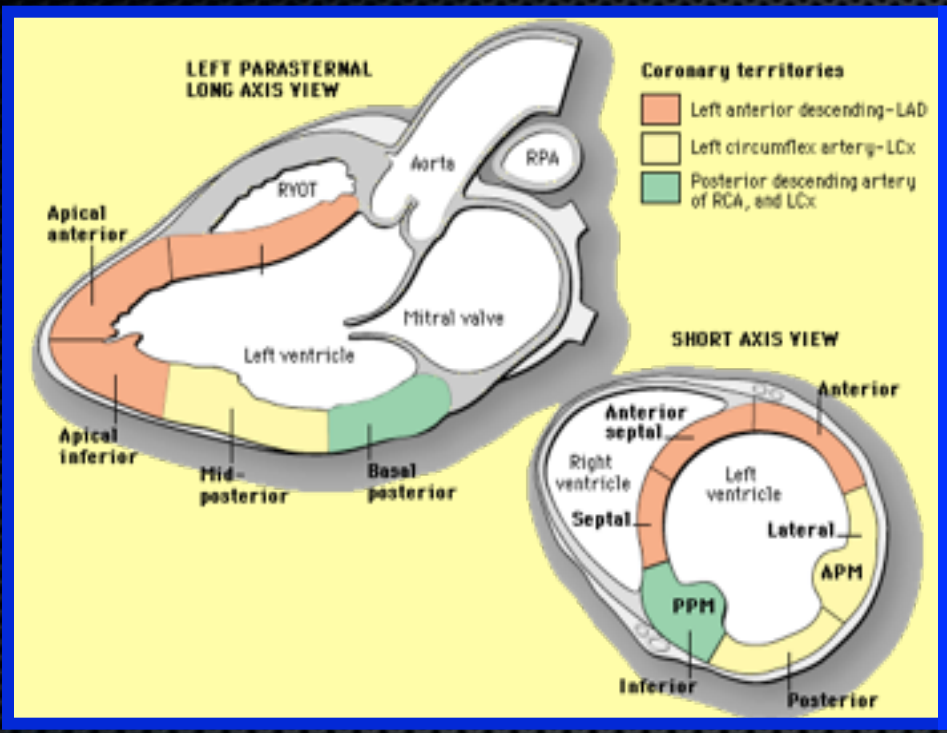


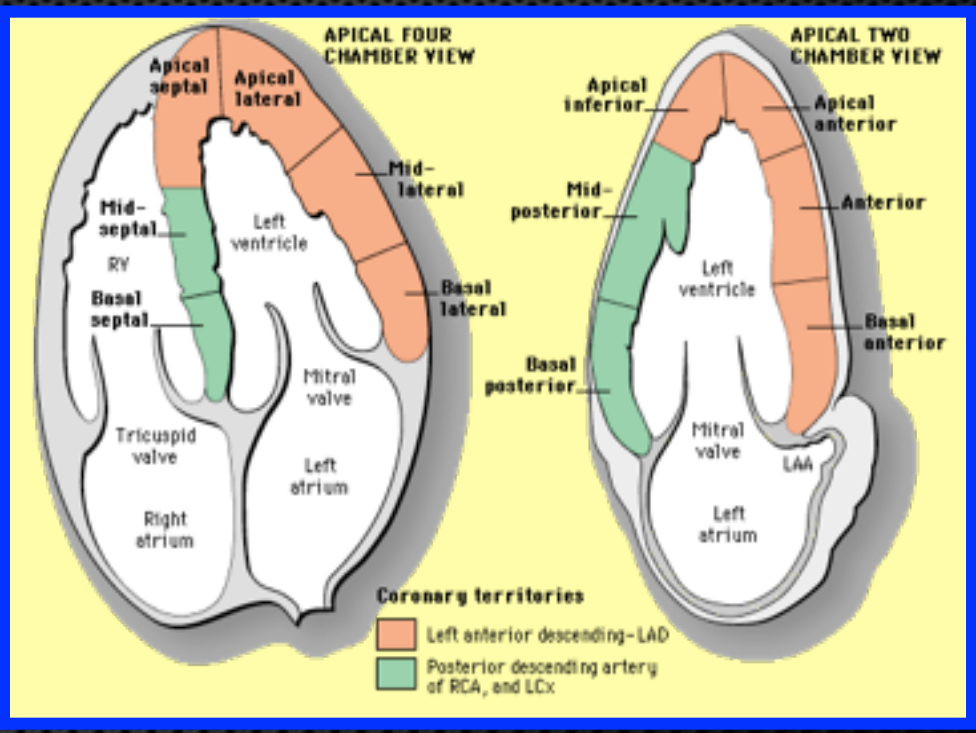
S2 ≧ 8 cm/s



S1: evidente in ipertensione, ipertrofia, anziani, CMP ipocinetica, CAD

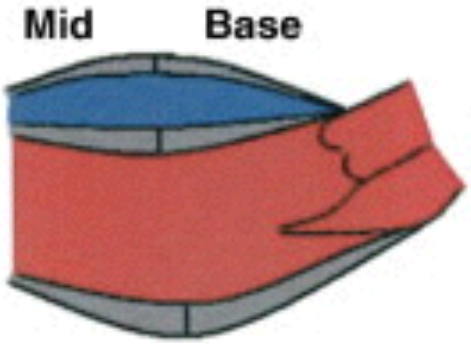
CINESI SEGMENTARIA - WMSI



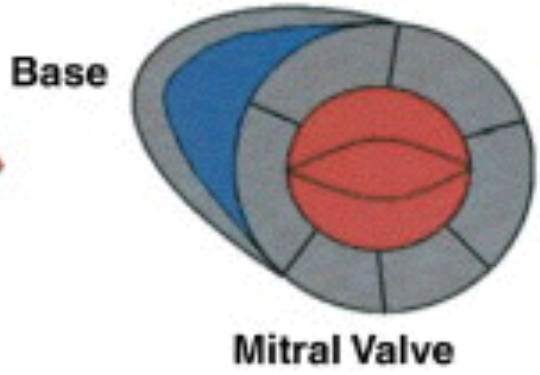


WALL MOTION SCORE INDEX

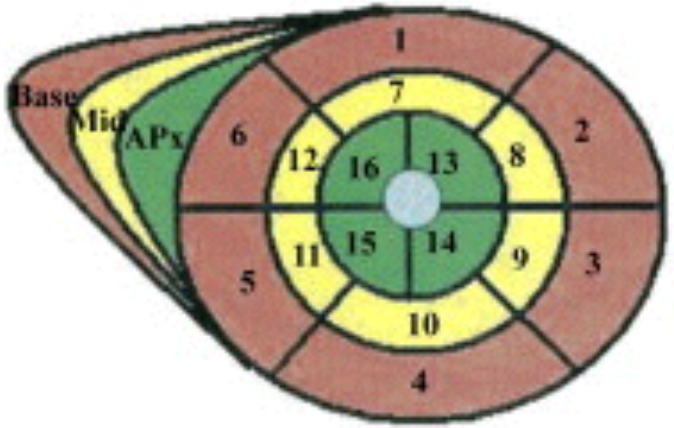
Parasternal Long Axis



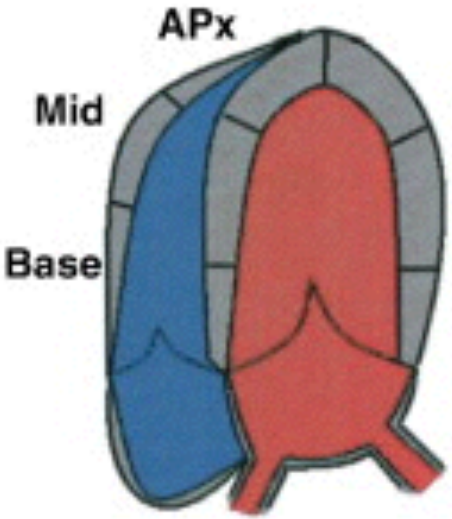
Parasternal Short Axis

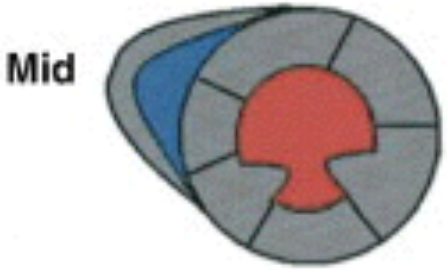


RV Wall Motion Score

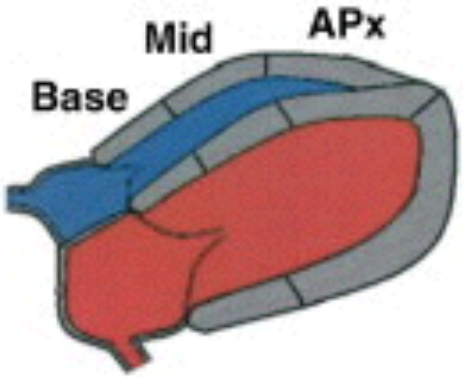


Apical 4-Chamber

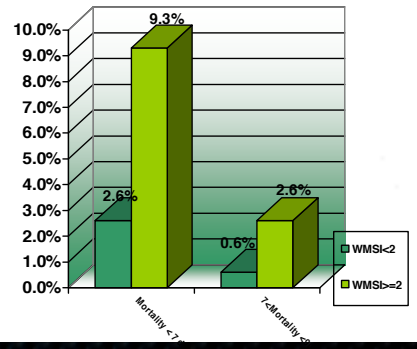




Subcostal



1 = Normal
2 = Mild-Mod Hypokinesis
3 = Severe Hypokinesis
4 = Akinesis
5 = Dyskinesis



FUNZIONE SISTOLICA SEGMENTARIA: WMSI

SISTEMA NUMERICO di PUNTEGGIO ad ogni segmento (punteggio ALTO -> alterazione SEVERA) **(V.N.=1)**

1. NORMALE: inspessimento sist > 40% (>5 mm)
2. IPOCINESIA: inspessimento sist < 30% (2-5 mm)
3. ACINESIA: inspessimento sist < 10% (≤ 2 mm)
4. DISCINESIA: movimento di estroflessione
5. ANEURISMA

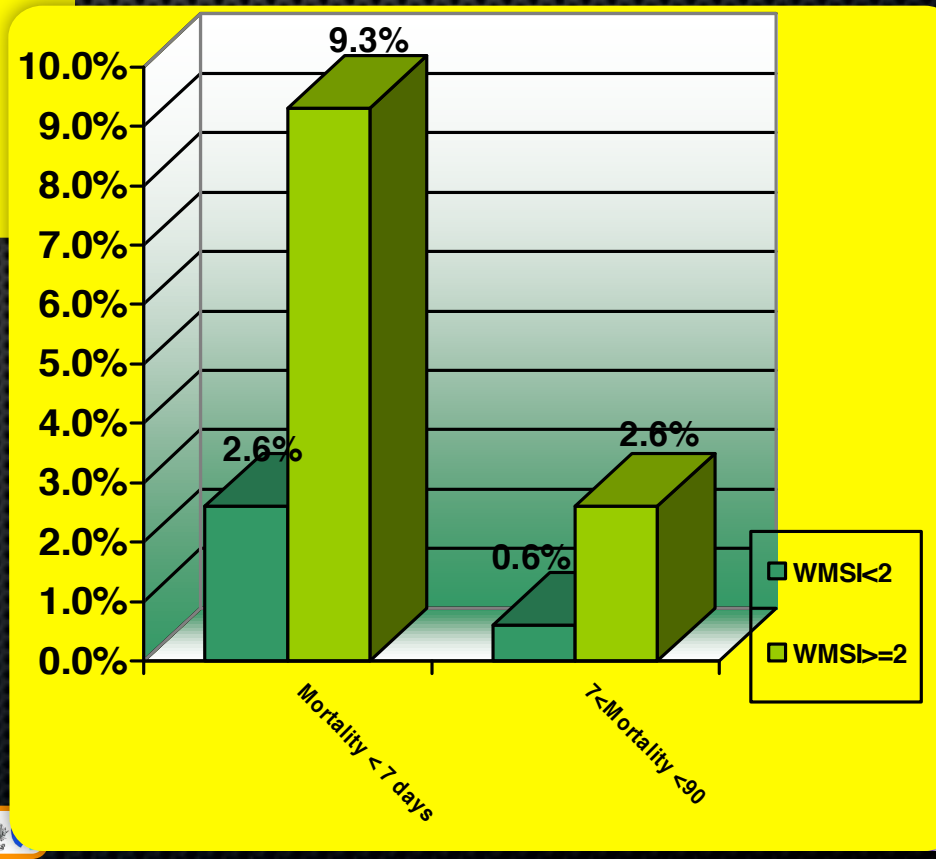
WMSI ≥1.7 ➔ difetto di PERFUSIONE ≥20%

Wall Motion Score Index

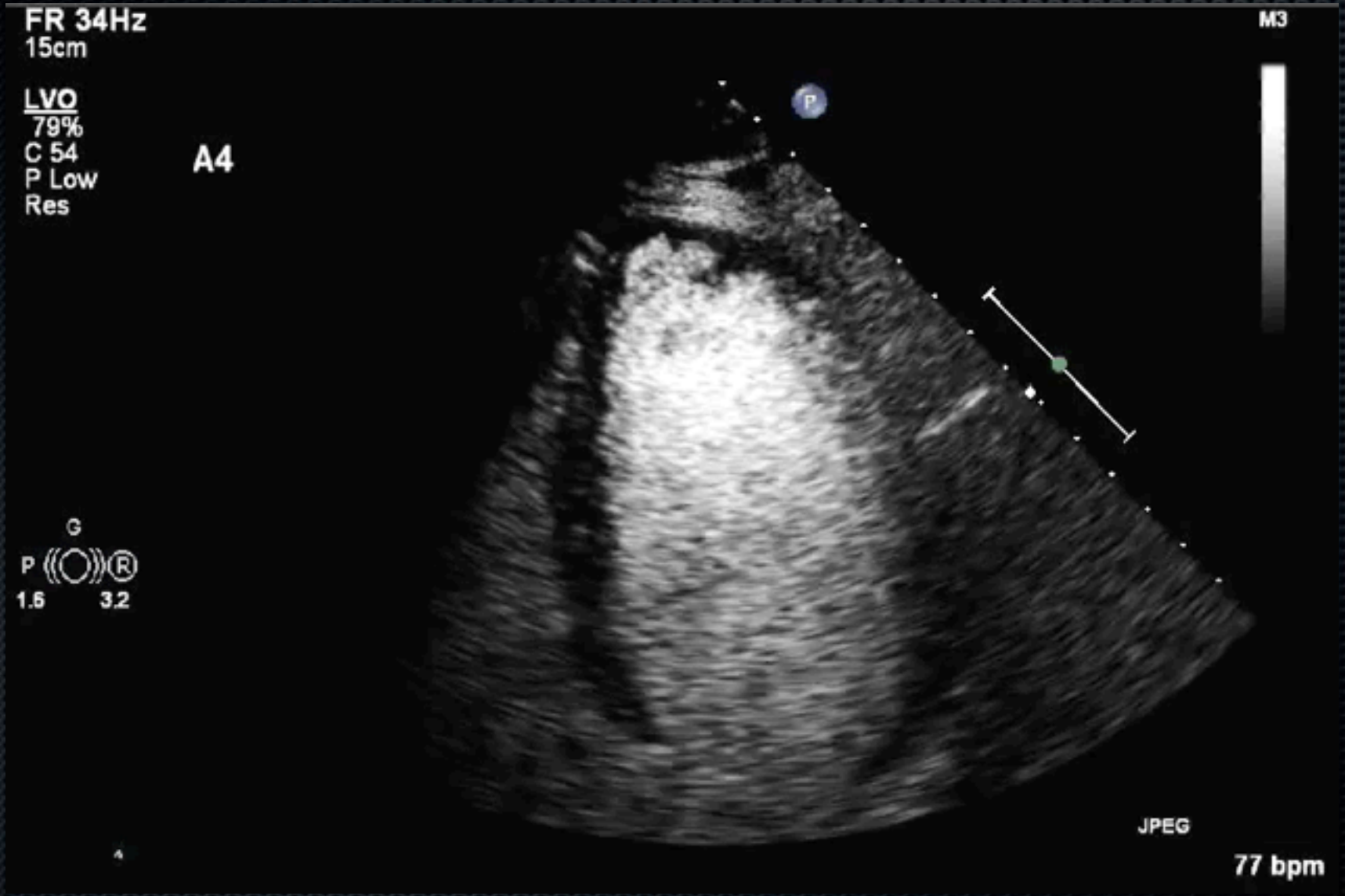
Table I. Distribution of mean EF, mean peak CPK-MB and different type of Killip's class in two groups of WMSI.

	Killip Class 1	Killip Class 2	Killip Class 3	Killip Class 4
WMSI<2	44	19	0	0
WMSI>=2	28	39	13	7

WMSI ≥ 2 correlazione con sintomi e mortalità



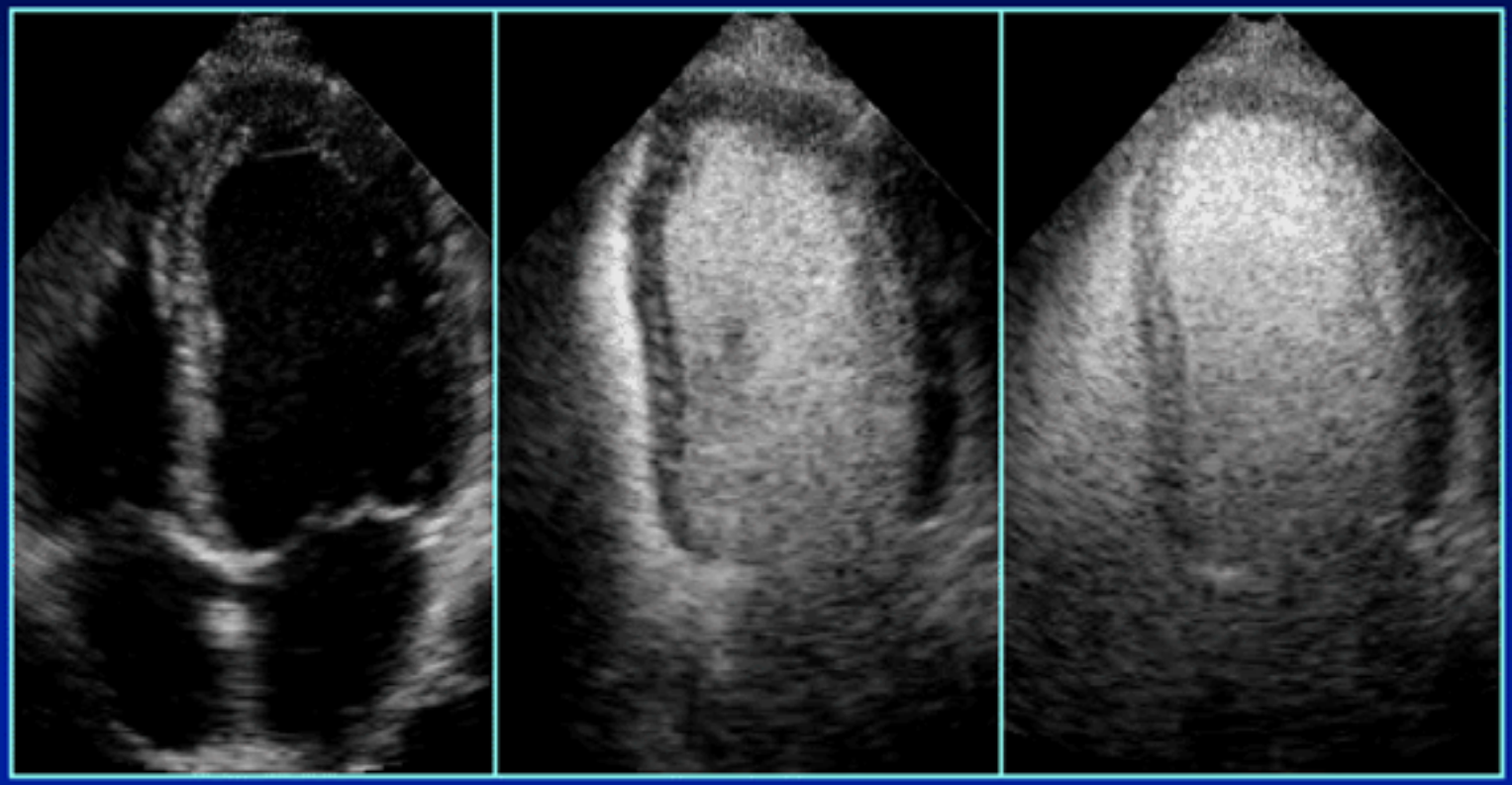
ECOCONTRASTO (SonoVue)



MIOCARDIO CONTRASTO PERFUSIONE

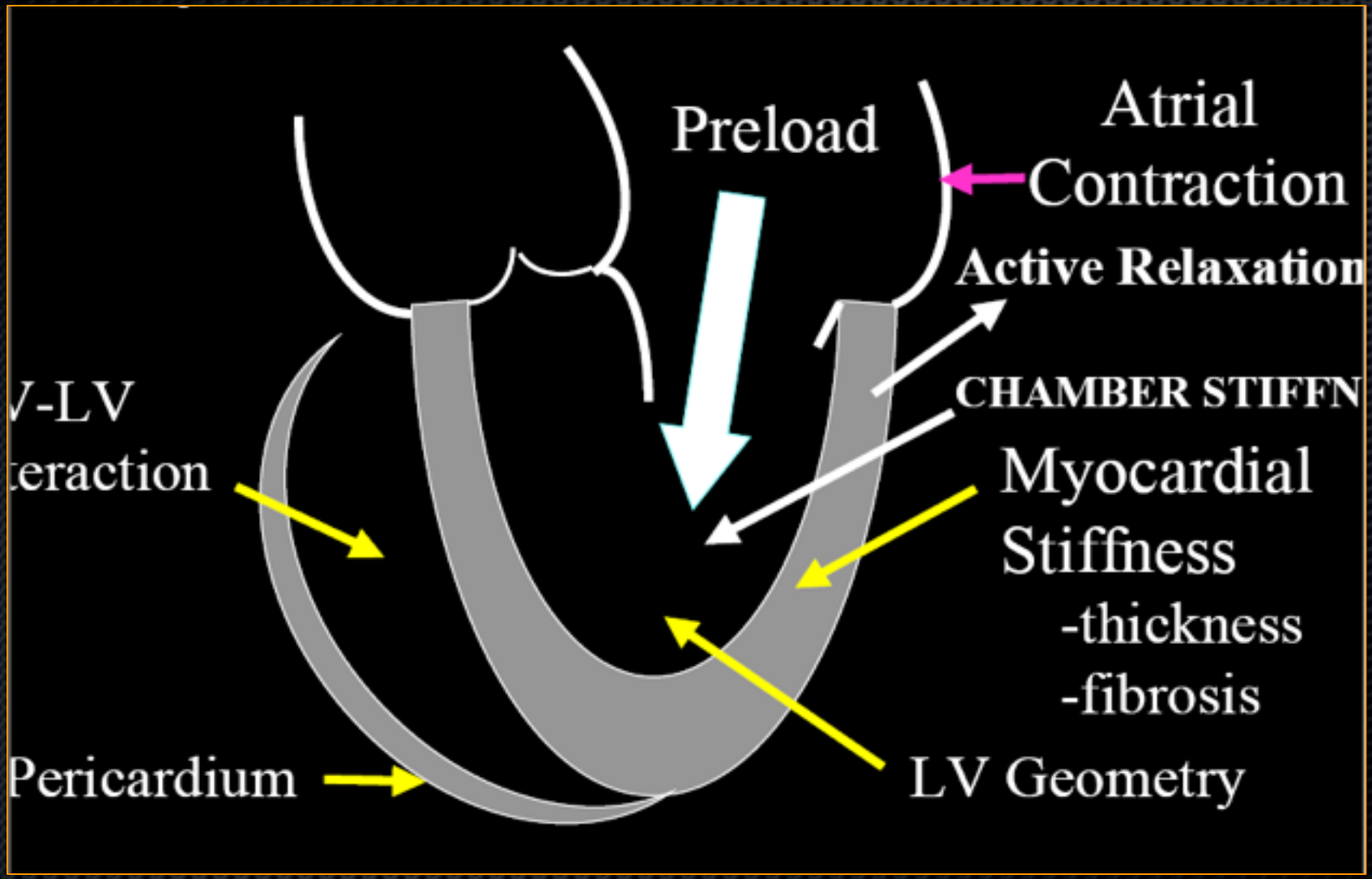
Contrast Echocardiography

Evidence for Perfusion

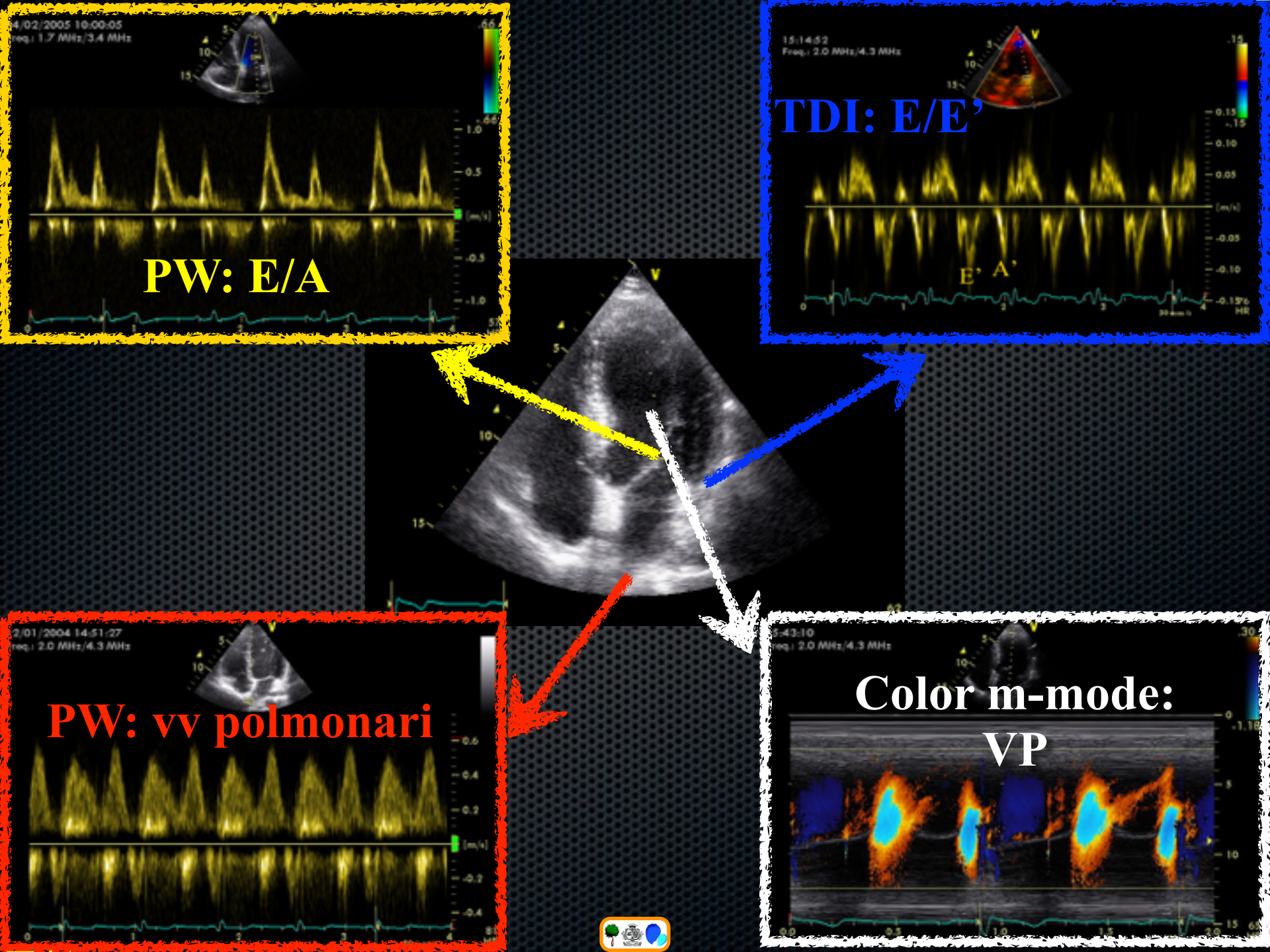


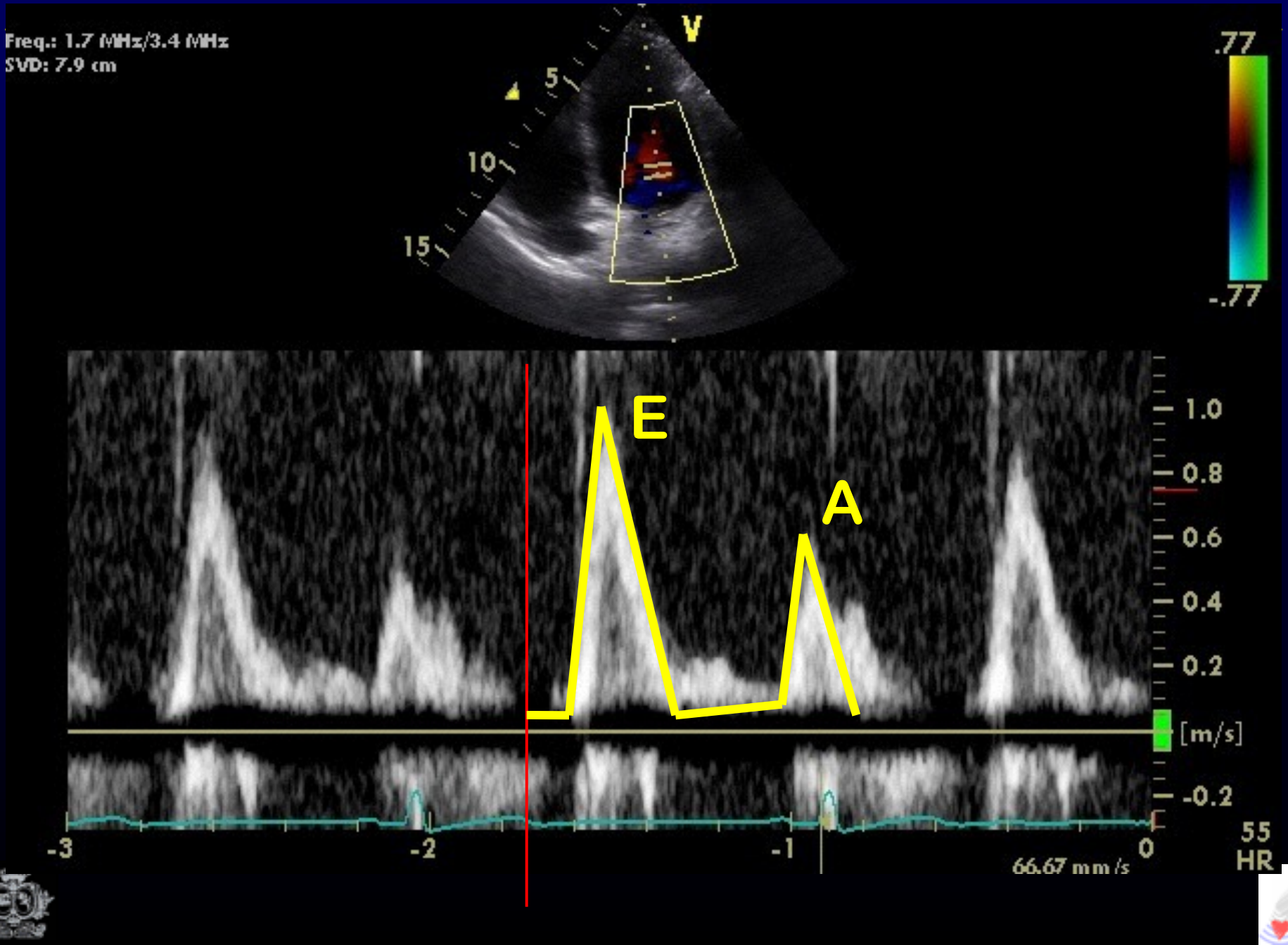
Baseline *LV Phase* *Myocardial Phase*

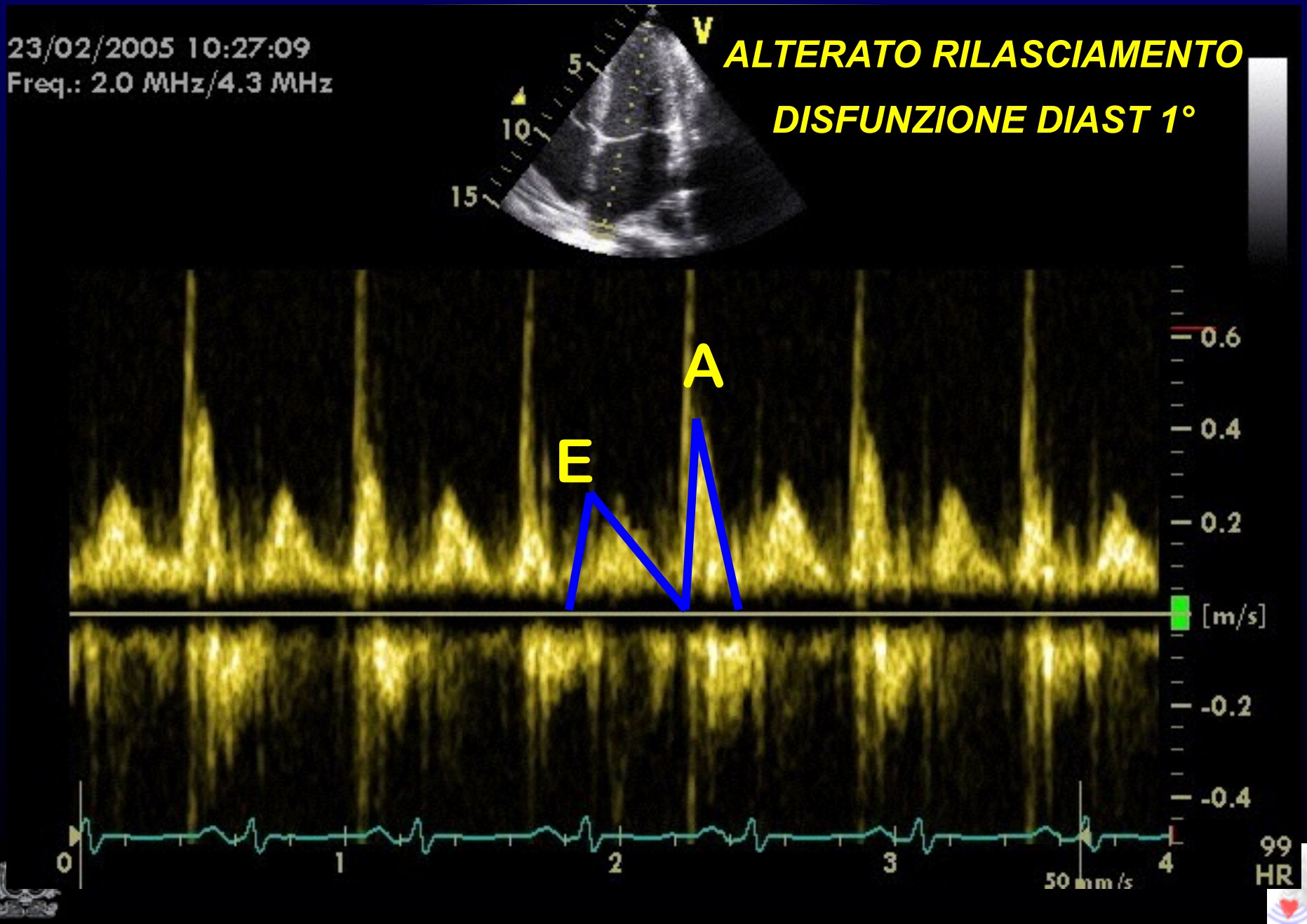
FUNZIONE DIASTOLICA

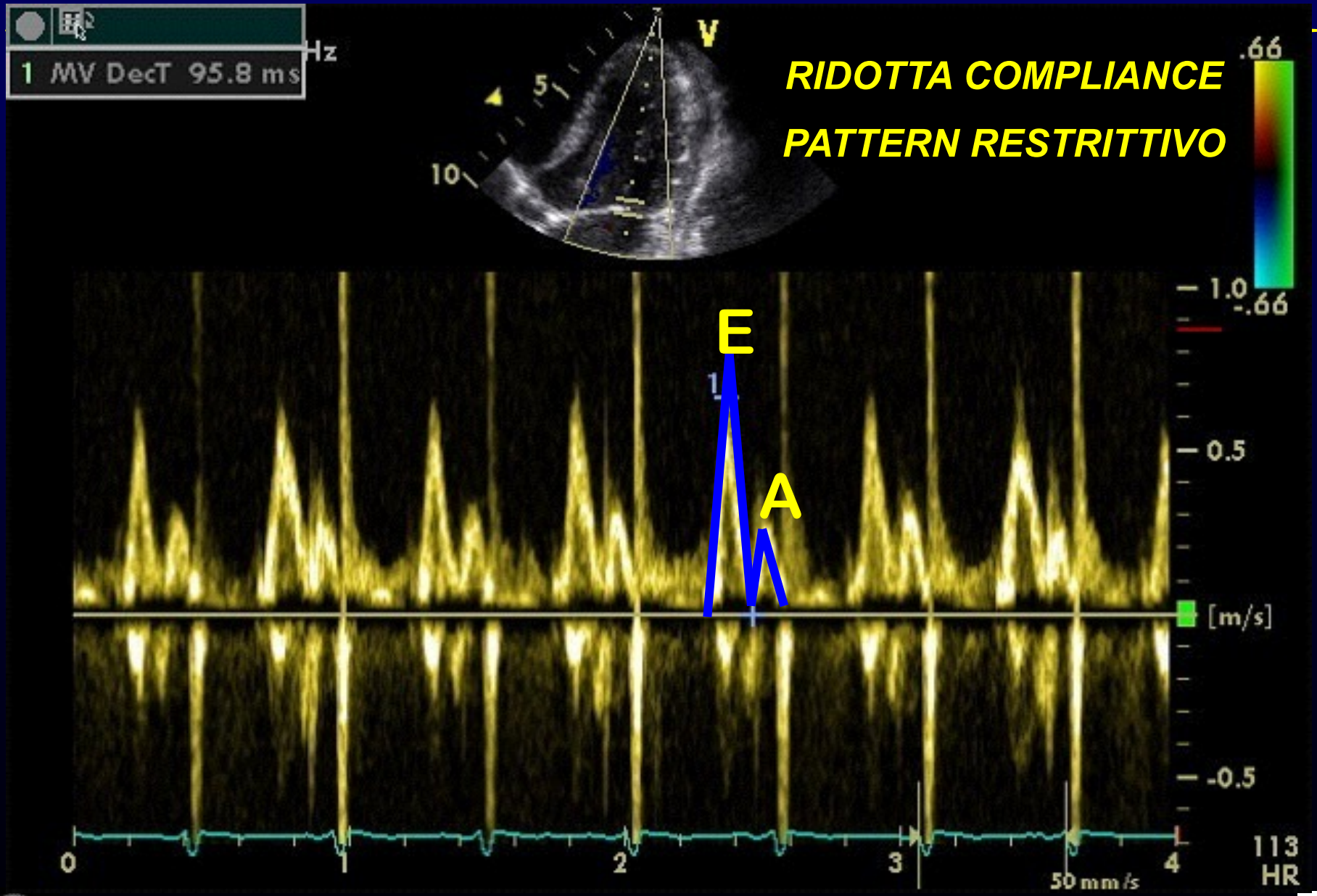


Quinones ASE Review 2007

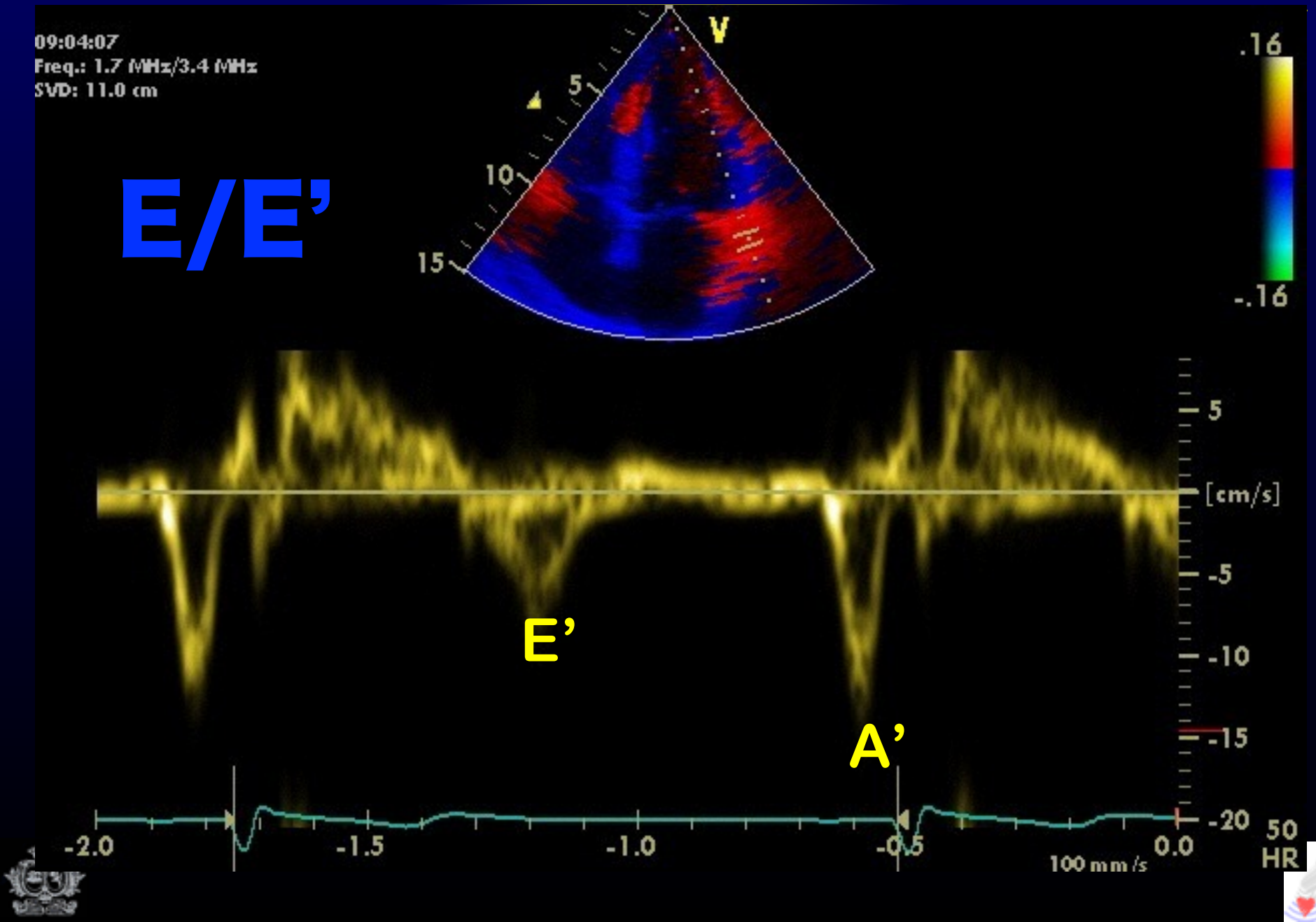

PW: E/A
TDI: E/E’
E’ A’
PW: vv polmonari
Color m-mode:
VP


Freq.: 1.7 MHz/3.4 MHz
SVD: 7.9 cm
V
5
10
15
.77
-.77
E
A
1.0
0.8
0.6
0.4
0.2
[m/s]
-0.2
-3
-2
-1
0
55
HR
66.67 mm/s

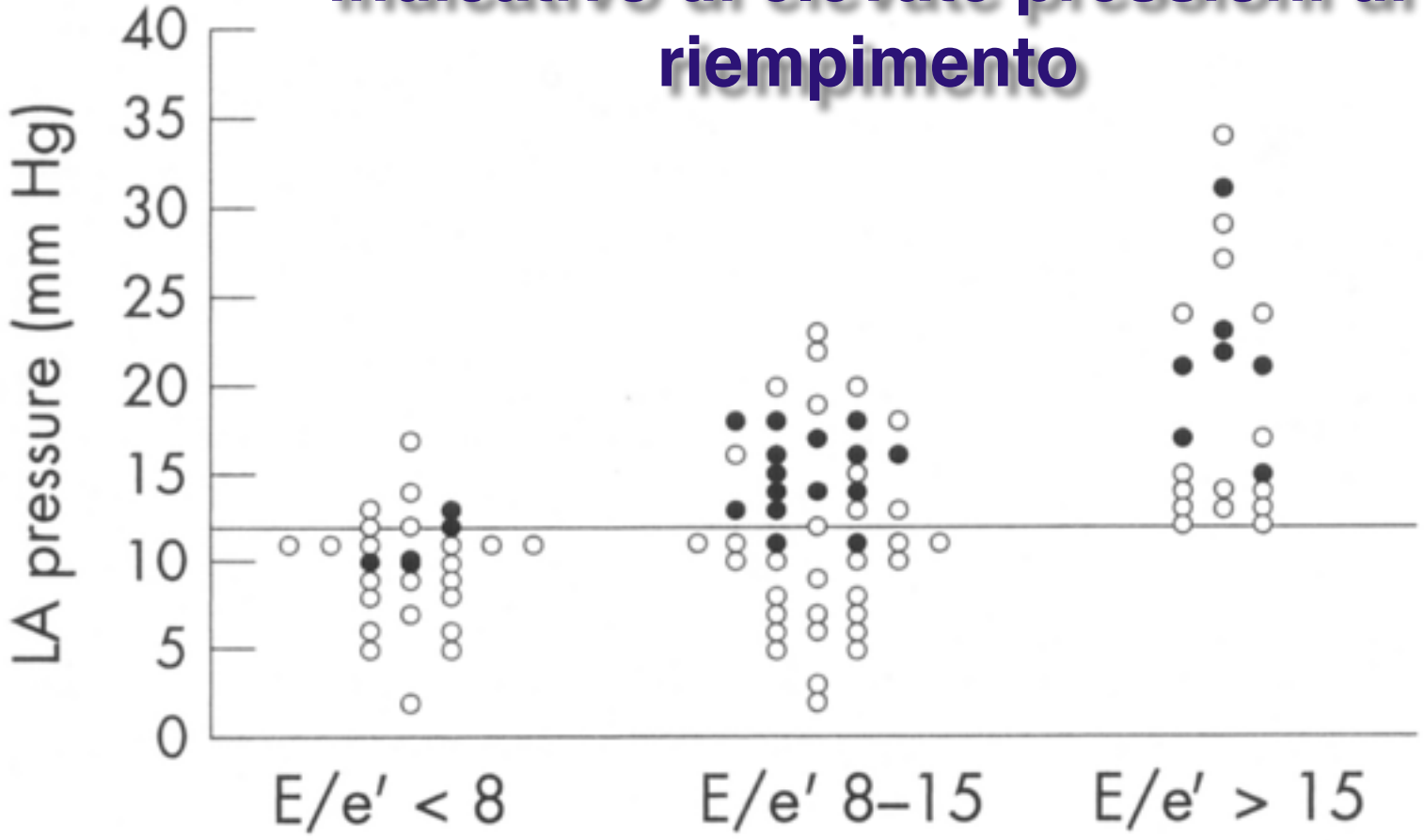

23/02/2005 10:27:09
Freq.: 2.0 MHz/4.3 MHz
ALTERATO RILASCIAMENTO
DISFUNZIONE DIAST 1°
A
E
0.6
0.4
0.2
[m/s]
-0.2
-0.4
0
1
2
3
4
50 mm/s
99
HR


1 MV DecT 95.8 ms
Hz
5
10
V
.66
RIDOTTA COMPLIANCE
PATTERN RESTRITTIVO
E
A
1.0
-.66
0.5
[m/s]
-0.5
0
1
2
3
4
50 mm/s
113
HR

TDI: TISSUE DOPPLER IMAGING



Un rapporto E/E' > 15 e' indicativo di elevate pressioni di riempimento

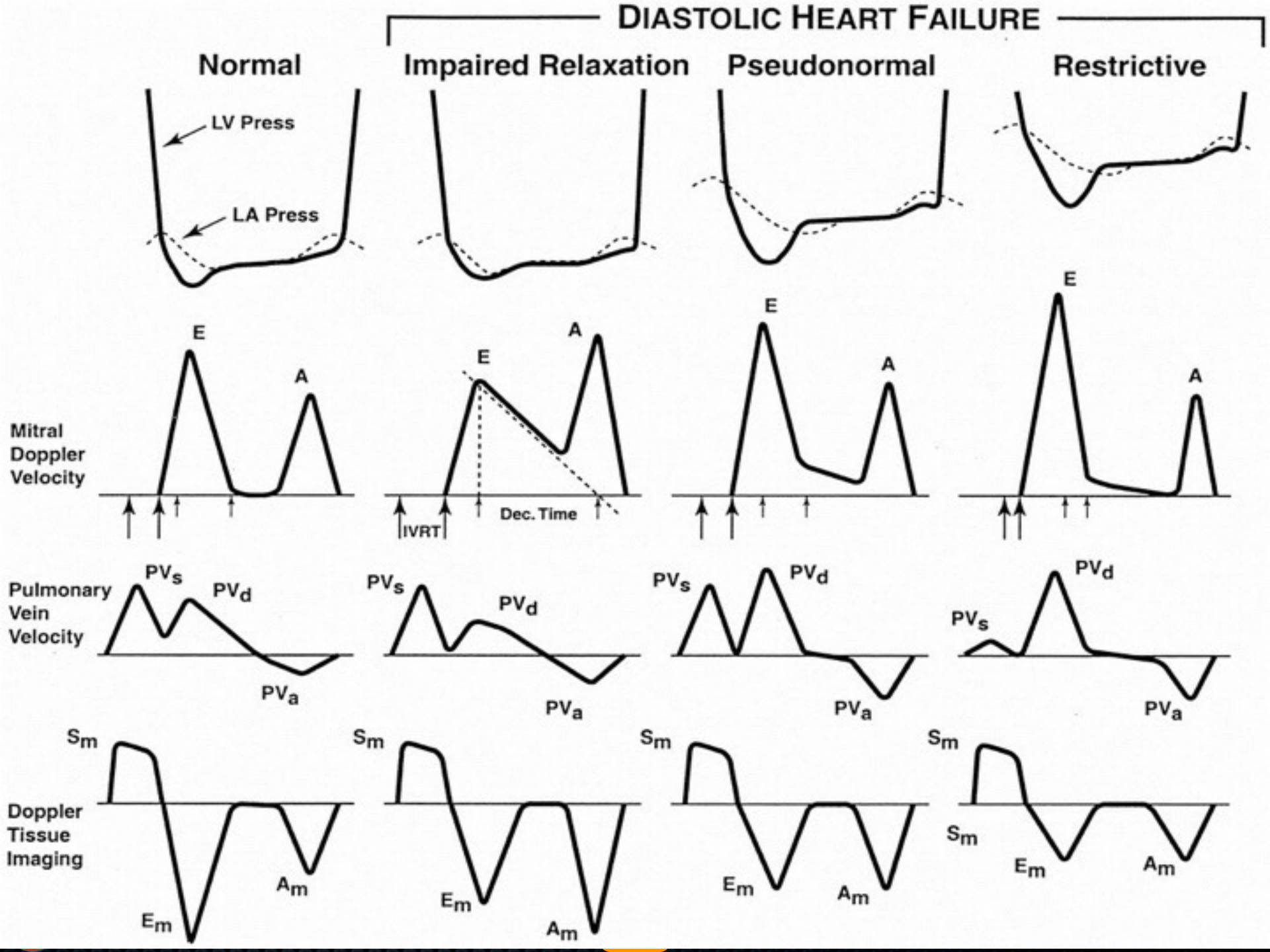


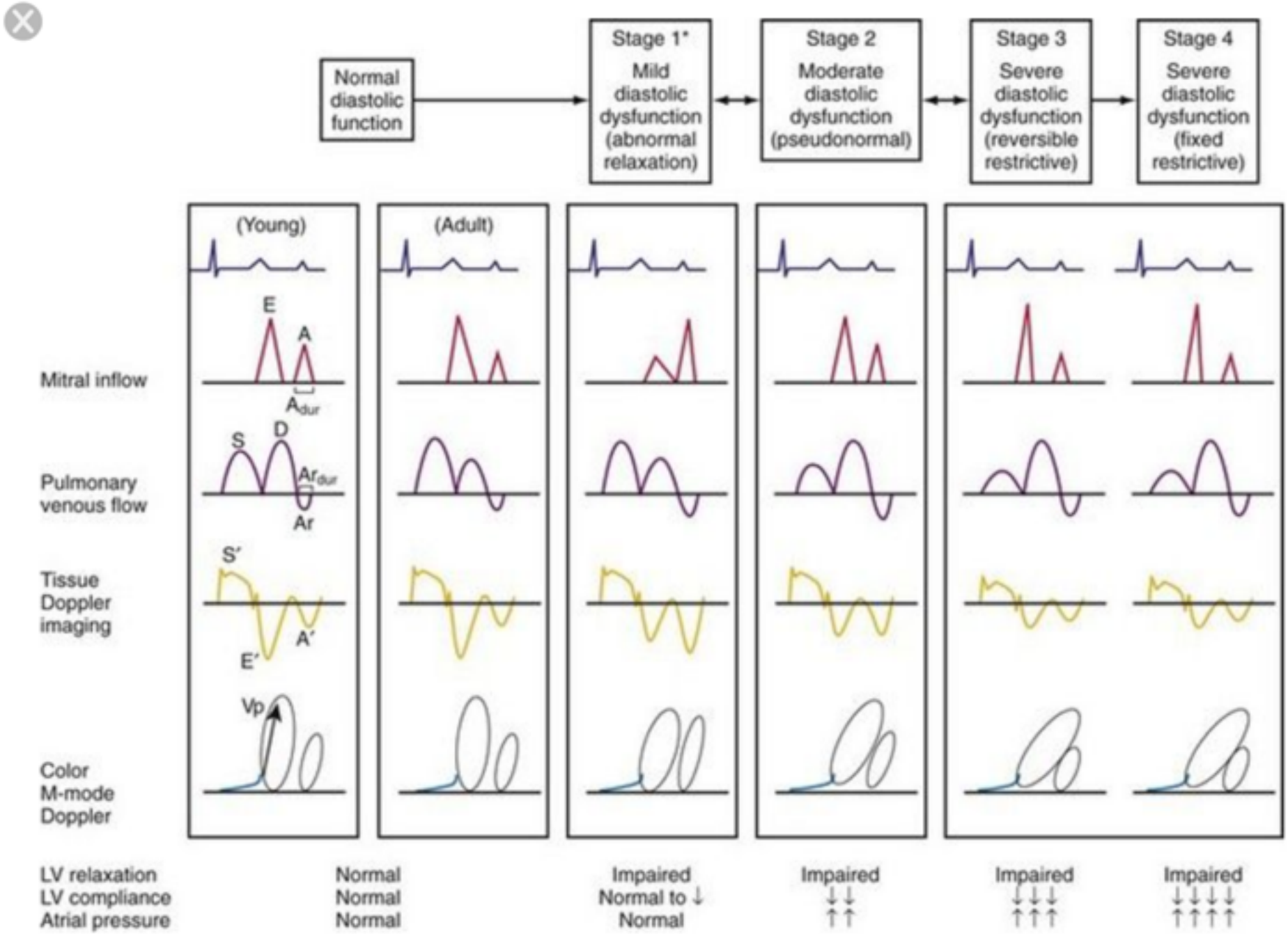
Ommen SR et al, Circulation 2000

FUNZIONE DIASTOLICA

- Rapporto E/A e Deceleration Time al PW
- *Consigliato* Doppler Tissutale (TDI):
  - ✓ **E' (v.n. > 8 cm/s)**
  - ✓ **rapporto E/E' (v.n. < 9)**

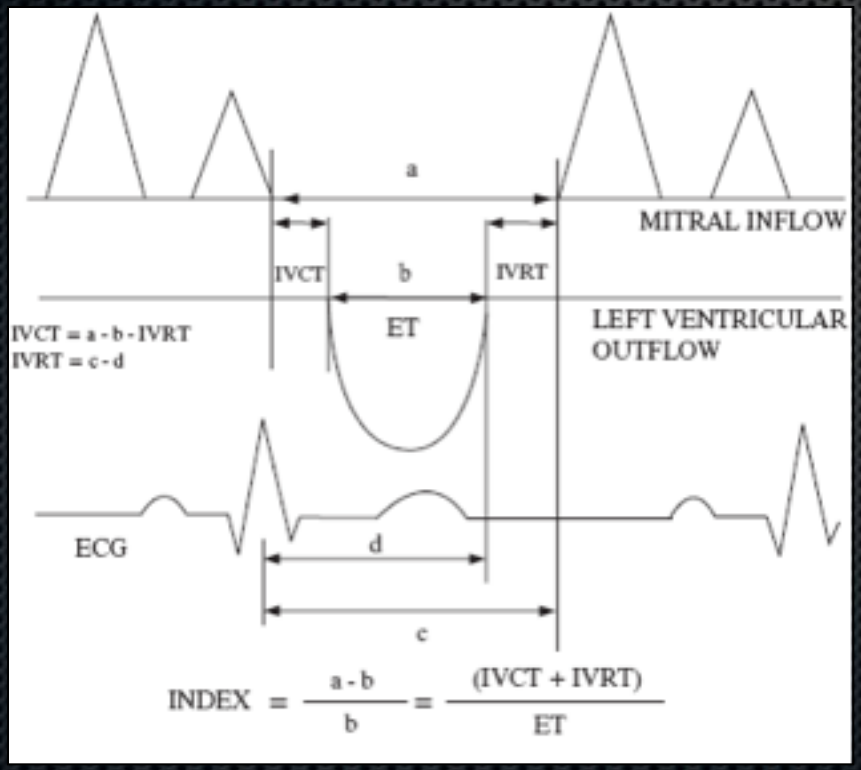
- **FUNZIONE SISTODIASTOLICA**:
- **IMP (Tei index)**: v.n. < 0.4 (PW) - < 0.55 (TDI)

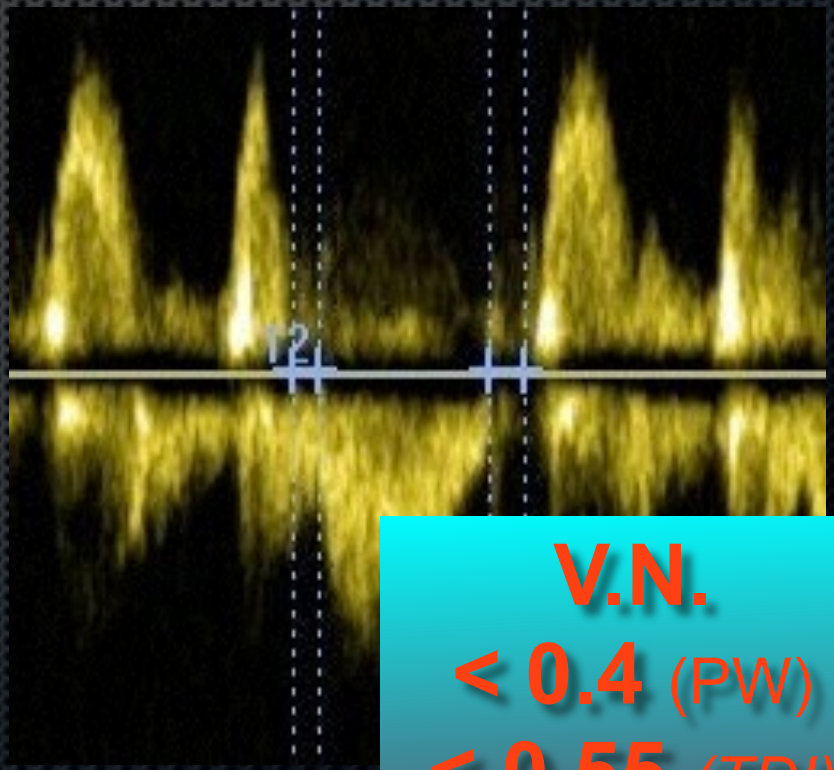

DIASTOLIC HEART FAILURE
Normal
Impaired Relaxation
Pseudonormal
Restrictive
LV Press
LA Press
Mitral Doppler Velocity
E
A
IVRT
Dec. Time
Pulmonary Vein Velocity
PVs
PVd
PVa
Doppler Tissue Imaging
Sm
Em
Am


Normal diastolic function
Stage 1*
Mild diastolic dysfunction (abnormal relaxation)
Stage 2
Moderate diastolic dysfunction (pseudonormal)
Stage 3
Severe diastolic dysfunction (reversible restrictive)
Stage 4
Severe diastolic dysfunction (fixed restrictive)
(Young)
(Adult)
Mitral inflow
E
A
Adur
Pulmonary venous flow
S
D
Ardur
Ar
Tissue Doppler imaging
S′
A′
E′
Color M-mode Doppler
Vp
LV relaxation
LV compliance
Atrial pressure
Normal
Normal
Normal
Impaired
Normal to ↓
Normal
Impaired
↓↓
↑↑
Impaired
↓↓↓
↑↑↑
Impaired
↓↓↓↓
↑↑↑↑

Index of Myocardial Performance (IMP)

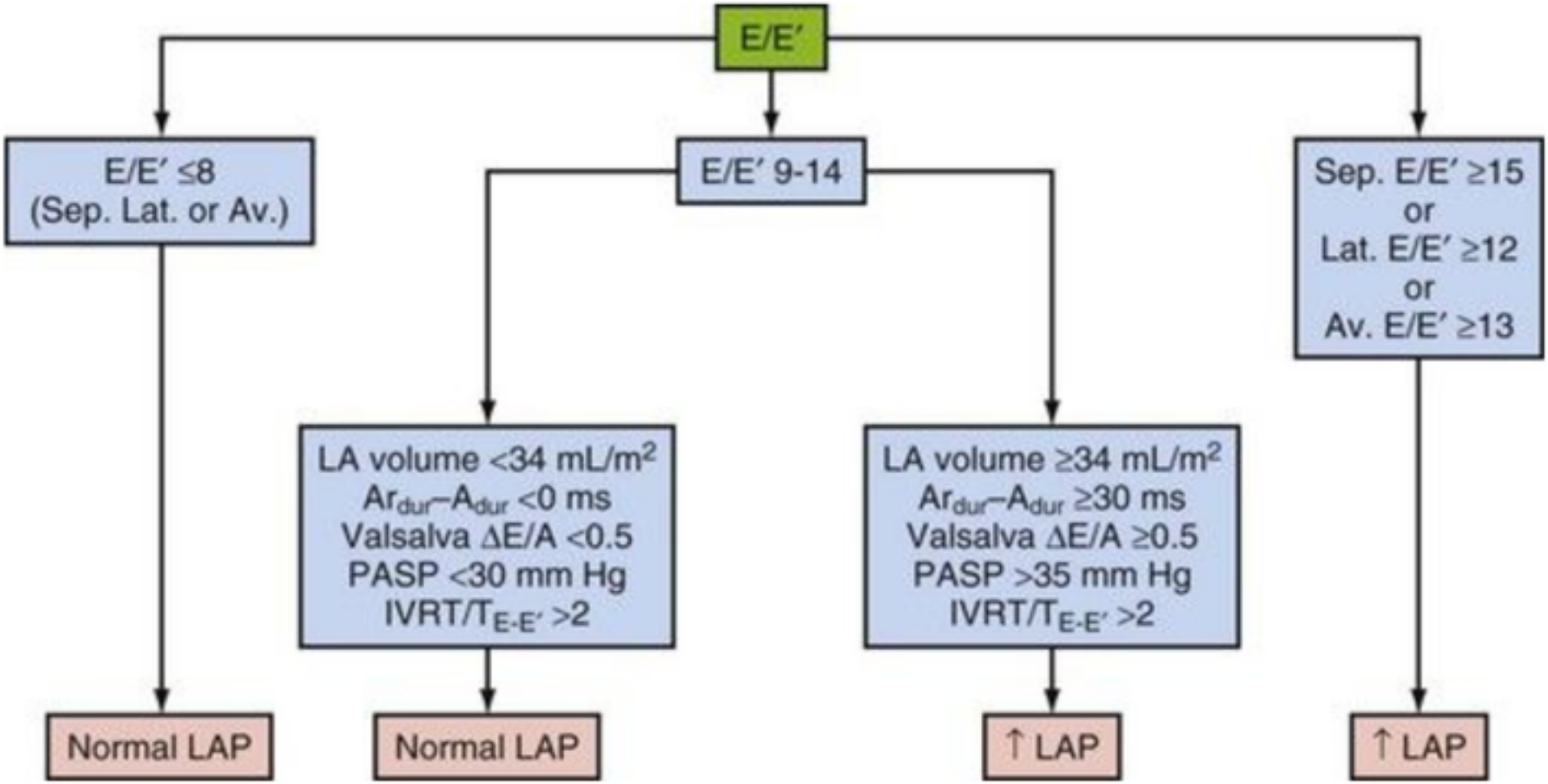
Valutazione sisto-diastolica: durata del periodo di contrazione isovolumetrica (IVCT) e di rilasciamento isovolumetrico (IVRT) su eiezione ao (ET) = *TEI Index*



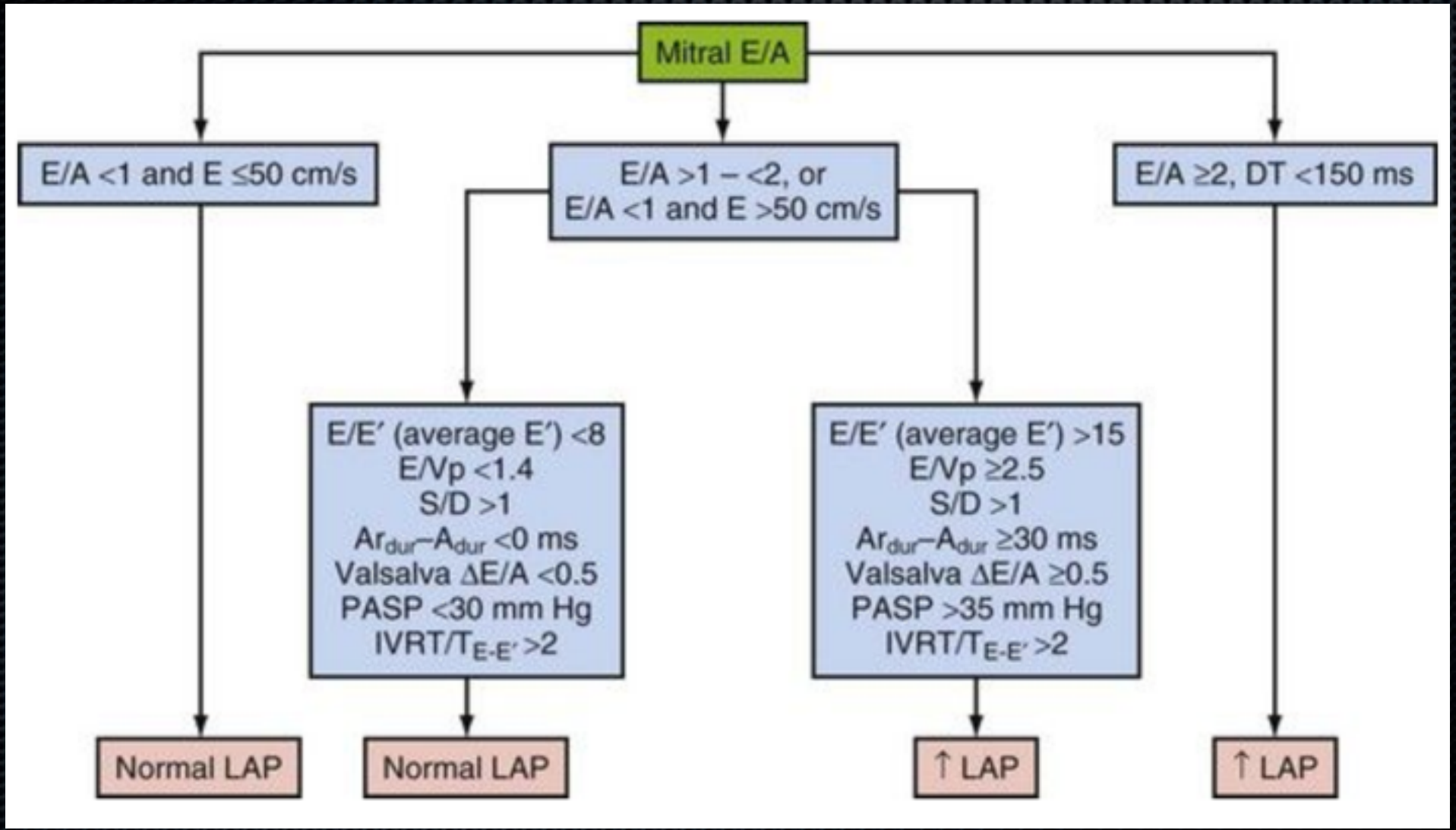


V.N.
< 0.4 (PW)
< 0.55 *(TDI)*

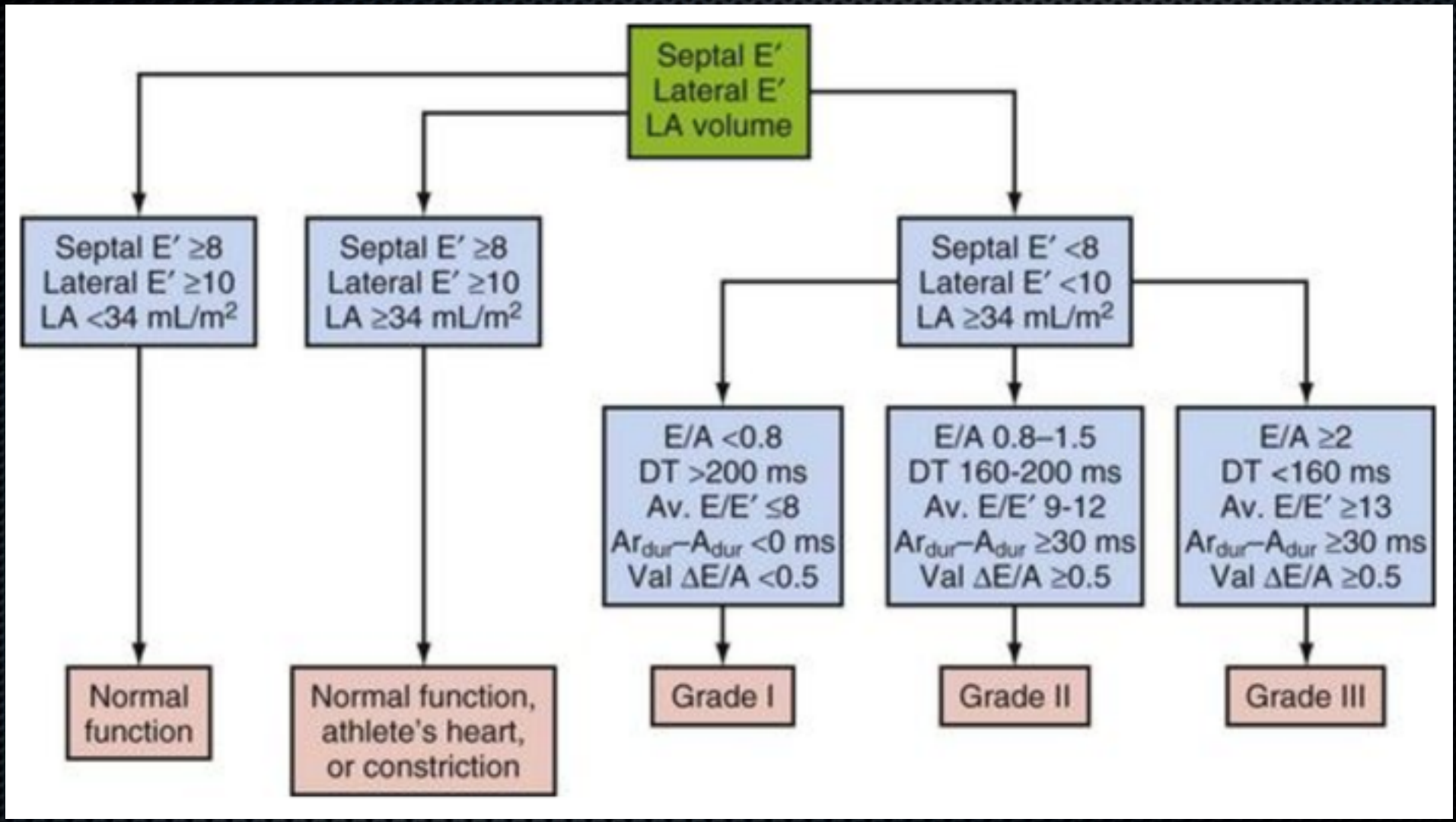
EF NORMALE


E/E′
E/E′ ≤8
(Sep. Lat. or Av.)
E/E′ 9-14
Sep. E/E′ ≥15
or
Lat. E/E′ ≥12
or
Av. E/E′ ≥13
LA volume <34 mL/m²
Ardur–Adur <0 ms
Valsalva ΔE/A <0.5
PASP <30 mm Hg
IVRT/TE-E′ >2
LA volume ≥34 mL/m²
Ardur–Adur ≥30 ms
Valsalva ΔE/A ≥0.5
PASP >35 mm Hg
IVRT/TE-E′ >2
Normal LAP
Normal LAP
↑ LAP
↑ LAP

EF RIDOTTA


Mitral E/A
E/A <1 and E ≤50 cm/s
E/A >1 – <2, or
E/A <1 and E >50 cm/s
E/A ≥2, DT <150 ms
E/E′ (average E′) <8
E/Vp <1.4
S/D >1
Ar_{dur}–A_{dur} <0 ms
Valsalva ΔE/A <0.5
PASP <30 mm Hg
$IVRT/T_{E\text{-}E'}$ >2
E/E′ (average E′) >15
E/Vp ≥2.5
S/D >1
Ar_{dur}–A_{dur} ≥30 ms
Valsalva ΔE/A ≥0.5
PASP >35 mm Hg
$IVRT/T_{E\text{-}E'}$ >2
Normal LAP
Normal LAP
↑ LAP
↑ LAP

GRADING DISFUNZIONE DIAST.



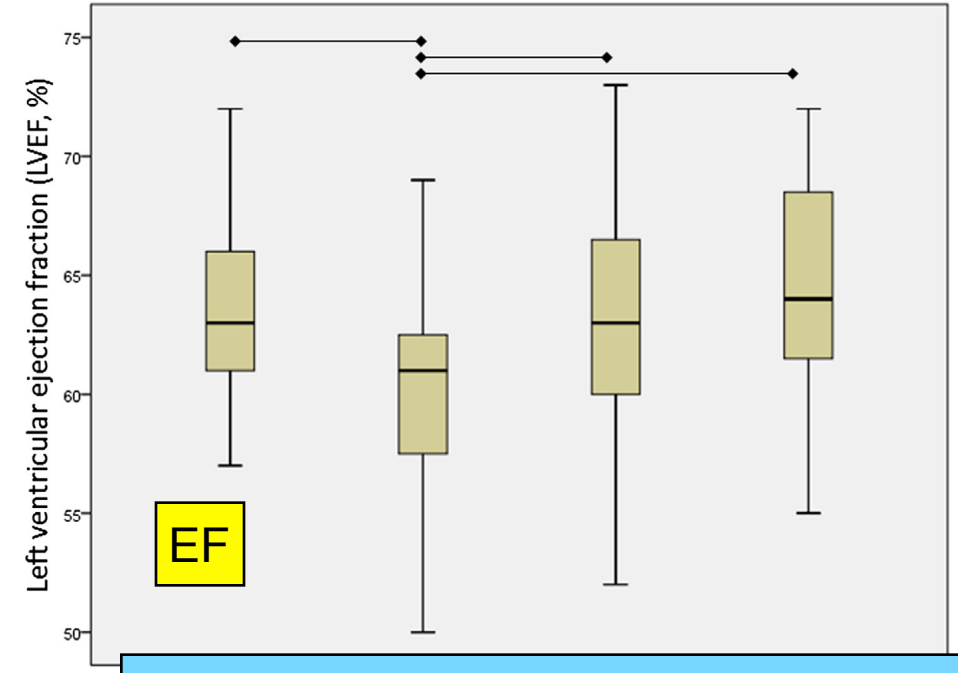
Temporal Changes in Standard and Tissue Doppler Imaging Echocardiographic Parameters After Anthracycline Chemotherapy in Women With Breast Cancer

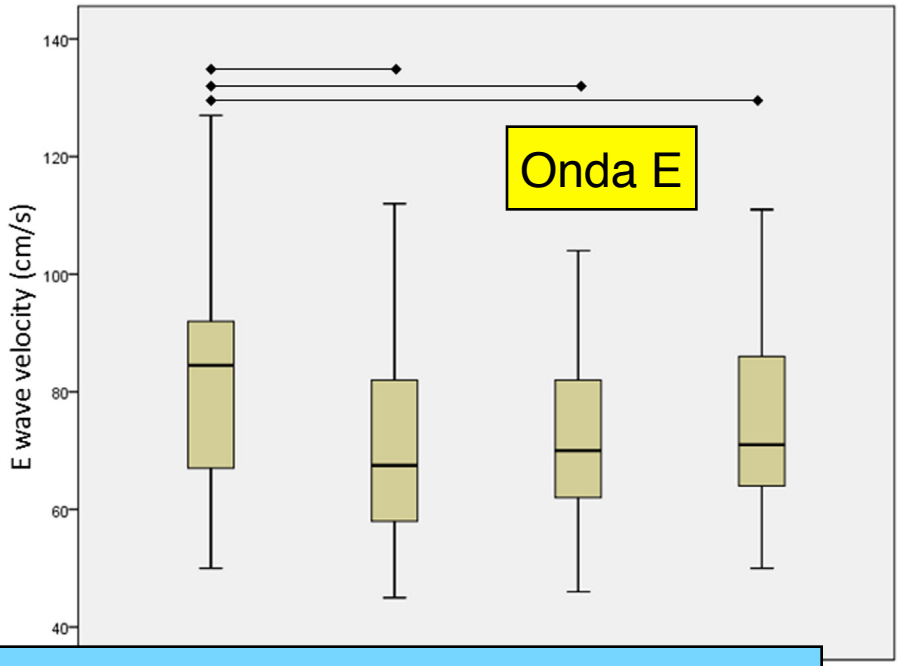
Marzia Lotrionte, MD[a], Elena Cavarretta, MD, PhD[b], Antonio Abbate, MD, PhD[c], Eleonora Mezzaroma, PhD[c], Eugenia De Marco, MD[a], Silvia Di Persio, RN[a], Francesco Loperfido, MD[a], Giuseppe Biondi-Zoccai, MD[b,*], Giacomo Frati, MD[b,d], and Giovanni Palazzoni, MD, PhD[e]

Anthracyclines are established cardiotoxic agents; however, the exact extent and time course of such cardiotoxicity has not been appraised in detail. We aimed to exploit serial measurements of standard and tissue Doppler imaging (TDI) echocardiographic parameters collected in a prospective clinical trial to clarify the outlook of cardiac function during and long after anthracycline chemotherapy. Women enrolled in a randomized trial focusing on liposomal doxorubicin-based chemotherapy for breast cancer and providing ≥4 separate echocardiographic assessments were included. Repeat-measure nonparametric analyses were used to appraise changes over time in the standard and tissue Doppler imaging echocardiographic parameters. A total of 39 patients with serial imaging evaluations were enrolled. Significant temporal changes were found for the left ventricular ejection fraction and diastolic parameters, despite different temporal trends. Specifically, the left ventricular ejection fraction exhibited a ∨-shaped trend, decreasing initially from 63% to 61% but then recovering to 64% ($p < 0.001$), with a similar trend in the TDI E/Em ratio ($p = 0.011$). In contrast, persistent impairments typical of an ∟-shaped trend were found for the E wave ($p = 0.006$), TDI lateral Em wave ($p = 0.001$), and TDI septal Em wave ($p = 0.001$). In conclusion, subclinical temporal changes in the standard and TDI echocardiographic parameters after anthracycline chemotherapy showed a distinctive pattern of transient impairment followed by full recovery of the left ventricular ejection fraction versus a persistent impairment of the diastolic parameters, which must be taken into account in the everyday treatment of such patients. **(Am J Cardiol 2013;112:1005−1012)**

39 ♀, liposomal-doxo, 4 f.u.: fine, 6, 12, 18-24 m

EF e funzione diastolica

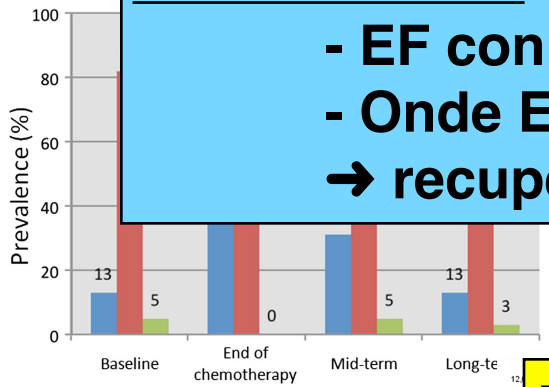


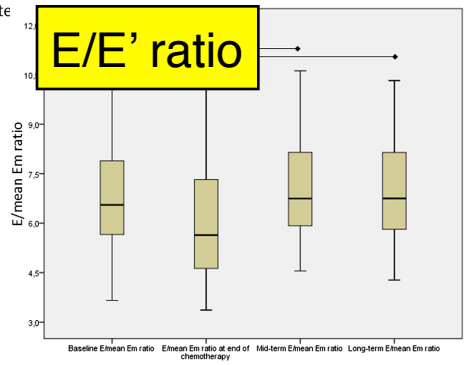


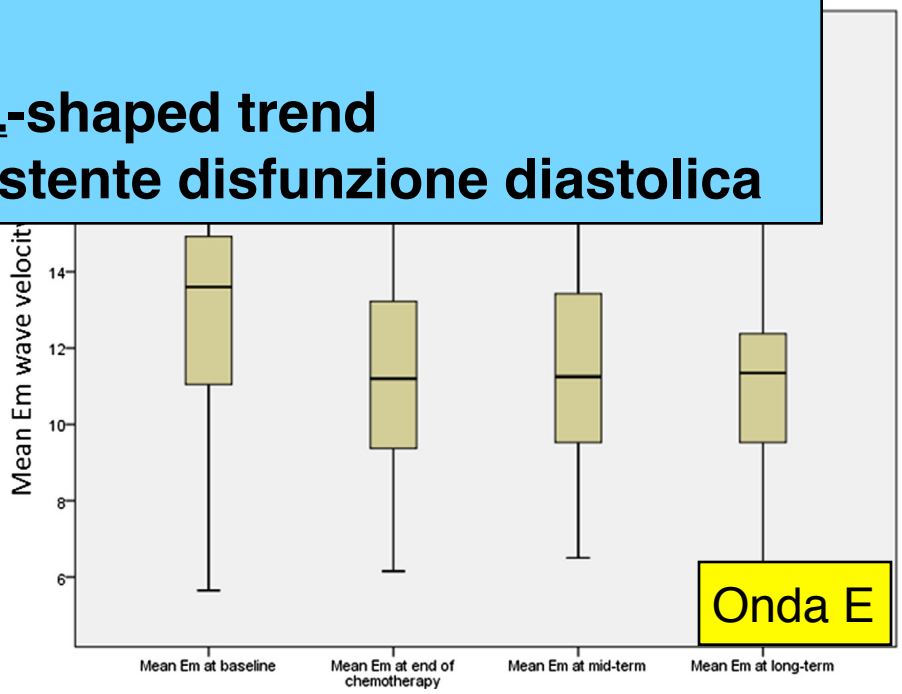
CONCLUSIONI:

- **EF con V-shaped trend**
- **Onde E ed E'$_{lat/sett}$ con L-shaped trend**

➜ recupero EF, ma persistente disfunzione diastolica







Evaluation of early subclinical cardiotoxicity of chemotherapy in breast cancer

Hayri Alıcı, Ozan Balakan[1], Süleyman Ercan[2], Musa Çakıcı[3], Fethi Yavuz[4], Vedat Davutoğlu[2]

Clinic of Cardiology, 25 Aralık State Hospital, Gaziantep-*Turkey*
[1]Department of Oncology, Faculty of Medicine, Sütçü İmam University; Kahramanmaraş-*Turkey*
[2]Department of Cardiology, Faculty of Medicine, Gaziantep University; Gaziantep-*Turkey*
[3]Department of Cardiology, Faculty of Medicine, Adıyaman University; Adıyaman-*Turkey*
[4]Clinic of Cardiology, Dr. Ersin Arslan State Hospital; Gaziantep-*Turkey*

Tissue Doppler imaging may be more sensitive than ECG, conventional ECHO and Doppler for determining the subclinical cardiac damage.

Methods: Fifty-one patients consecutively enrolled to this prospective cohort study. All patients were diagnosed as breast cancer at oncology hospital in University of Gaziantep. Before chemotherapy, all of the patients underwent to detailed ECG and echocardiography (ECHO) examinations. After 6 months, detailed ECG and ECHO examinations were repeated and compared with baseline values. Statistical analysis was performed using Shapiro-Wilk tests, Student t-test and Spearman correlation test.

Results: The average age of patients was 51 and one was male. Statistically significant decrease in ejection fraction was found after treatment (62.3%±3.3 and 59.9%±5.9, p=0.002). Evaluation of diastolic parameters; significant increase in the transmitral A flow velocity and significant decrease of E/A ratio were observed on Doppler ECHO analysis (77.4±19.1 cm/sec versus 86±18 cm/sec, p<0.001; 1.01±0.3 versus 0.9±0.2, p=0.03, respectively). On tissue Doppler analysis we observed that significant reduction in the value of E' and significantly increase E/E' ratio were present (12.5±3.6 cm/sec versus 10.7±2.9 cm/sec, p=0.001; 6.6±2.9 versus 7.7±3.3, p=0.04, respectively).

Conclusion: Chemotherapy has detrimental subclinical effect on both of systolic and diastolic function in early six months period despite the prescription of lower dosage of chemotherapy than well-known cardiac safety dosage limits. Tissue Doppler imaging may be more sensitive than ECG, conventional ECHO and Doppler for determining the subclinical cardiac damage. *(Anadolu Kardiyol Derg 2015; 15(0): 000-000)*

Key words: breast cancer, chemotherapy, echocardiography, tissue Doppler imaging, cardiotoxicity

Incidence, Predictors, and Impact on Survival of Left Ventricular Systolic Dysfunction and Recovery in Advanced Cancer Patients

Guilherme H. Oliveira, MD[a,*], Siddarth Mukerji, MD[b], Adrian V. Hernandez, MD[c,d], Marwan Y. Qattan, MD[a], Jose Banchs, MD[e], Jean-Bernard Durand, MD[e], Cezar Iliescu, MD[e], Juan Carlos Plana, MD[f], and W.H. Wilson Tang, MD[f]

Although left ventricular (LV) dysfunction occurs not uncommonly in the course of cancer therapy, little is known about its natural history and prognostic impact on patients. To investigate the incidence, predictors, and impact on survival of LV systolic dysfunction and recovery during cancer therapy, we conducted a retrospective cohort observational study over 1 year at the University of Texas MD Anderson Cancer Center. We enrolled patients with a decrease in ejection fraction by echocardiography to <50% while undergoing cancer therapy from January 2009 to December 2009. We collected and analyzed their chart data. Of 7,648 patients with echocardiograms in 2009, 366 (4.8%) had ejection fraction <50% and 104 met study criteria. LV systolic dysfunction was associated with cardiotoxic therapy in 53 patients (51%). Recovery occurred in 57 patients (55%) and was independently predicted by younger age, smaller left atrial volume index, and lower B-type natriuretic peptide. At last follow-up, 69 patients (66%) were dead, and 35 (34%) were alive. There was a 20% advantage in 2-year survival among patients with LV systolic recovery compared with those without (95% confidence interval 4% to 41%, p = 0.02). In this retrospective study, LV systolic dysfunction recovery occurred in over half of the patients, appeared independent of cardiotoxic etiology, and associated with a 20% survival benefit at 2 years. Multivariable predictors of recovery are

CONCLUSIONI - PREDITTORI DI RECUPERO (EF ↑ 10%):

- **Età più giovane** (52 ± 16 vs 58 ± 16 aa)
- **Volumetria atrio sn più bassa** (26 ± 8 vs 33 ± 10 ml/m²)**: < 30 ml/m²**
- **Valori più bassi di BNP** (577 vs 1332) - non variazioni TnI

Assessing Anthracycline-Treated Childhood Cancer Survivors With Advanced Stress Echocardiography

A. Blythe Ryerson, PhD, MPH,[1]* William L. Border, MBChB, MPH,[2,3] Karen Wasilewski-Masker, MD, MSc,[3,4] Michael Goodman, MD, MPH,[1] Lillian Meacham, MD,[3,4] Harland Austin, DSc,[1] and Ann C. Mertens, PhD[1,3,4]

Background. Surveillance for anthracycline cardiotoxicity in cancer survivors typically utilizes resting M-mode and two-dimensional echocardiography, which are insensitive to detection of subtle myocardial changes. We examined childhood cancer survivors treated with anthracyclines during exercise using various echocardiography techniques to investigate if these tools can better detect subclinical cardiac dysfunction. ***Procedure.*** We recruited asymptomatic survivors at least five years post treatment. Echocardiography was performed at rest and at termination of exercise utilizing tissue Doppler techniques and strain rate imaging. ***Results.*** Eighty participants were characterized by cardiotoxicity risk status (high [12], moderate [23], low [24], no risk [21]) as defined by the Children's Oncology Group Long Term Follow-Up Guidelines v3.0. The high-risk group had a higher resting heart rate than controls (100 vs. 88 bpm [*P* for trend = 0.049]). Peak aerobic capacity in all groups was similar. Compared to controls at rest, the high-risk group had evidence of diastolic dysfunction with lower E/A ratios (1.4 vs. 2.0, $P = 0.008$) and higher septal early diastolic velocities (E/E′) of 11.7 versus 9.9 ($P = 0.165$). With exercise, this difference resolved and myocardial contractile reserve was preserved. ***Conclusions.*** Asymptomatic, pediatric cancer survivors at high-risk for anthracycline cardiotoxicity have some evidence of diastolic filling abnormalities at rest. With exercise, they augment their systolic and diastolic function to achieve normal maximal aerobic capacity suggesting they are able to compensate for mild cardiac dysfunction in the early years after exposure. Additionally, findings suggest that routine exercise echocardiography may not be a useful surveillance tool to assess anthracycline cardiotoxicity. Pediatr Blood Cancer

Key words: anthracyclines; echocardiography; neoplasms; pediatrics; stress; survivors

CONCLUSIONI:

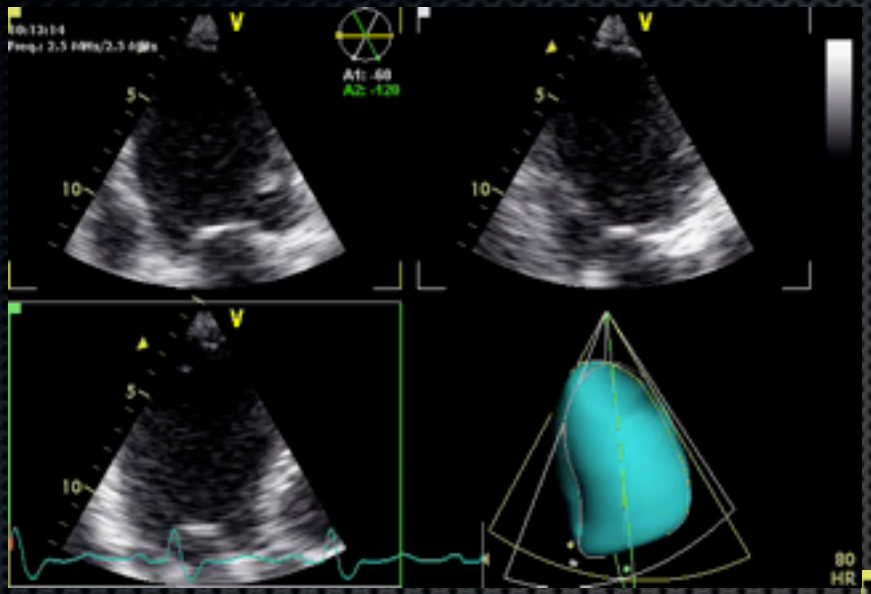
- **nei survivors EF normale, ma presenza di disfunzione diastolica**
- **durante esercizio aumento funzione sistodiastolica**

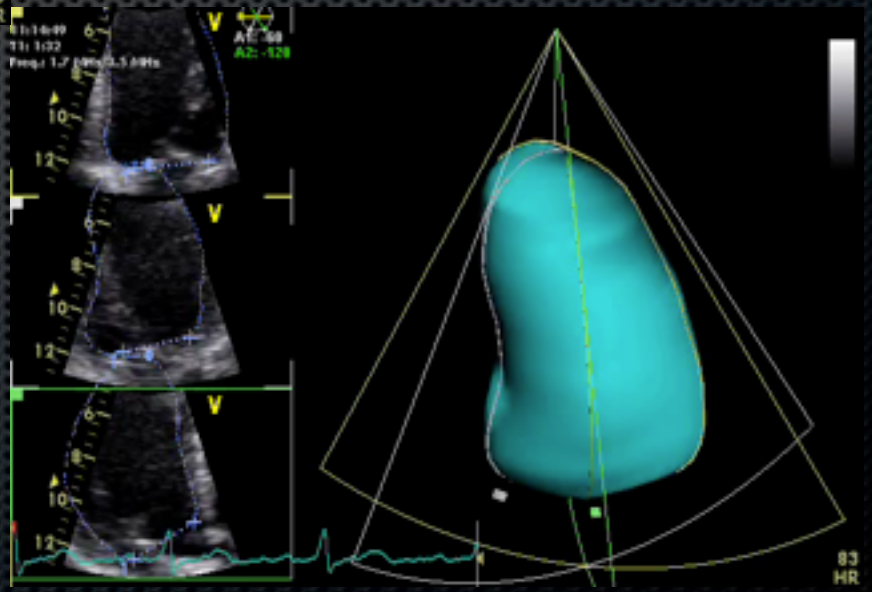
NUOVE TECNOLOGIE

3D-ECHO REAL TIME

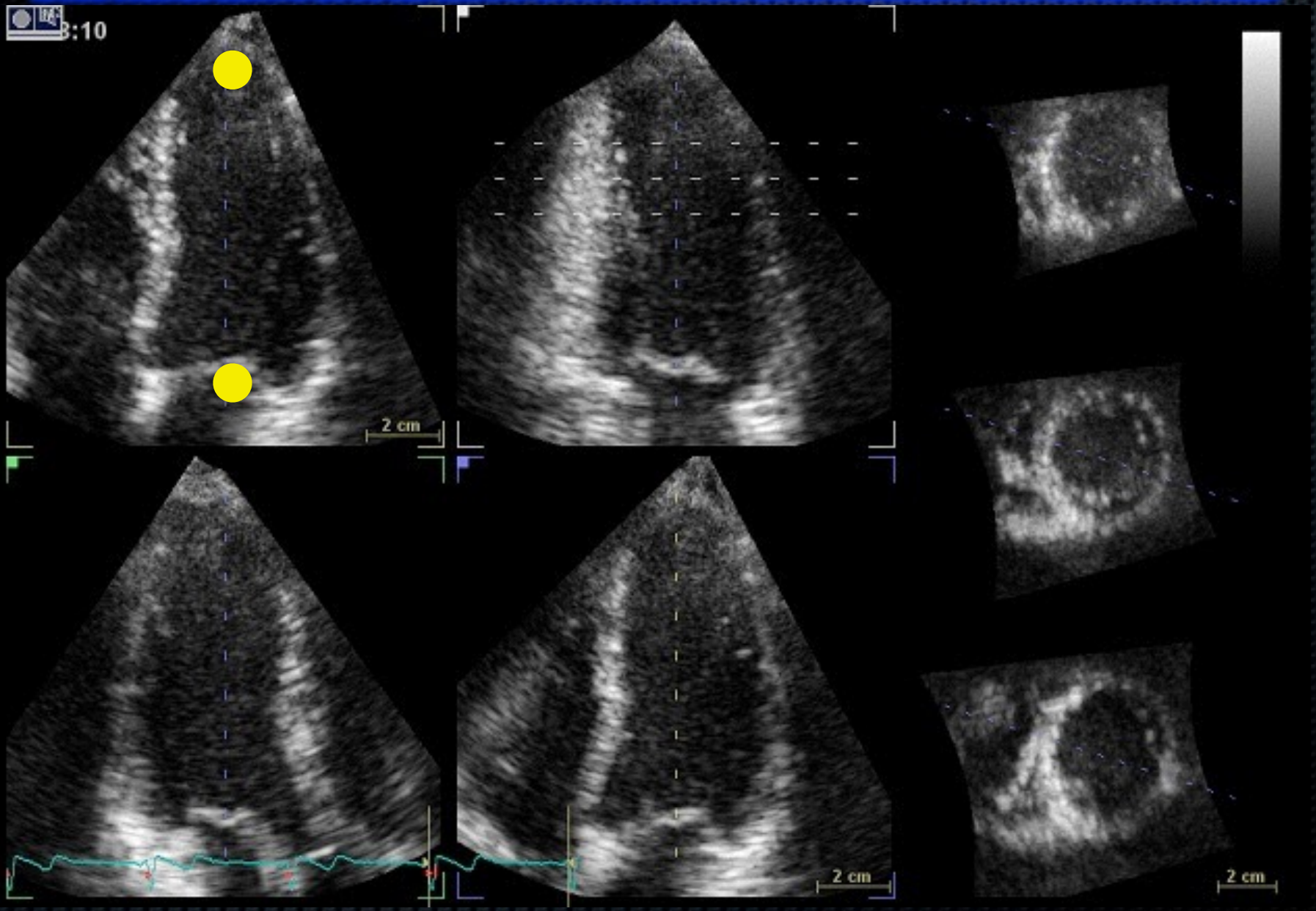
2D/3D STRAIN

3D TRIPLANO

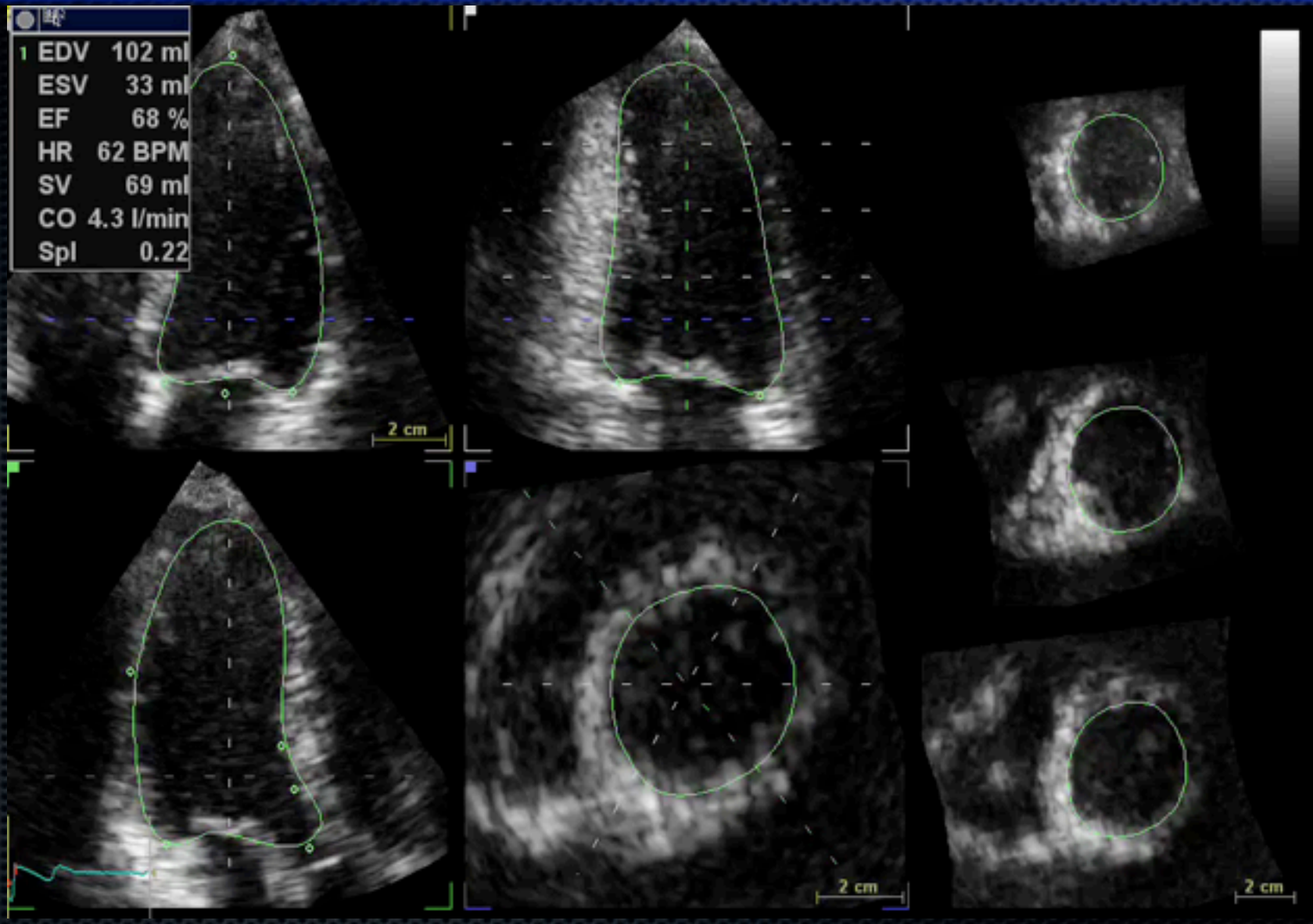




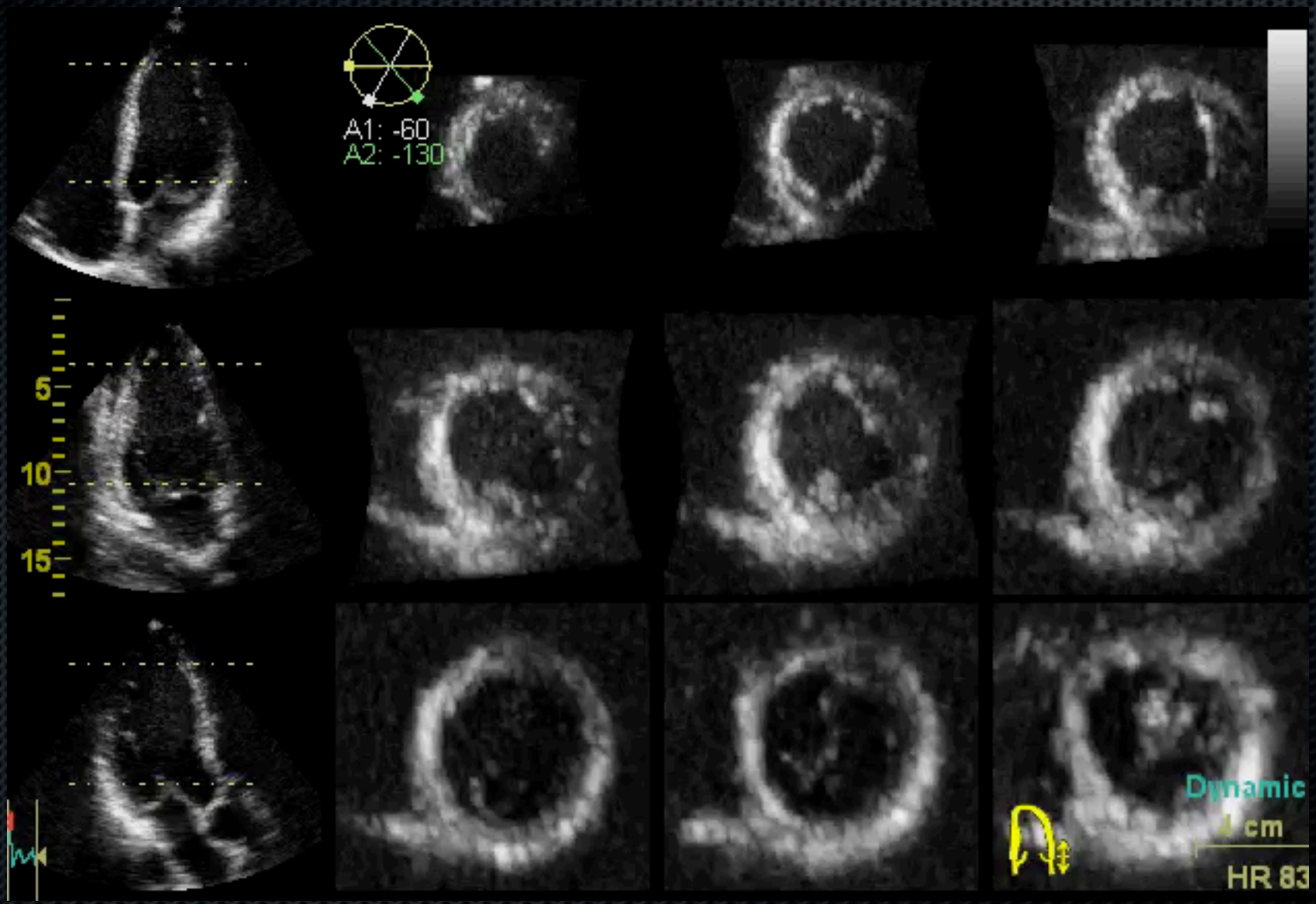
SINGLE BEAT



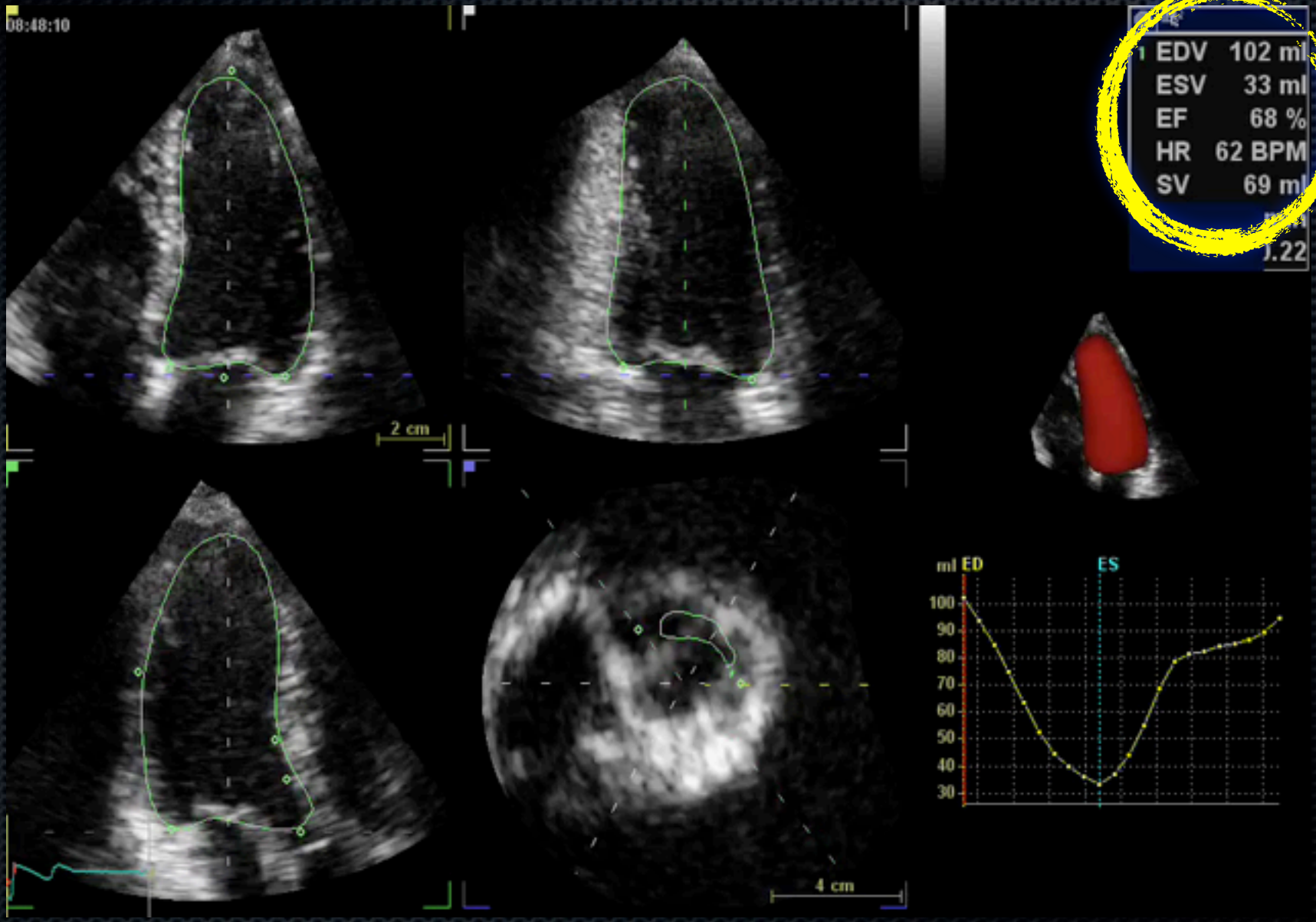
BORDO SEMI-AUTOMATICO



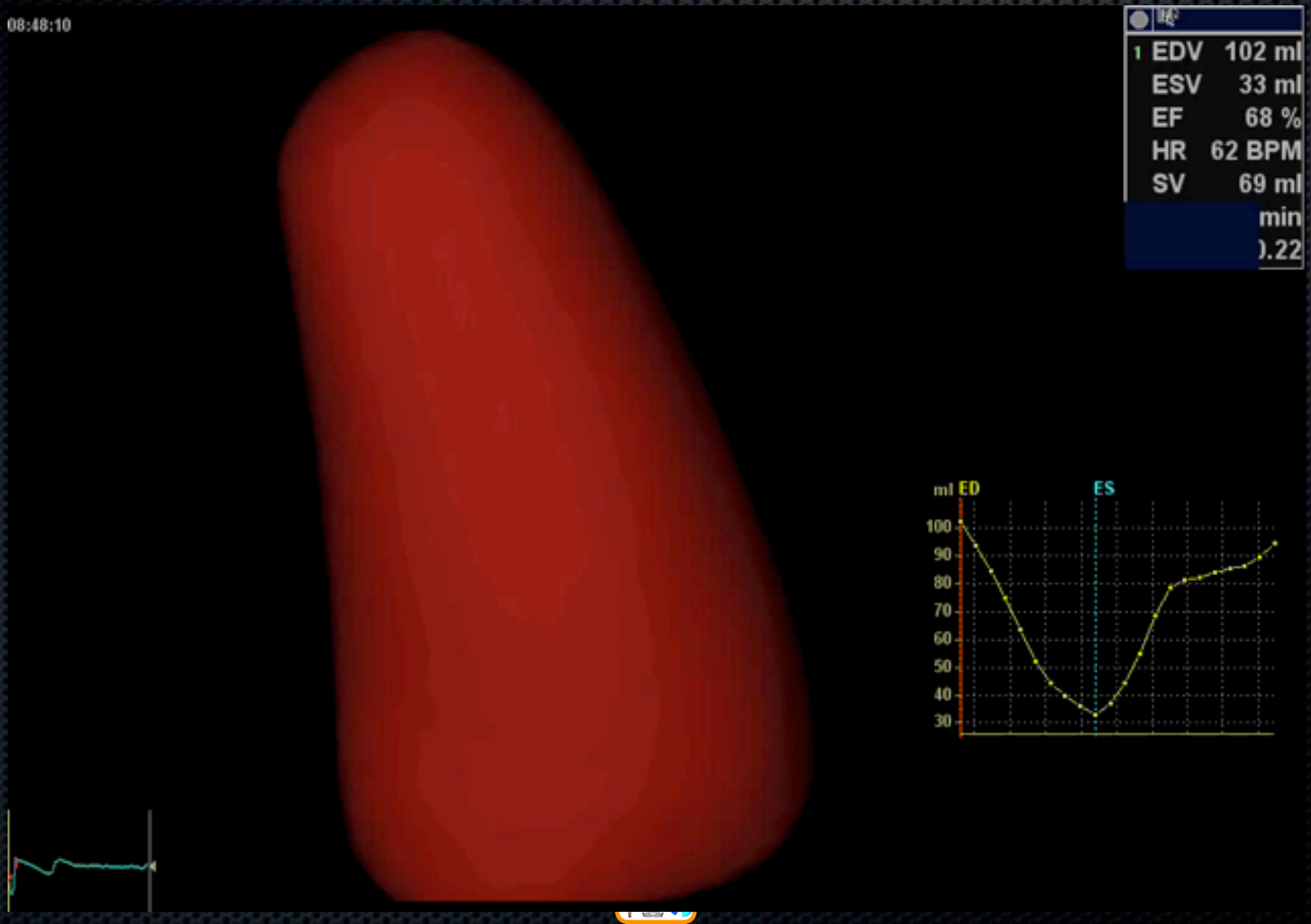
SINGLE BEAT: DYNAMIC 12 SLICES



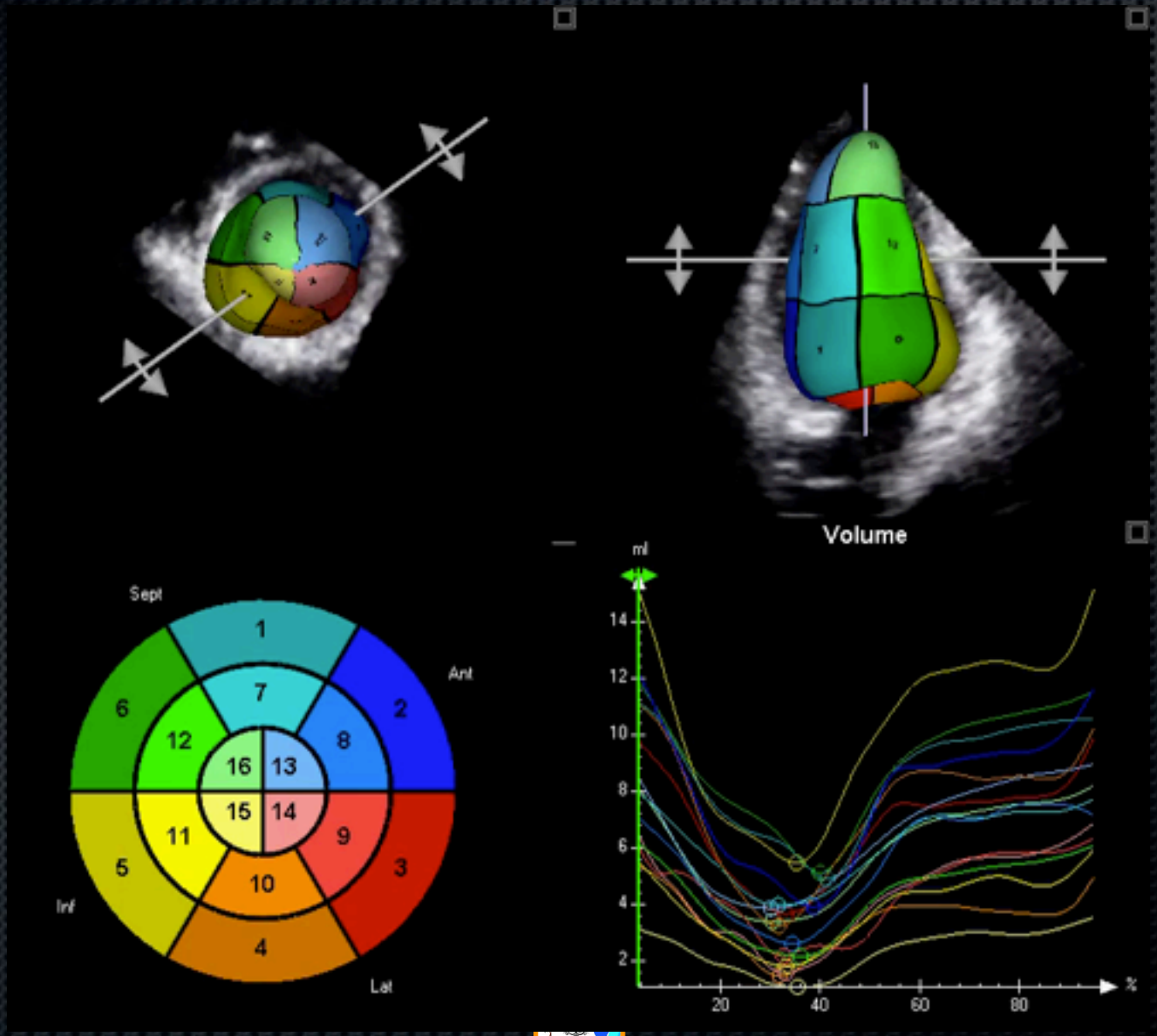
CURVA VOLUME - TEMPO



RENDERING 3D



CURVE VOLUME-TEMPO 16 SEGM.



European Journal of Echocardiography Advance Access published January 6, 2010

European Journal of Echocardiography
doi:10.1093/ejechocard/jep217

Validation of a novel automated border-detection algorithm for rapid and accurate quantitation of left ventricular volumes based on three-dimensional echocardiography

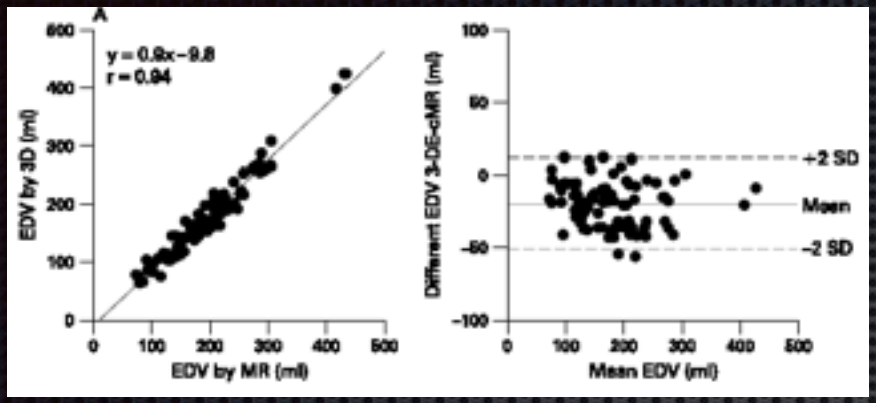
Denisa Muraru[1*], Luigi P. Badano[2], Gianluca Piccoli[3], Pasquale Gianfagna[2], Lorenzo Del Mestre[2], Davide Ermacora[2], and Alessandro Proclemer[2]

Table 2 Comparison of left ventricular volumes and ejection fraction of the 23 patients in the validation group with the results of cardiac magnetic resonance (means ± SD)

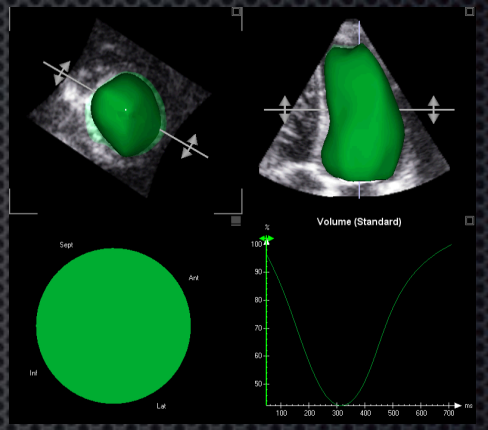
n = 23	2DE	Corrected 4D AutoLVQ	Fully automated 4D AutoLVQ	4D TomTec	CMR
EDV (mL)	110 ± 30*	126 ± 34	104 ± 30*	129 ± 34	137 ± 36
ESV (mL)	49 ± 17*	56 ± 20	51 ± 17*	58 ± 21	65 ± 20
EF (%)	55 ± 9	56 ± 8	52 ± 7	56 ± 8	53 ± 8

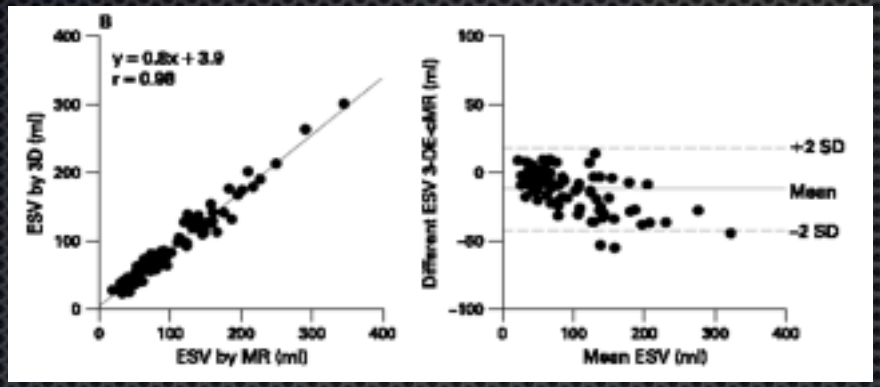
EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; 2DE, two-dimensional echocardiography; CMR, cardiac magnetic resonance.
*$P \leq 0.01$, paired *t*-test compared with CMR values.

Eco 3D vs MRI in pz con/senza anomalie del wall motion: Volumi e Frazione di Eiezione

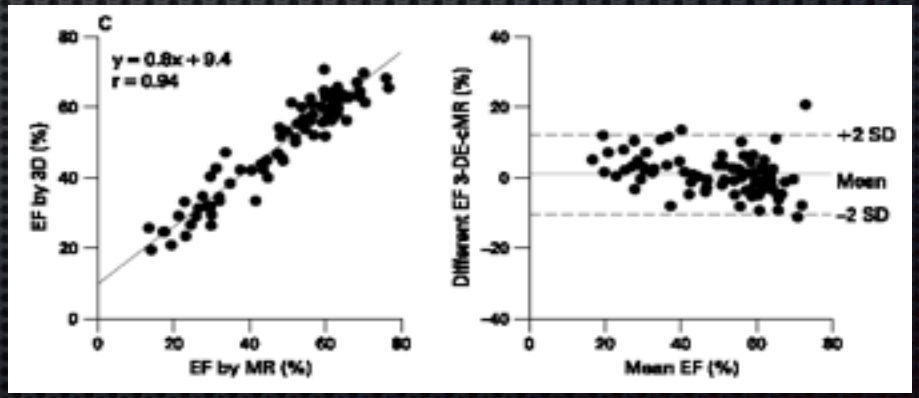


-20 ± 31





-12 ± 21



5 ± 10

Pouleur AC et al, Heart 2008;94:1050-1057

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Cardiac Imaging

Reproducibility of Echocardiographic Techniques for Sequential Assessment of Left Ventricular Ejection Fraction and Volumes

Application to Patients Undergoing Cancer Chemotherapy

Paaladinesh Thavendiranathan, MD, MSc, Andrew D. Grant, MD, Tomoko Negishi, MD, Juan Carlos Plana, MD, Zoran B. Popović, MD, PhD, Thomas H. Marwick, MD, PhD, MPH

Cleveland, Ohio

Confronto tra 2D-biplano, 2D-biplano/contrasto, Triplano, Triplano/contrasto, 3D, 3D/contrasto

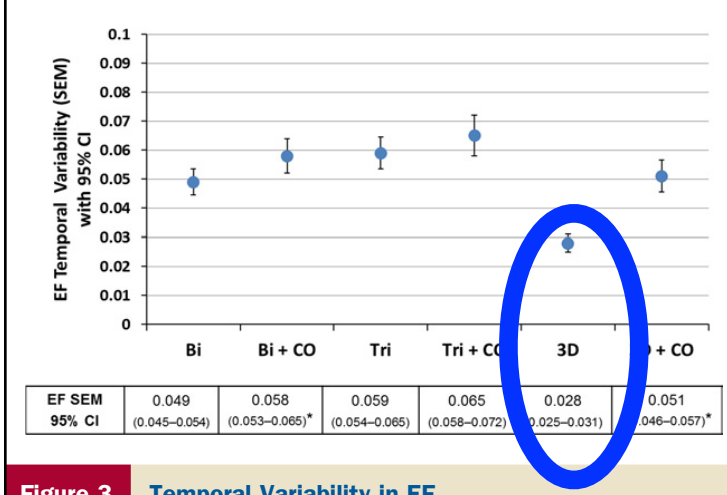


Figure 3 **Temporal Variability in EF**

The temporal variability is defined as the standard error of measurement (SEM) and 95% confidence intervals (CIs) for each technique for the entire follow-up period. Noncontrast 3D had the lowest temporal variability and 95% CI for EF measurements **(lower panel)** compared with all methods ($p < 0.01$ for all comparisons against noncontrast 3D). *$p < 0.05$ for comparison of contrast enhanced to noncontrast acquisition for the respective technique. Abbreviations as in Figure 1.

Conclusions Noncontrast 3DE was the most reproducible technique for LVEF and LV volume measurements over 1 year of follow-up. (J Am Coll Cardiol 2013;61:77–84) © 2013 by the American College of Cardiology Foundation

Table 2 **Interobserver and Intraobserver Variability and Minimal Detectable Change for EF Measurements by All 6 Techniques**

	Bi	Bi + Co	Tri	Tri + Co	3D	3D + Co
Intraobserver	0.033*	0.035*	0.038*	0.037*	0.017	0.026
Min Δ detectable	0.090	0.098	0.104	0.102	0.048	0.072
Interobserver	0.040	0.051*	0.049*	0.048*	0.027	0.038
Min Δ detectable	0.111	0.142	0.135	0.133	0.075	0.100
Interobserver test-retest	0.047*	0.055*	0.058*	0.069*	0.022	0.042*
Min Δ detectable	0.013	0.152	0.162	0.192	0.060	0.115

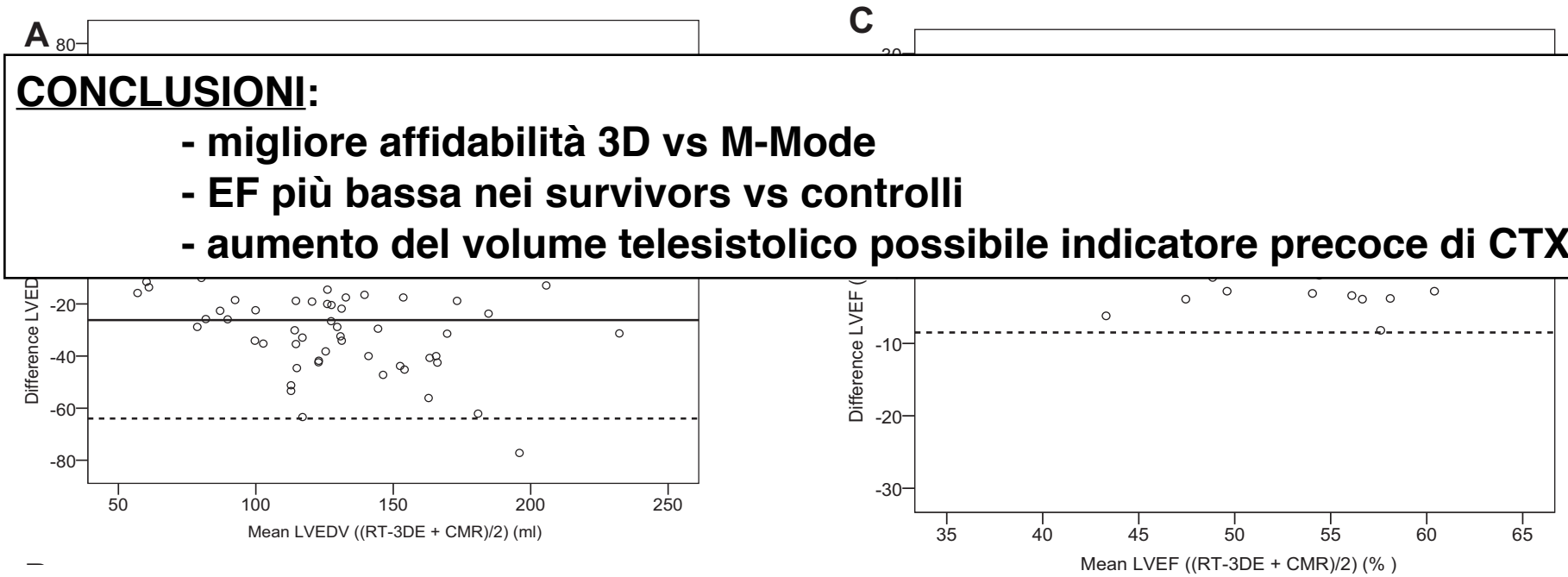
Noncontrast 3D had the lowest intraobserver and interobserver test-retest observer variability and the smallest minimal detectable change. An ejection fraction (EF) of .033 corresponds to 3.3%. *$p < 0.01$ *t* test compared with noncontrast 3D.

Bi = biplane Simpson's; BP + Co = biplane Simpson's with contrast; Tri = triplane; Tri + Co = triplane + contrast; 3D = 3-dimensional; 3D + Co = 3-dimensional with contrast.

Three-Dimensional Echocardiography and Cardiac Magnetic Resonance Imaging in the Screening of Long-Term Survivors of Childhood Cancer After Cardiotoxic Therapy

Kaisa Ylänen, MD[a,b,*], Anneli Eerola, MD, PhD[a], Kim Vettenranta, MD, PhD[c,d], and Tuija Poutanen, MD, PhD[a,b]

3D vs m-mode

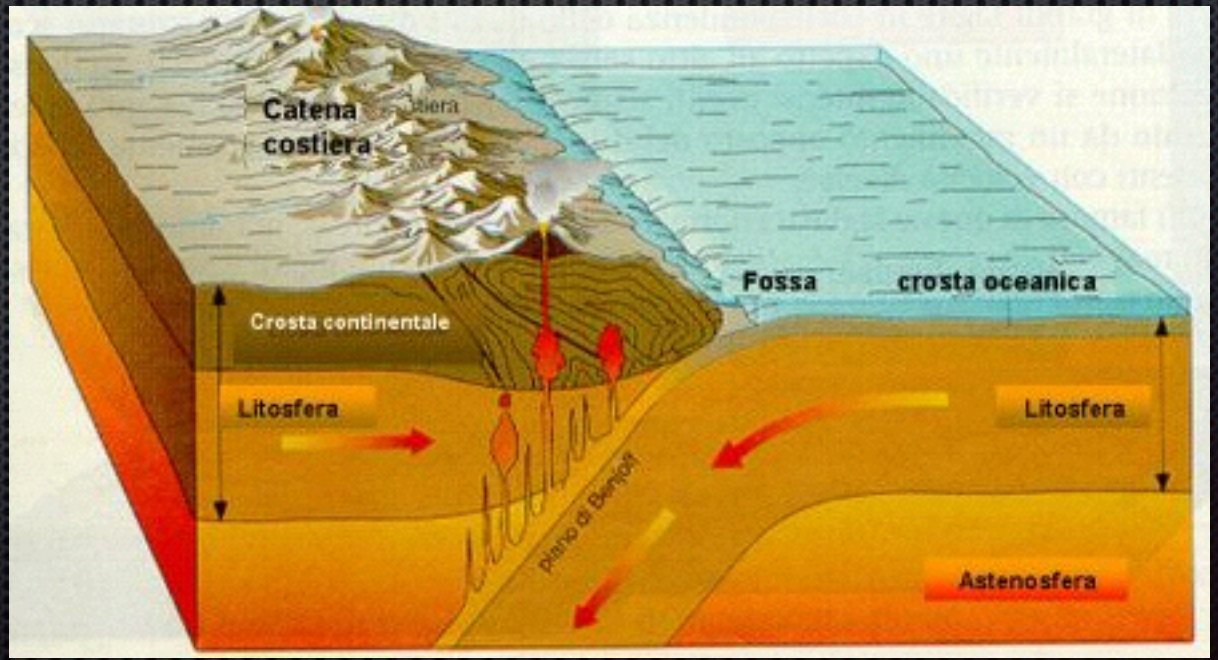


CONCLUSIONI:

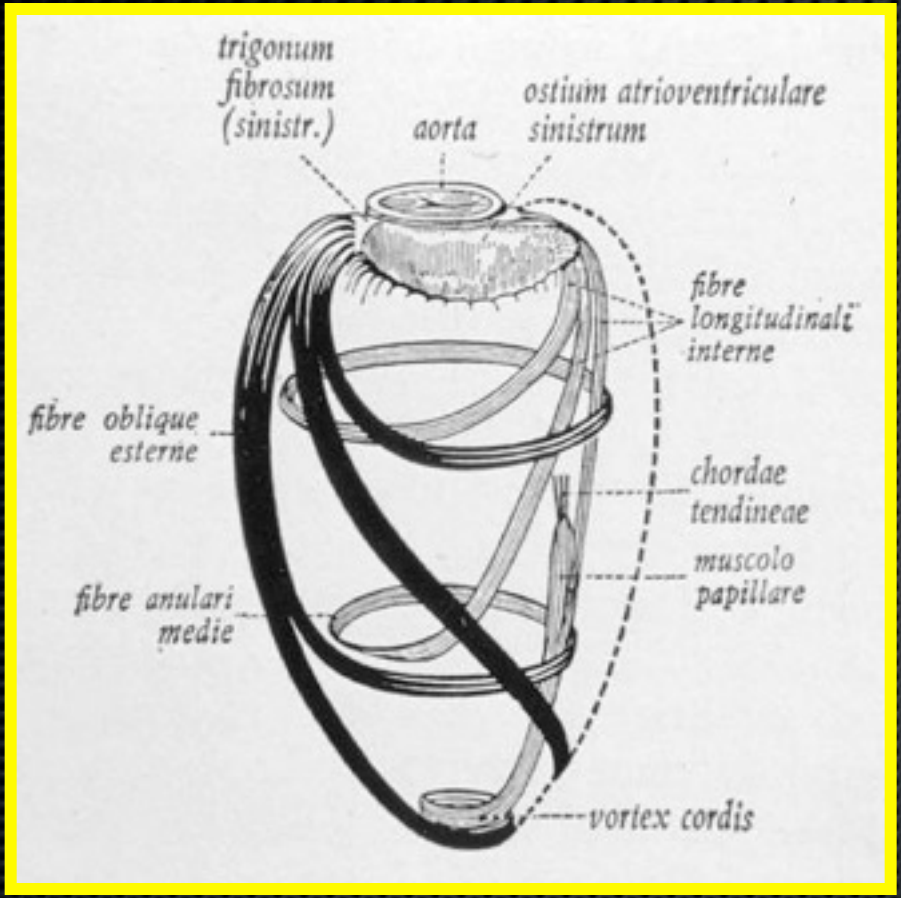
- **migliore affidabilità 3D vs M-Mode**
- **EF più bassa nei survivors vs controlli**
- **aumento del volume telesistolico possibile indicatore precoce di CTX**

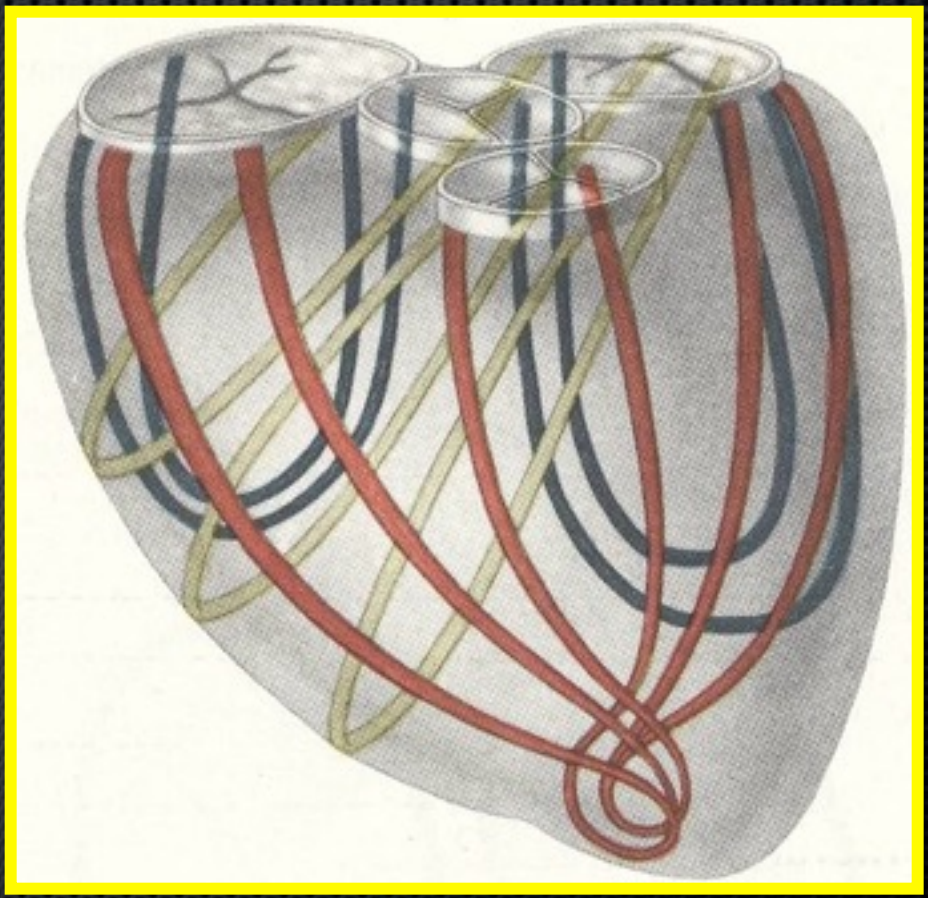
71 survivors - GRUPPO 1: ANTH (n = 63); GRUPPO 2: ANTH + RXTH N = 8)

LO STRAIN
MOVIMENTO e DEFORMAZIONE



IL CUORE: FASCI MUSCOLARI





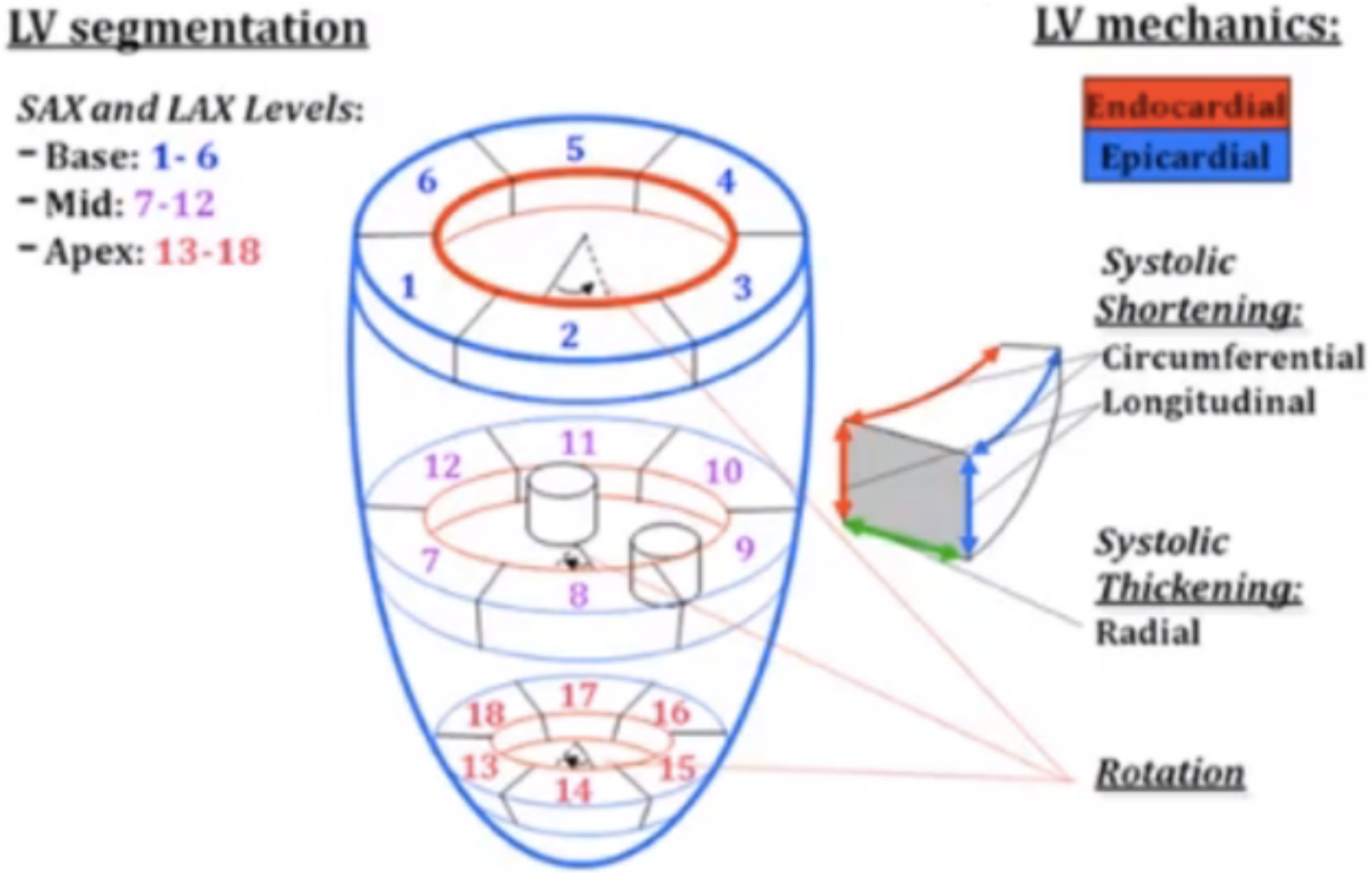
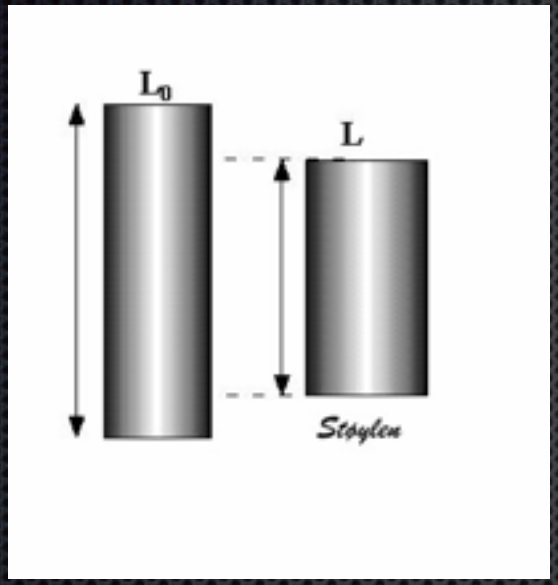


Figure 1 LV mechanical parameter orientation. LV segmentation and myocardial mechanical parameters analyzed by VVI. *LAX*, Long-axis; *SAX*, short-axis.

STRAIN RATE e STRAIN (ε) e



Derivato dal Tissue doppler

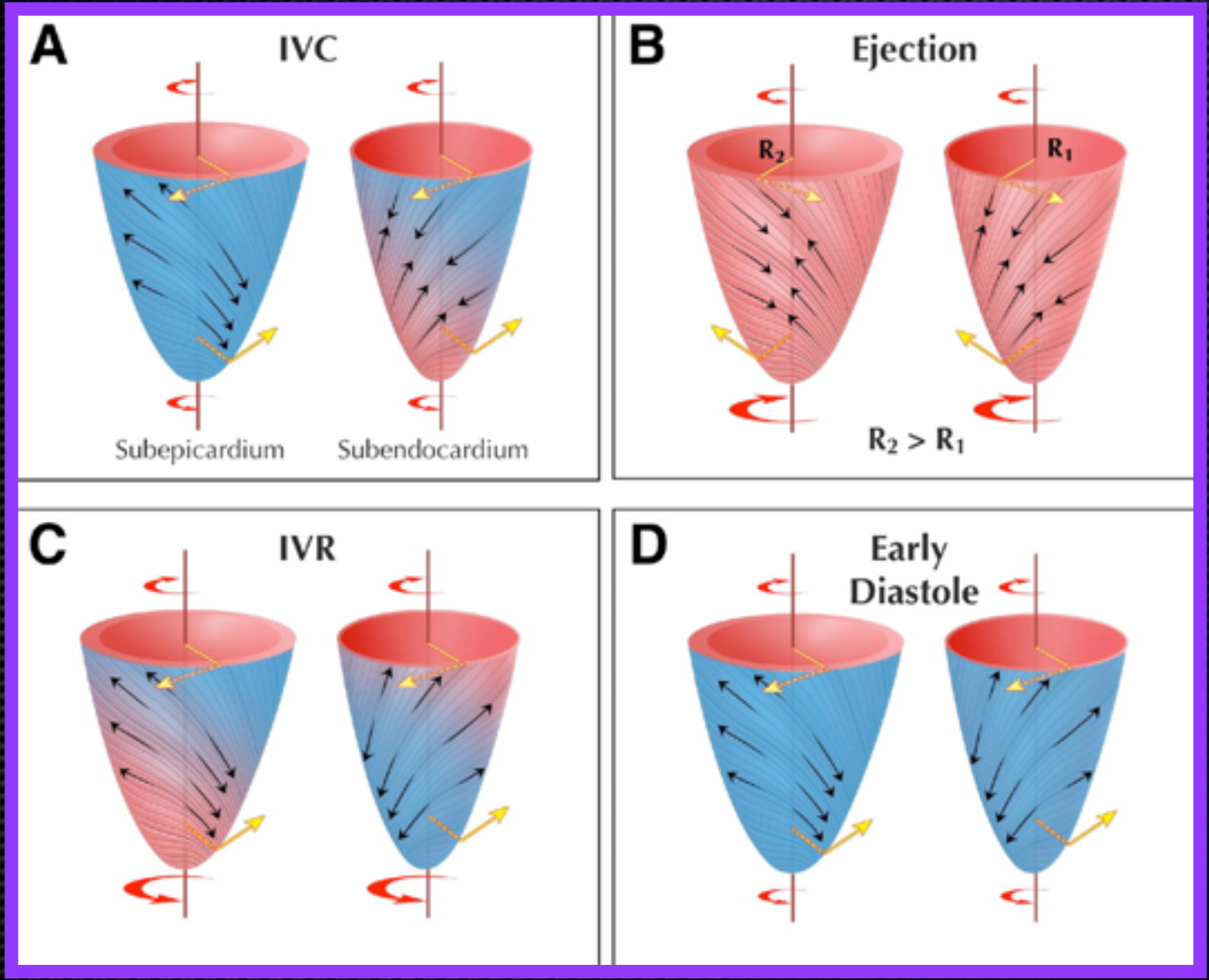
Strain rate = velocità di deformazione

Strain = quantità di deformazione (%)

$$\varepsilon = \frac{L - L_0}{L_0} = \frac{\Delta L}{L_0}$$

Stoylen

TWISTING


A
IVC
Subepicardium
Subendocardium
B
Ejection
R_2
R_1
$R_2 > R_1$
C
IVR
D
Early
Diastole

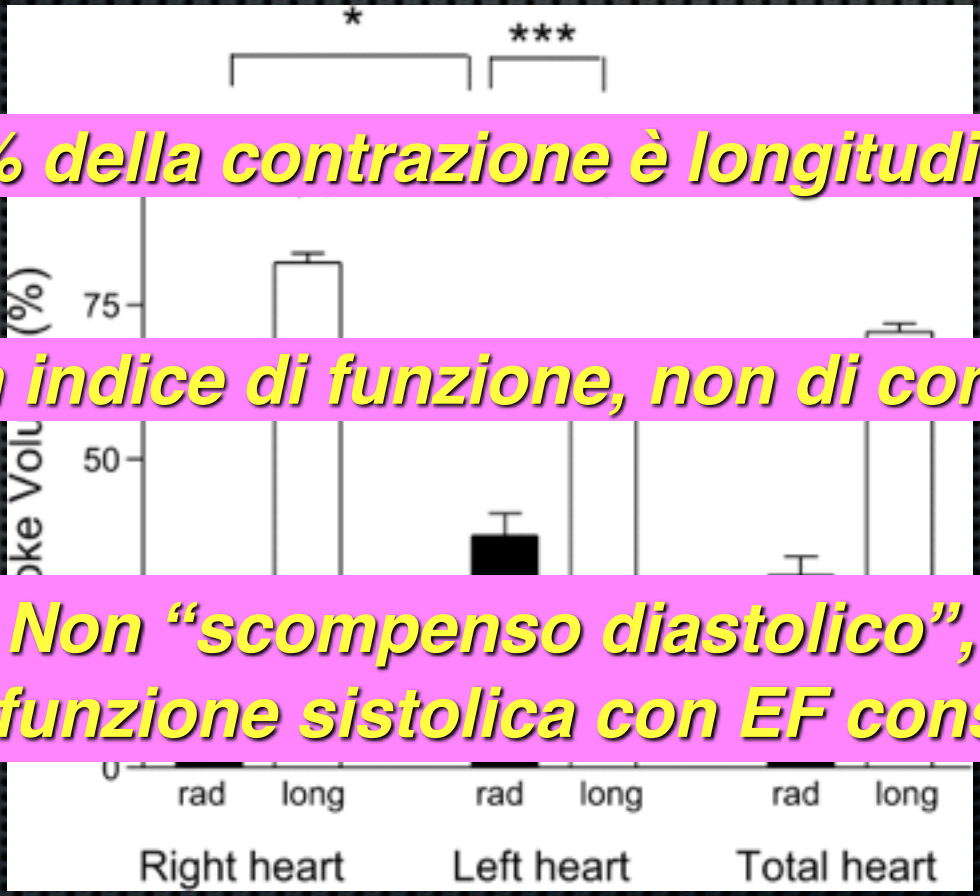
Le FIBRE MIOCARDICHE

- Subendocardio: longitudinali
- Midwall: circonferenziali
- Subepicardio: longitudinali (radiali)

L'EF valuta solo l'accorciamento radiale !

The quantitative relationship between longitudinal and radial function in left, right, and total heart pumping in humans

Marcus Carlsson, Martin Ugander, Einar Heiberg, and Hakan Arheden
Department of Clinical Physiology, Lund University Hospital, Lund, Sweden - AM J PHYSIOL HEART CIRC 2007

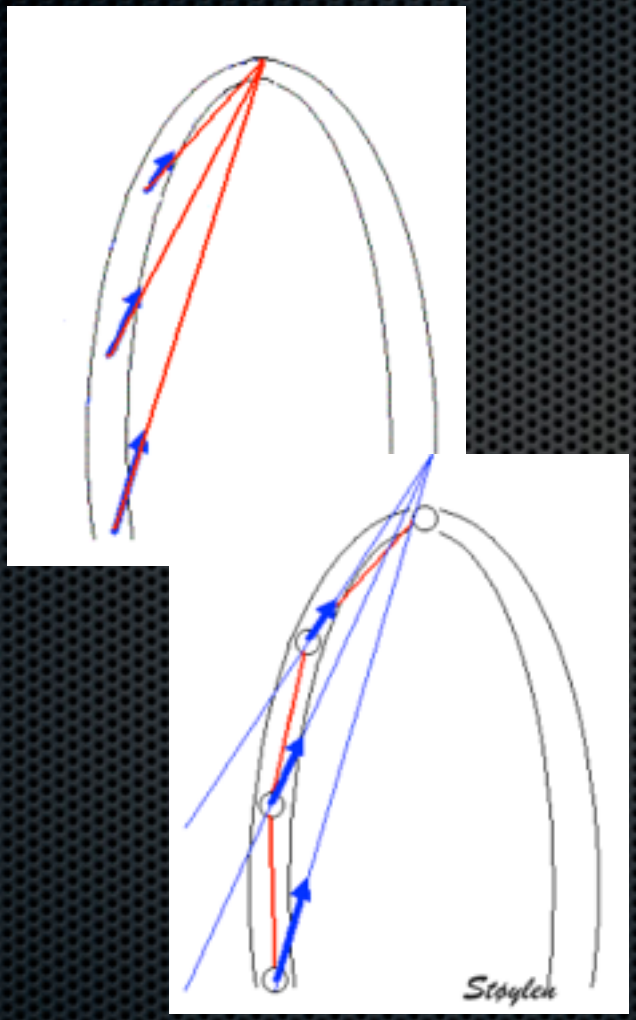


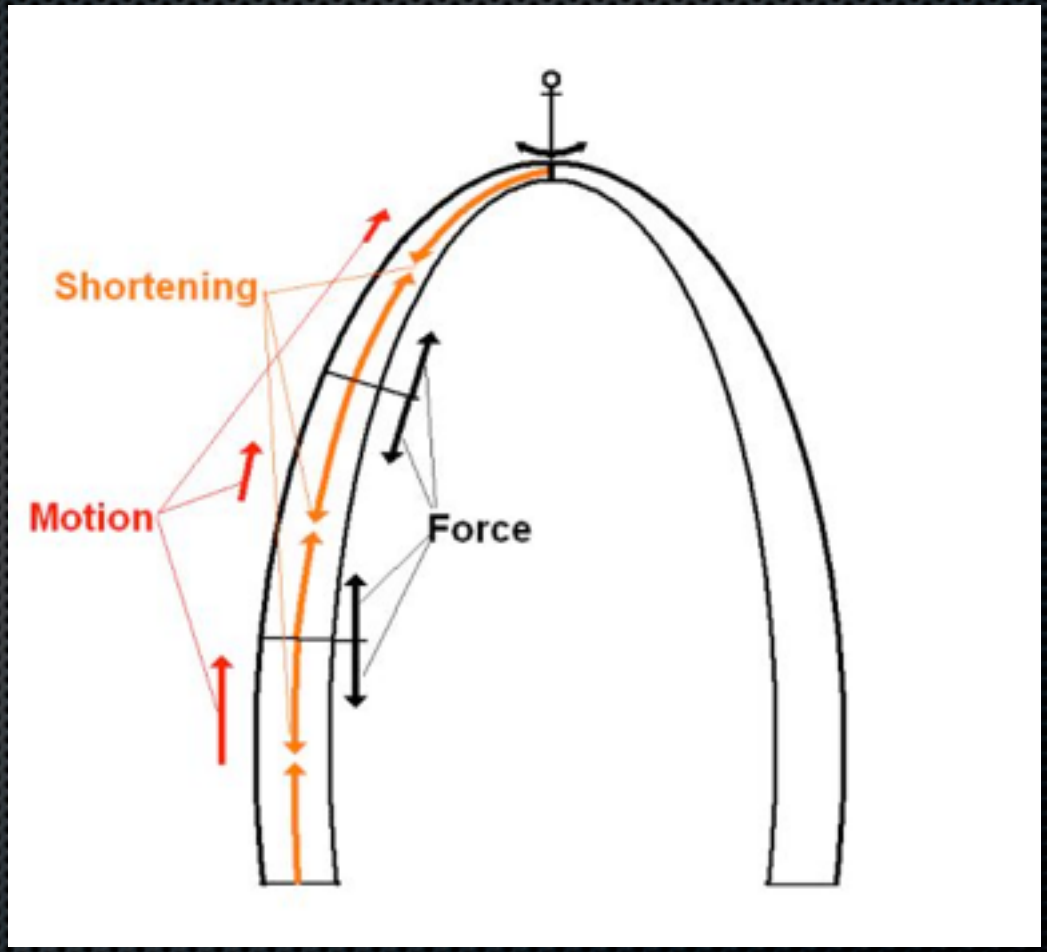
Il 60% della contrazione è longitudinale !

L'EF è un indice di funzione, non di contrattilità !

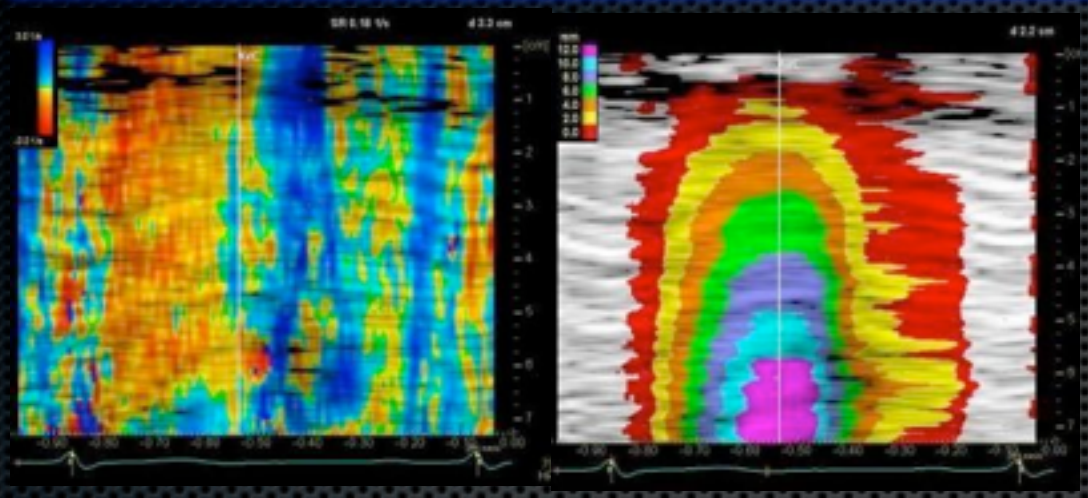
Non "scompenso diastolico",
ma disfunzione sistolica con EF conservata

MOVIMENTO SISTOLICO

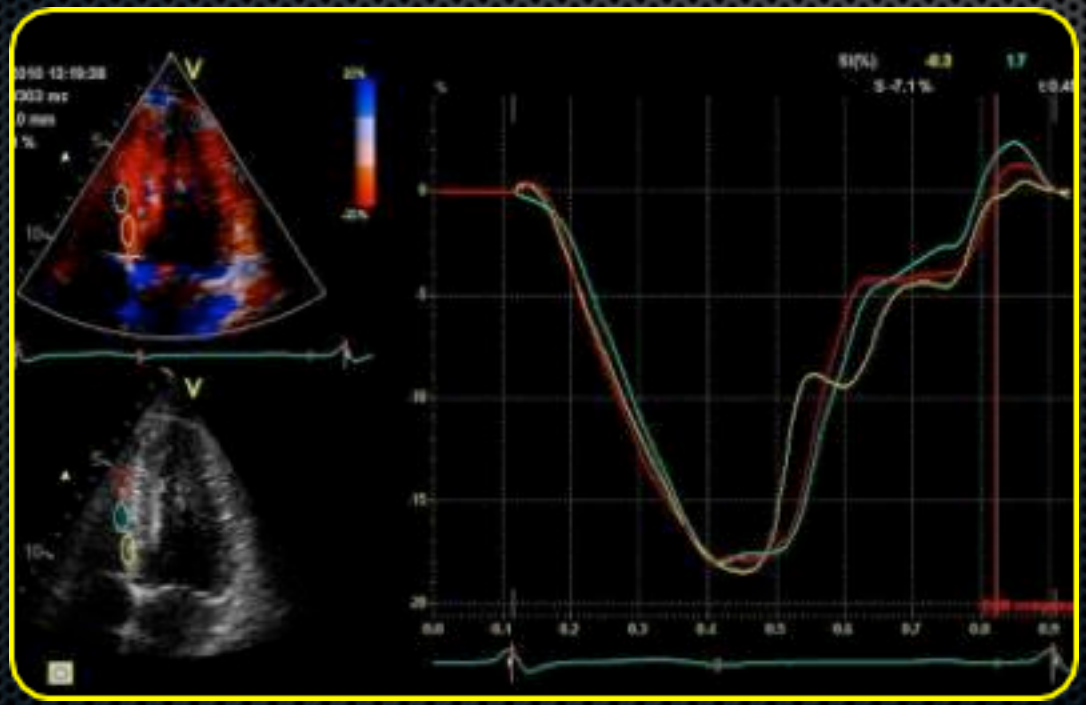




Dallo STRAIN RATE allo STRAIN

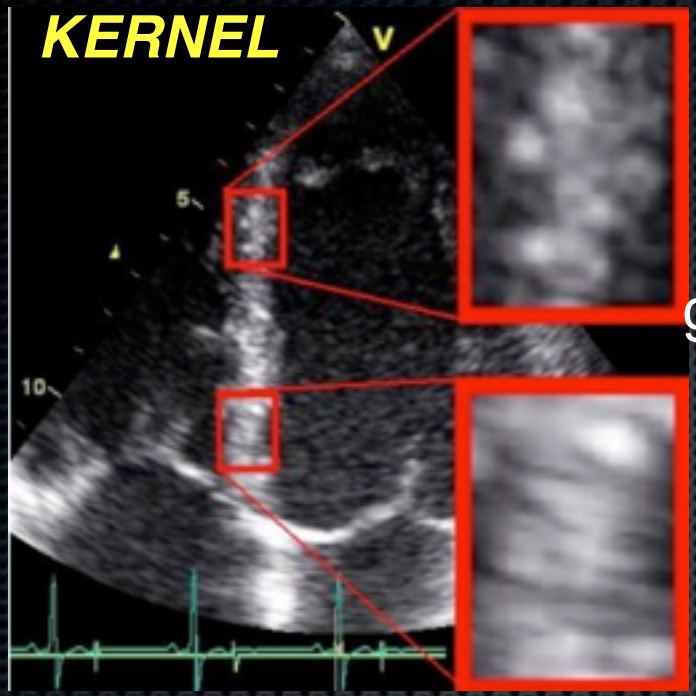


STRAIN RATE

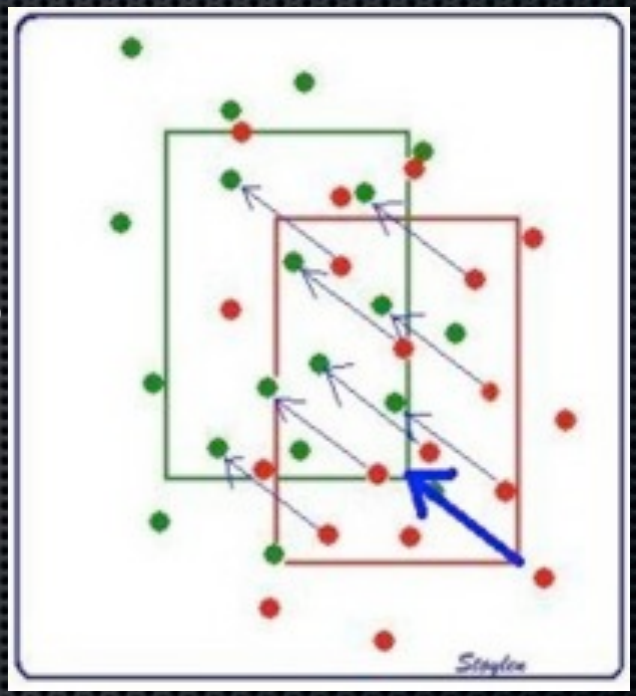


STRAIN

SPECKLE TRACKING



Lo **speckle** è una nuova metodica in grado di valutare lo strain tramite un'acquisizione standard 2D

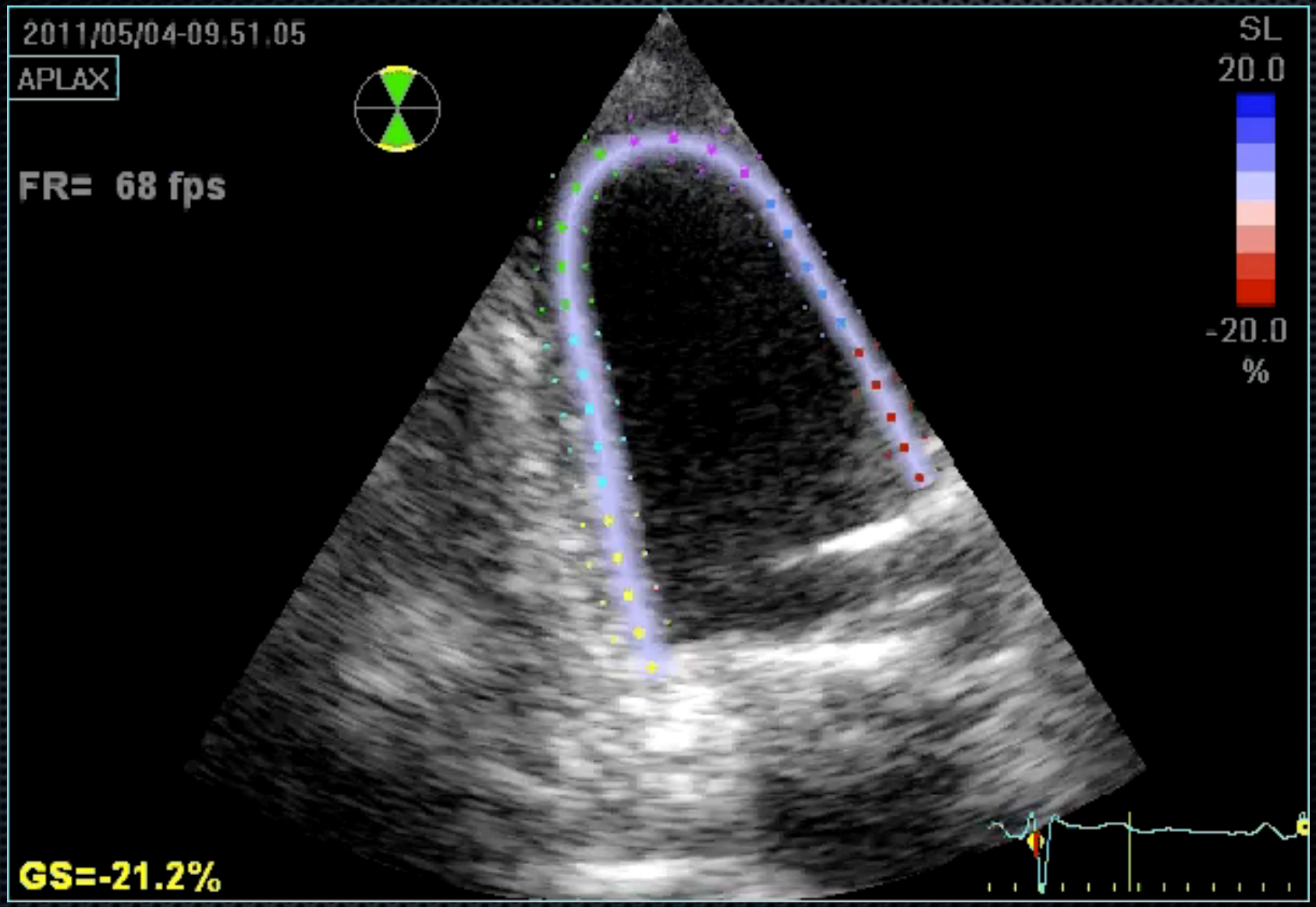


• The random distribution of the speckles ensures that each region of the myocardium has an unique pattern, a fingerprint.

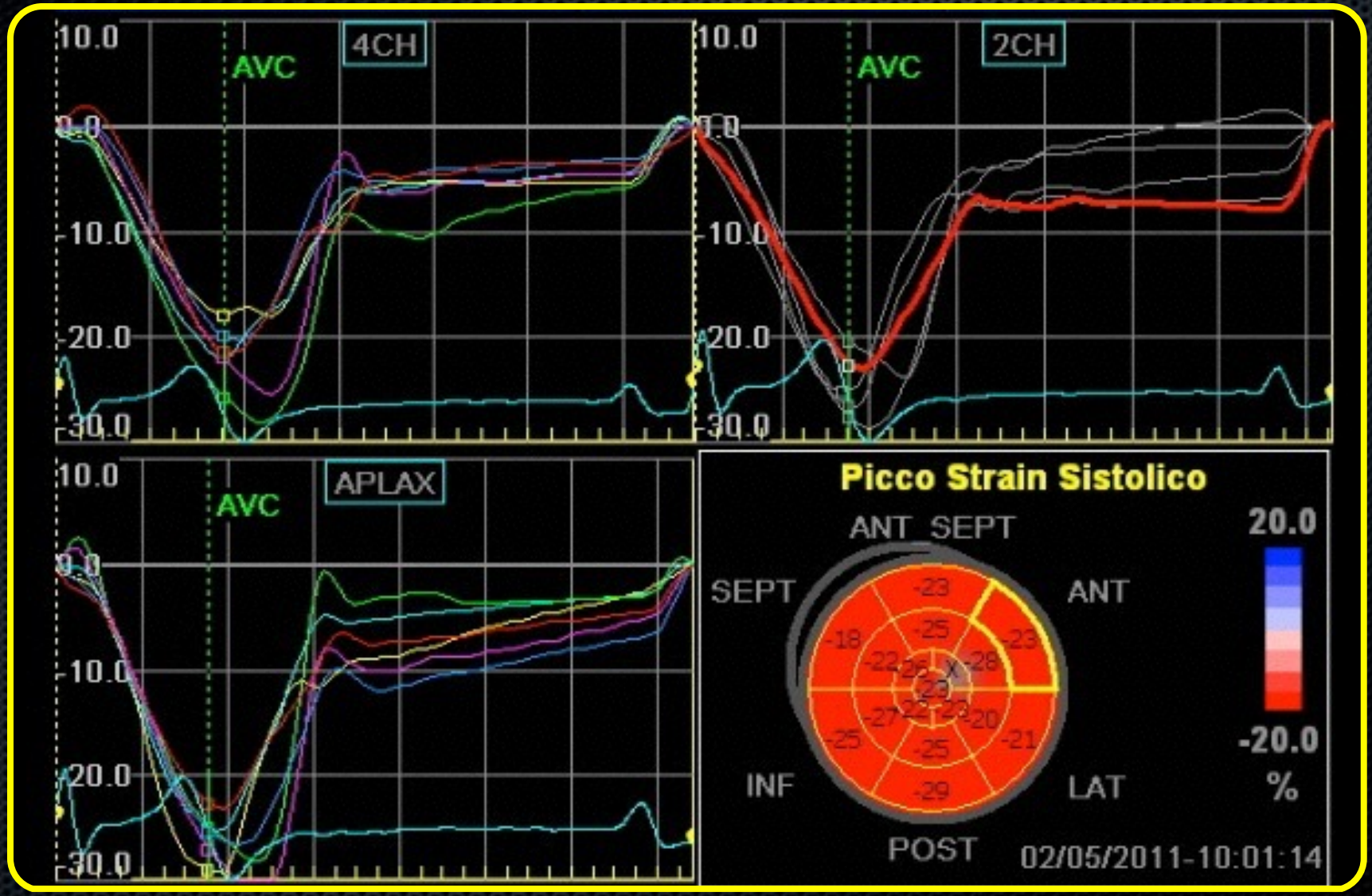
•The speckles follow the motion of the myocardium so when the myocardium moves from one frame to the next, the position of this fingerprint will shift slightly, remaining fairly constant.

•Thus, if a region (***kernel***) is defined in one frame, a search algorithm will be able to recognise the lie sized and shaped area with the most similar speckle pattern in the next frame, within a defined search area and hence, to find the new position of the kernel

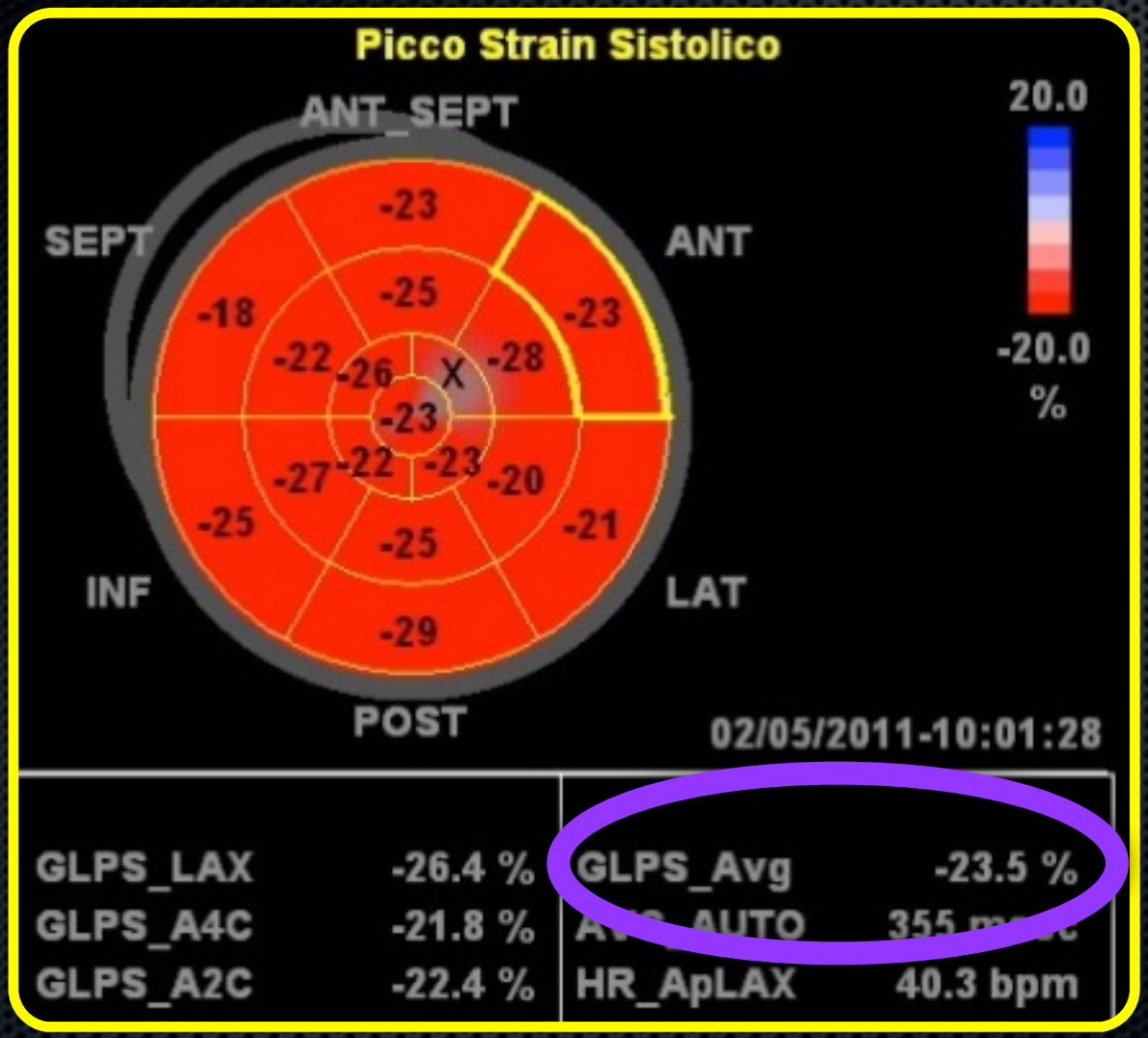
2D STRAIN: AFI



2D STRAIN: AFI



2D STRAIN: AFI - BULL'S EYE

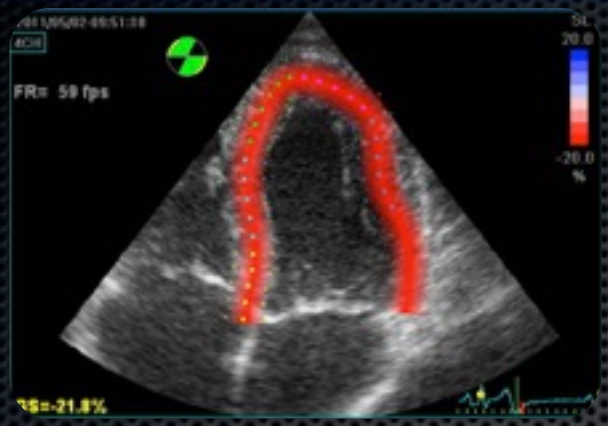


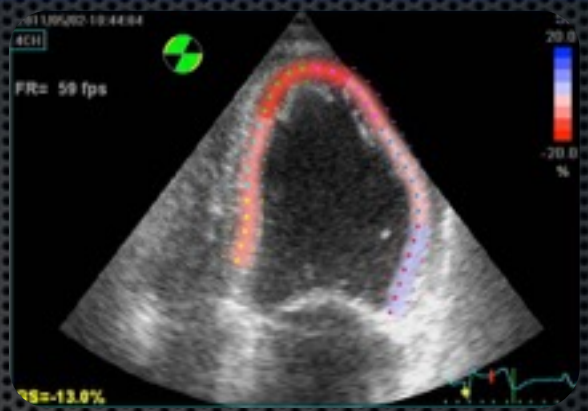
GLPS

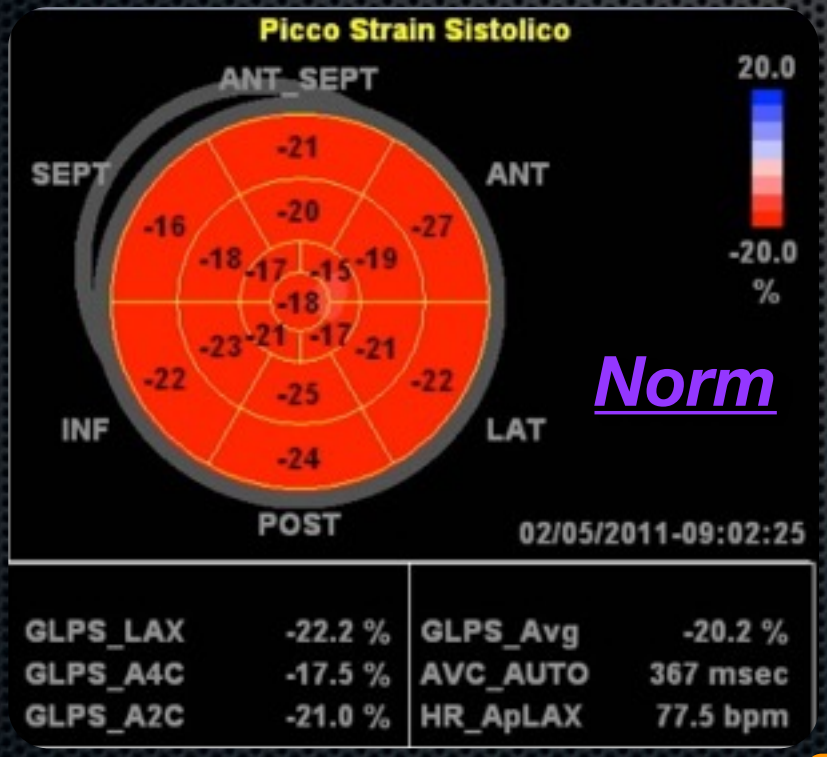
Global
Longitudinal
Peak
Systolic

V.N. < -16%

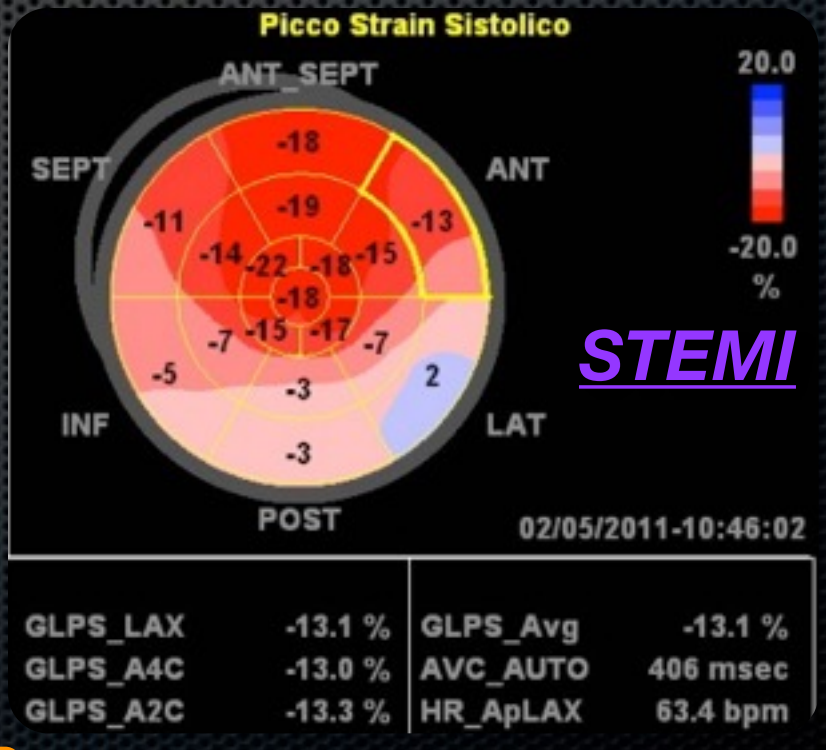
2D STRAIN ed INFARTO







Norm



STEMI

STRAIN

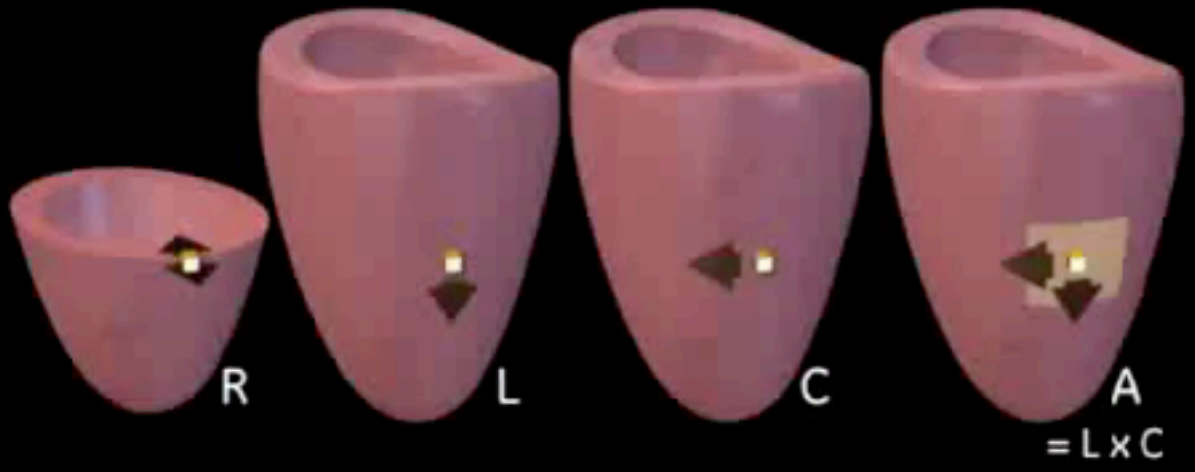
LONGITUDINALE

CIRCONFERENZIALE

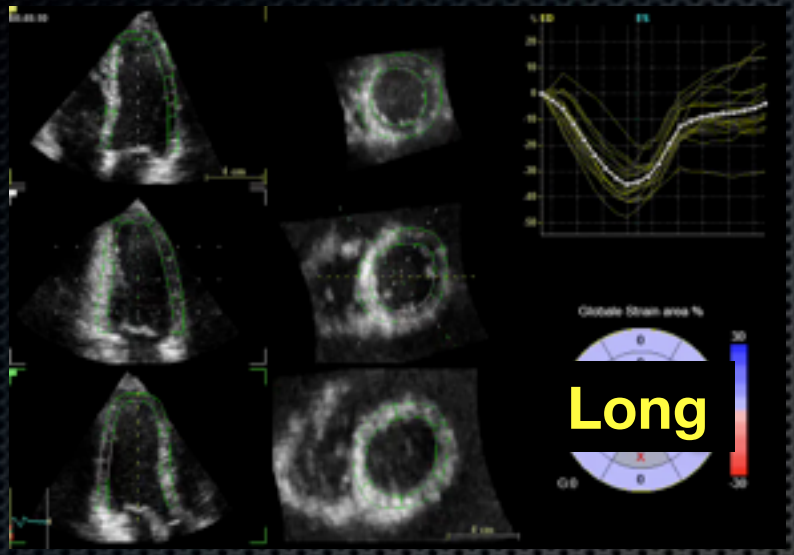
RADIALE

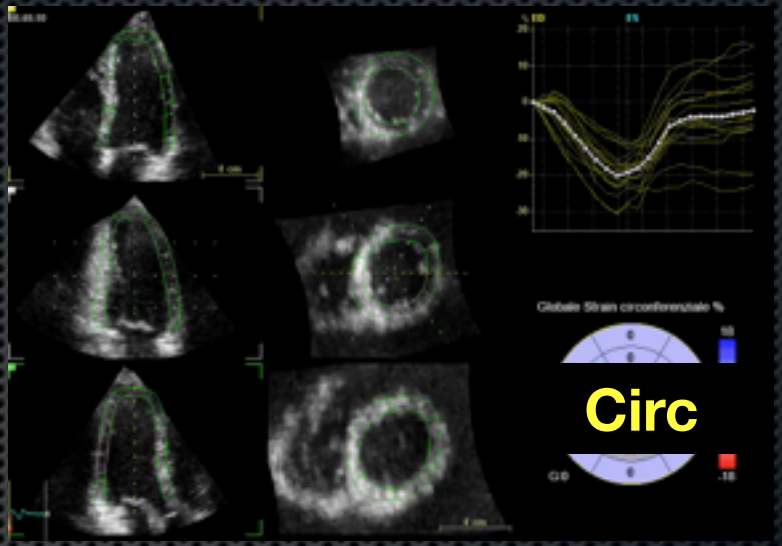
4D STRAIN

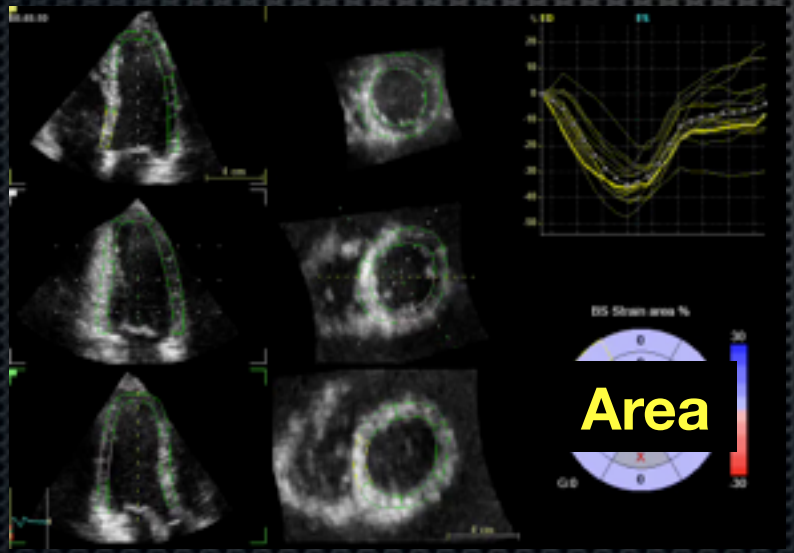
Radial strain, Longitudinal strain,
Circumferential strain and Area strain.



4D STRAIN







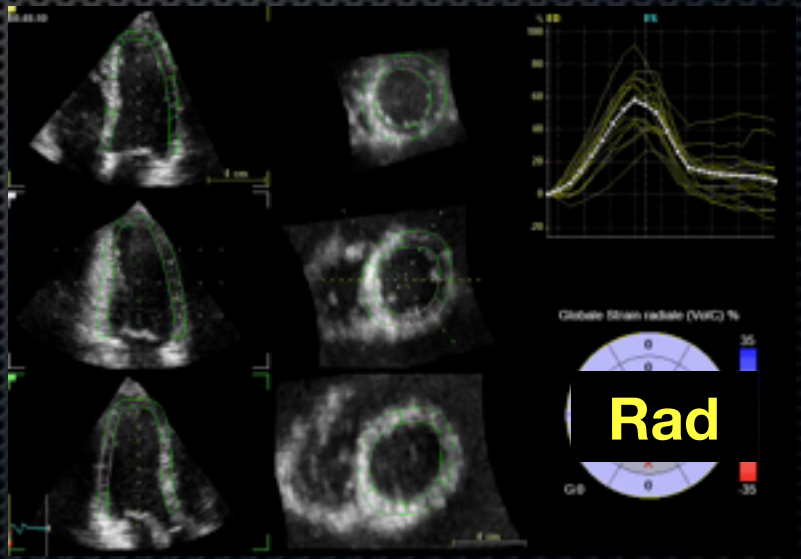


Table 4 Clinical studies using STE-derived deformation indices during or early after cancer treatment

Study	Echocardiographic method	Cancer type	n	Age, yrs	Female, %	Treatment	Echocardiography timing	Pre-echo	Post-echo	Cardiotoxicity Rate (%)	Thresholds for Toxicity Prediction	Vendor, Reproducibility
Mornos *et al.* (2013)[234]	STE	Breast lymphoma, ALL, AML, osteosarcoma	74 & 37 controls	51 ±11	58	Anthracyclines	Pre, post, and 6, 12, 24 and 52 weeks	GLS -21.2 ± 2.5% GRS 47.8 ± 5.3%	GLS -19.0 ± 2.4% GRS 41.1 ± 5.4% (6 weeks)	13	ΔGLS 2.8% (13.1% relative), sensitivity 79% and specificity 73% at 6 weeks for toxicity at 24 -52 weeks	GE, intraobserver ICC for GLS 0.95, interobserver 0.91
Negishi *et al.* (2013)[155]	STE	Breast	81	50 ± 11	100	Trastuzumab, doxorubicin 46% RT 62%	Pre-trastuzumab, and 6 and 12 months later	GLS -20.7 ± 2.6% GLSR -1.17 ± 0.24/s GLSR-E 1.36 ± 0.28/s	GLS -18.3 ± 2.1% GLSR -1.00 ± 0.15/s GLSR-E 1.20 ± 0.28/s (at 6 months in patients who later had toxicity)	30	GLS change ≥11% between pre-treatment and 6 months, sensitivity 65%, spec 95% or absolute GLS >-20.5 at 6 months, sensitivity 96%, spec 66% for toxicity at 12 months	GE, intraobserver ICC (95% CI) for GLS 0.85 (0.54%-0.96%), GSLR 0.91 (0.70-0.98/s), GLSR-E 0.90 (0.66-0.97/s), Interobserver 0.71 (0.23%-0.92%), 0.85 (0.28-0.97/s), 0.87 (0.56-0.97/s)
Baratta *et al.* (2013)[235]	STE	Breast	36	47 ± 16	58	Doxorubicin 58% trastuzumab 22%	Pre- and 2,3,4, and 6 months after start of therapy	GLS -20.3 ± 2.7% GRS 53.1 ± 4%	GLS -18.9 ± 2.5% (3 months) GRS 50 ± 3.9% (4 months)	19.4	GLS fall ≥ 15% at 3 months, sensitivity 86%, spec 86%. GRS fall ≥ 10% at 4 months, sensitivity 86% spec 69%	GE, mean (SD) absolute difference inter/intraobserver GLS 0.6 (1.4%)/0.2 (1/1%), GRS 3.4 (7.1%)/3.2 (6.6%)
Sawaya *et al.* (2012)[160]	STE	Breast	81	50 ± 10	100	Doxorubicin, epirubicin, trastuzumab, RT 60%	Pre-anthracycline and at 3, 6, 9, 12, and 15 months	GLS -21 ± 2% GRS 53 ± 15% GCS -18 ± 4%	GLS -19 ± 2% GRS 50 ± 17% GCS -16 ± 4% at 3 months	32	Absolute GLS < -19% at 3 months, sensitivity 74%, spec 73% for subsequent toxicity	GE, same variability as in previous study (153)
Sawaya *et al.* (2011)[153]	STE	Breast	43	49 ± 10	100	Doxorubicin, epirubicin, trastuzumab, RT 11.6%	Pre-anthracycline and at 3 and 6 months	GLS -20.5 ± 2.2% GCS 18 ± 4%	GLS -19.3 ± 2.4% GCS 15 ± 4%	21	GLS fall > 10% at 3 months, sensitivity 78%, spec 79% for toxicity at 6 months	GE, intraobserver as absolute mean error (SD) GLS -0.14 (1.1%), interobserver 0.5 (1.5%)
Fallah-Rad *et al.* (2011)[156]	STE	Breast	42	47 ± 9	100	Epirubicin, doxorubicin, trastuzumab, RT 98%	Pre-anthracycline, Pre-trastuzumab and at 3, 6, 9, and 12 months	GLS -19.8 ± 1.8% GLS 41.4 ± 15.2%	GLS -16.4 ± 1.1% GRS 34.5 ± 15.2% (3 months into trastuzumab)	24	Absolute GLS fall of 2.0%, sensitivity 79%, spec 82%. Absolute GRS fall of 0.8%, sensitivity 86%, spec 81% for subsequent toxicity	GE, intraobserver as ICC (COV) GLS 0.94 (3.5%), GRS 0.91 (3.2%). Interobserver 0.90 (5.2%), 0.82 (5.4%)
Hare *et al.* (2009)[162]	TDI and STE	Breast	35	51 ± 8	100	Doxorubicin, epirubicin, trastuzumab, RT 77%	Pre- and/or post-anthracycline and at 3-month	STE GLSR -1.30 ± 0.21/s STE RSR 2.02 ± 0.61/s	STE GLSR -1.24 ± 0.18/s (by 3 months) STE RSR 1.75 ± 0.41/s (by	14	A >1 SD drop in GLSR (toxicity at mean follow-up of 22 ± 6 months)	GE, intra/interobserver as ICC for 2D GLS 0.94/0.91, GLSR

European Journal of Cancer (2013) **49**, 3396–3403

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Left ventricular systolic function in HER2/neu negative breast cancer patients treated with anthracycline chemotherapy: A comparative analysis of left ventricular ejection fraction and myocardial strain imaging over 12 months

Paul W. Stoodley [a], David A.B. Richards [b,c], Anita Boyd [c], Rina Hui [d,f], Paul R. Harnett [d,f], Steven R. Meikle [a,e], Karen Byth [f], Kirsty Stuart [d,f], Jillian L. Clarke [a], Liza Thomas [b,c,f,*]

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[b] *Department of Cardiology, Liverpool Hospital, Liverpool, NSW 2170, Australia*
[c] *Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia*
[d] *Crown Princess Mary Cancer Centre, Westmead Hospital, Westmead, NSW, Australia*
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[f] *Faculty of Medicine, University of Sydney, Sydney, NSW, Australia*

Table 3
Longitudinal peak systolic strain (LPSS) values in the basal, mid and apical left ventricle at four time points over 12 months.

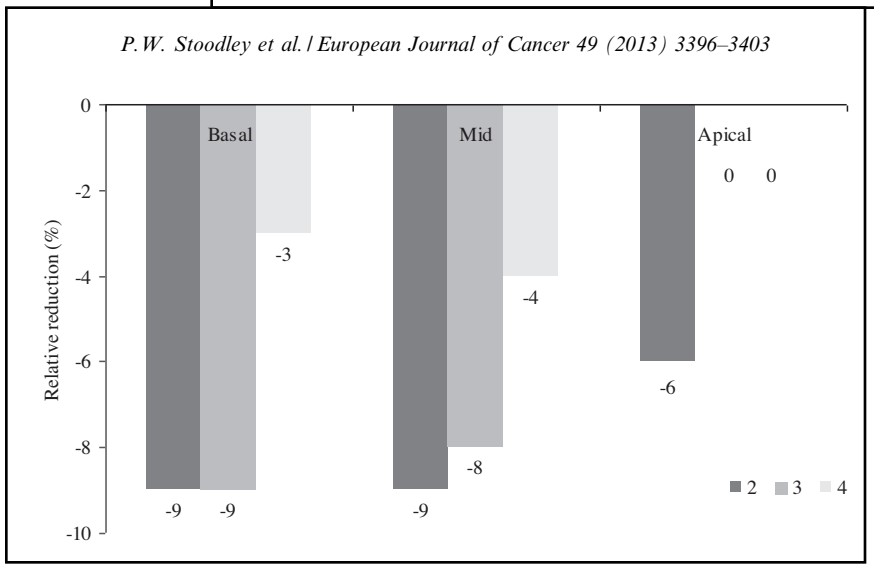
($n = 50$)	T1	T2	T3	T4
Basal left ventricular (LV)	−18.5 ± 2.4% [32%]	−16.6 ± 2.7%* [31%]	−16.9 ± 2.6%# [31%]	−17.9 ± 2.6% [31%]
Mid LV	−19.0 ± 2.7% [33%]	−17.2 ± 2.5%* [33%]	−17.4 ± 2.4%# [32%]	−18.2 ± 2.2% [32%]
Apical LV	−19.9 ± 4.1% [35%]	−18.9 ± 3.7% [36%]	−20.2 ± 3.5% [37%]	−21.2 ± 3.5% [37%]

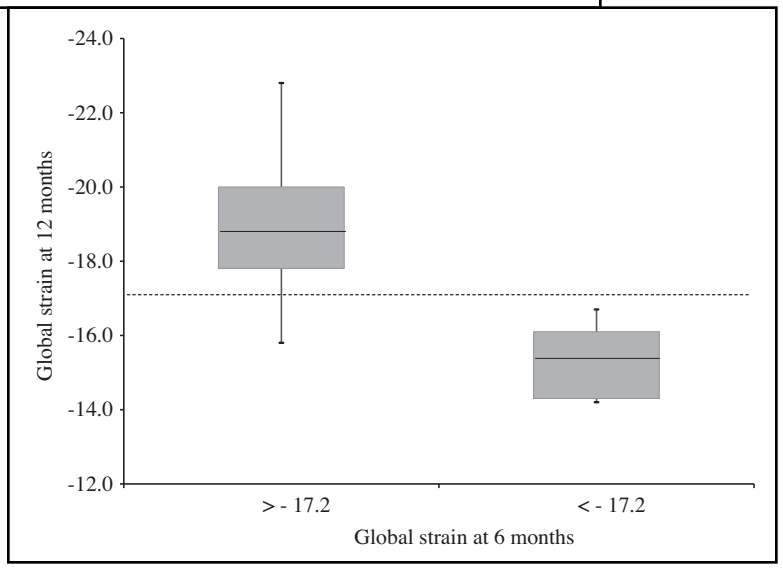
T1 = 7 days before anthracyclines, T2 = 7 days after anthracyclines, T3 = 6 months after anthracyclines and T4 = 12 months after anthracycline chemotherapy; the values in parentheses represent the relative contribution of the basal, mid and apical segments to the overall LPSS at each time point.

# $P < 0.01$.

* $P < 0.001$.

F.U.: 7 gg, 6 m, 12 m





CONCLUSIONI:

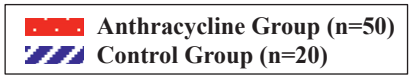
- **non significative alterazioni dell'EF**
- **riduzione 2D-strain già entro 7 gg dopo Anth**
- **danno non uniforme (apice risparmiato)**
- **disfunzione non permanente se basse dosi** (258 ± 75 mg/m²)
- **persistente riduzione GLS (< -17.2%) se alte dosi** (318 ± 115 mg/m²)

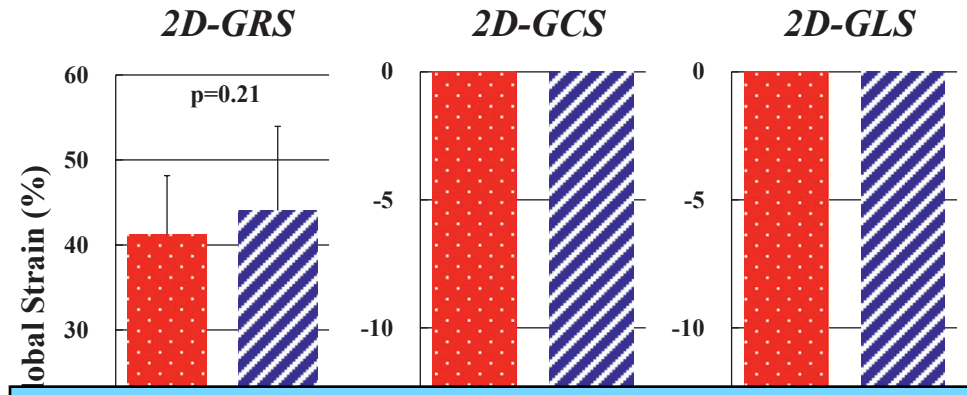
Left Ventricular Endocardial Dysfunction in Patients with Preserved Ejection Fraction after Receiving Anthracycline

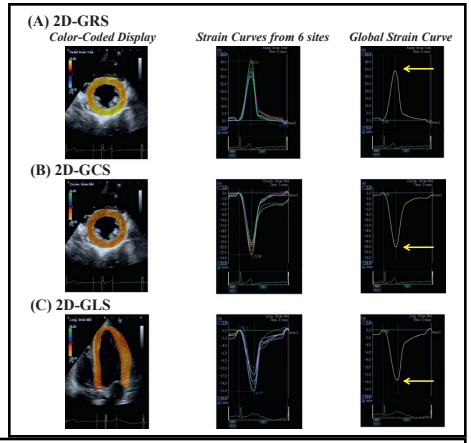
Tatsuya Miyoshi, M.D.,* Hidekazu Tanaka, M.D., Ph.D.,* Akihiro Kaneko, M.D., Ph.D.,* Kazuhiro Tatsumi, M.D., Ph.D.,* Kensuke Matsumoto, M.D.,* Hironobu Minami, M.D., D.Med.Sci.,† Hiroya Kawai, M.D., Ph.D.,* and Ken-ichi Hirata, M.D., Ph.D.*

*Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan; and †Division of Medical Oncology and Hematology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

Background: Anthracycline chemotherapy generates progressive dose-dependent left ventricular (LV) dysfunction associated with a poor prognosis. Early detection of minor LV myocardial dysfunction caused by the cardiotoxicity of anthracycline is thus important for predicting global LV dysfunction. Methods: Fifty patients with preserved ejection fraction (all ≥55%) after receiving anthracycline chemotherapy were recruited for this study. Two-dimensional speckle tracking was used to assess global radial and circumferential strains from mid-LV short-axis views and global longitudinal strain from the apical four- and two-chamber view as peak global strain curves. Three-dimensional (3D) radial, circumferential, and longitudinal myocardial function was quantified as a peak global strain curve using 3D speckle tracking from all 16 LV segments. 3D speckle tracking imaging was used to evaluate LV endocardial area change ratio (area strain) quantified as peak global area strain curve (3D-GAS) to determine LV endocardial function. Twenty age-, gender-, and EF-matched normal volunteers were studied for comparisons. Results: Only 3D-GAS and peak 3D global circumferential strains of the anthracycline group were significantly worse than those of the control group (-43.3 ± 3.1 vs. $-45.8 \pm 4.3\%$ and $-31.6 \pm 3.5\%$ vs. $-34.4 \pm 4.2\%$, respectively; $P = 0.008$, $P = 0.004$) even though global LV systolic and diastolic functions were similar. 3D-GAS correlated significantly with the cumulative doxorubicin dose ($r = 0.316$, $P = 0.026$). It was noteworthy that multivariate analysis showed only 3D-GAS ($\beta = 0.323$, $P = 0.025$) was independently associated with cumulative doxorubicin dose. Conclusions: Three-dimensional speckle tracking area strain was found useful for early detection of minor LV endocardial dysfunction associated with the use of anthracycline, and may thus prove to be clinically useful for predicting global LV dysfunction. (Echocardiography 2014;31:848–857)

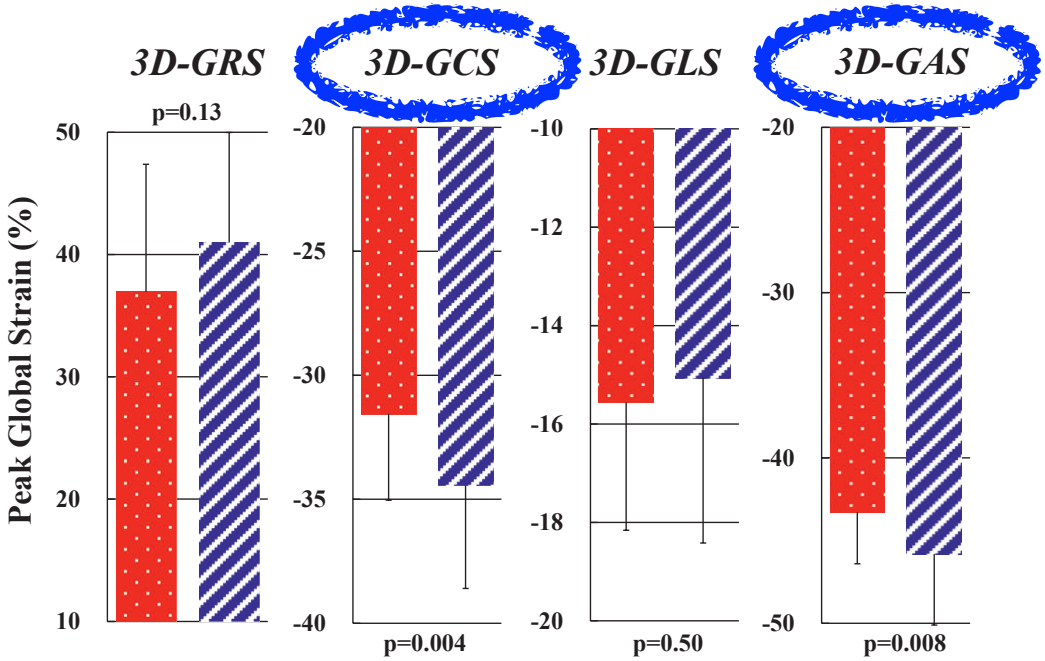


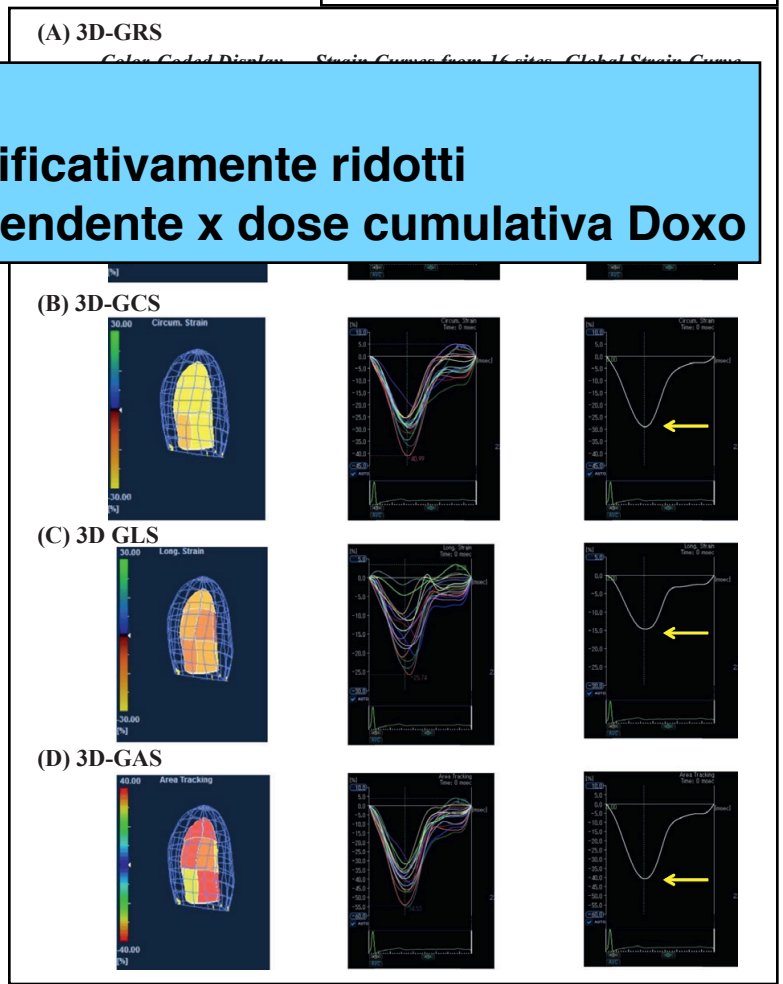




CONCLUSIONI :

- 3D-strain area e circonferenziale significativamente ridotti
- Solo 3D-strain area è parametro indipendente x dose cumulativa Doxo





Changes in Left Ventricular Longitudinal Strain with Anthracycline Chemotherapy in Adolescents Precede Subsequent Decreased Left Ventricular Ejection Fraction

Joseph T. Poterucha, DO, Shelby Kutty, MD, Rebecca K. Lindquist, RDCS, Ling Li, MD, PhD, and Benjamin W. Eidem, MD, *Omaha, Nebraska; Rochester, Minnesota*

Background: Pediatric cancer survivors who have been exposed to anthracycline (ANT) chemotherapy are an ever increasing population at risk for premature cardiac disease. Studies have shown that ANT is associated with impaired left ventricular (LV) myocardial deformation, but this has not been shown to be associated with traditional echocardiographic measures of LV systolic dysfunction. The aim of this study was to test the hypothesis that changes in LV longitudinal peak systolic strain (LPSS) would correlate with parameters of LV systolic dysfunction.

Methods: This study included 19 prospectively enrolled pediatric patients receiving ANT (mean dose, 296 $\pm$ 103 mg/m^2) and 19 controls matched for age, gender, and body surface area. For ANT patients, echocardiography was performed at baseline, mid, and final treatment points (0, 4, and 8 months). Standard echocardiographic parameters and two-dimensional speckle tracking–derived longitudinal strain parameters were obtained and compared with baseline measurements in controls. Associations between changes in LV global LPSS and standard echocardiographic indices were explored.

Results: Within the ANT group, the change in LV global LPSS showed a significant decrease compared with baseline at 4 months (8.7 $\pm$ 0.2%, P = .033) and 8 months (9.2 $\pm$ 0.3%, P = .015), while the percentage change in ejection fraction (EF) showed a statistically significant decrease at 8 months (4.3 $\pm$ 0.1%, P = .044). LV global LPSS was decreased in the ANT group compared with controls at 4 months (18.1 $\pm$ 2.5% vs 20.5 $\pm$ 1.5%, P = .011) and 8 months (18.1 $\pm$ 2.8%, P = .032). Segmental changes in mid and apical LV LPSS average were significantly correlated with change in EF (mid: $r = -0.49$, $\beta = -0.645$, P = 0.039; apical: $r = -0.48$, $\beta = -0.4126$, P = .046).

Conclusions: In adolescents who receive ANT therapy, changes in two-dimensional LV global LPSS precede decreases in EF, and segmental changes in mid and apical LV LPSS suggest an increased likelihood that depressed LV EF will be observed later in follow-up. Two-dimensional speckle tracking–derived LV LPSS is potentially useful in the serial clinical monitoring of ANT cardiotoxicity. (J Am Soc Echocardiogr 2012;25:733-40.)

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STATE-OF-THE-ART PAPERS

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,*† Frédéric Poulin, MD,* Ki-Dong Lim, MD,*

Miglior predittore CTX =

Global Longitudinal Strain S.T.: ⬇10-15%

small trials in the research setting. In this systematic review of the current literature, we describe echocardiographic myocardial deformation parameters in 1,504 patients during or after cancer chemotherapy for 3 clinically-relevant scenarios. The systematic review was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using the 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 left ventricular ejection fraction (LVEF). Using tissue Doppler-based strain imaging, peak systolic longitudinal strain rate has most consistently detected early myocardial changes during therapy, whereas with speckle tracking echocardiography (STE), peak systolic global longitudinal strain (GLS) appears to be the best measure. A 10% to 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 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. (J Am Coll Cardiol 2014;63:2751–68) © 2014 by the American College of Cardiology Foundation

Available online at www.sciencedirect.com

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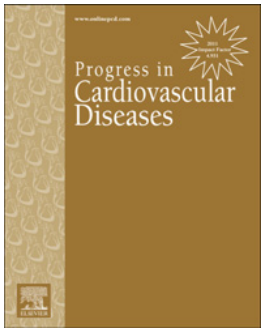
www.onlinepcd.com



Cardio-Oncology: Role of Echocardiography

Hector R. Villarraga, Joerg Herrmann, Vuyisile T. Nkomo*

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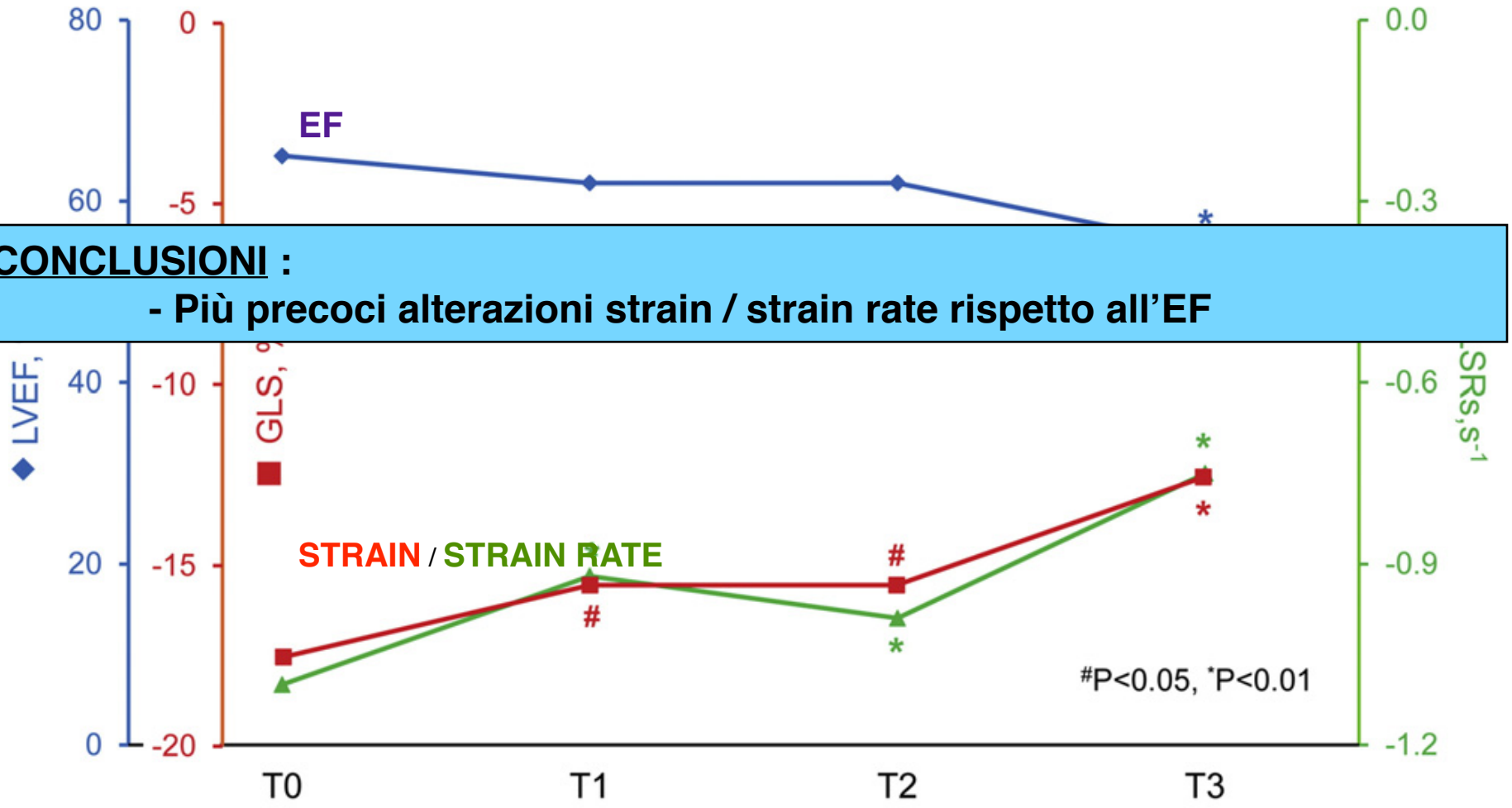
ARTICLE INFO

Keywords:
Cardio-oncology
Strain
Radiotherapy
Breast cancer
Lymphoma

ABSTRACT

Current therapies for cancer have improved life expectancy of patients. Breast cancer and lymphoma survivors in up to 26% of cases can develop complications as a consequence of the chemotherapeutic and radiotherapeutic treatments. Echocardiography is a noninvasive method that can in all stages of cancer treatment perform a comprehensive evaluation and detect coronary, myocardial, valve and pericardial disease complications secondary to the therapeutic regimen used (radiotherapy and/or chemotherapy). Three-dimensional echocardiography derived left ventricular ejection fraction (LVEF) has an excellent correlation with cardiac magnetic resonance imaging and can be used to monitor LVEF; 2-dimensional speckle tracking echocardiography (2D-STE) derived strain and strain rate can detect changes in myocardial mechanics before changes in LVEF occur and can predict a future decrease in ejection fraction to less than 50% or of greater than 10% indicative of cardiotoxicity. Echocardiography should be used as the method of choice to evaluate serial changes in heart function, detect late side effects of treatment, and to identify patients at risk of a future decrease in LVEF.

Dynamic changes of LVEF, GLS% and GLSRs s^{-1} at different time points (T0 – T3)



CONCLUSIONI :

- Più precoci alterazioni strain / strain rate rispetto all'EF

Modified from: Xu Y, Hermann J, Pellikka PA, Ansell SM, Cha S, **Villarraga HR**. Can early changes in 2-dimensional speckle tracking echocardiography predict a future decrease in left ventricular ejection fraction in lymphoma patients undergoing anthracycline chemotherapy? JASE. 2013; 26:B52

STRAIN CUT-OFF for INTERVENDORS

Table 1 – Values of strain and systolic strain rate (S and SRs) with standard deviation (SD).

	Strain %	Longitudinal SRs s^{-1}	Circumferential Strain %	Circumferential SRs s^{-1}	Radial Strain	Radial SRs s^{-1}
GE[40]	−18.6 ± 5.1		−22.9 ± 4.4		54.6 ± 12.6	
VVI[36]	−17.3 ± 2.5	−1.0 ± 0.1	−21.9 ± 4.0	1.3 ± 0.3	44.8 ± 21.7	**2.3 ± 0.7**
TOMTEC[38] (30FPS)	−16.1 ± 4.9		−22.3 ± 7.4		30.4 ± 13.5	
Toshiba[41]	−19.9 ± 2.4		−30.5 ± 3.8		51.4 ± 8.0	
Philips[41]	−18.9 ± 2.5		−22.2 ± 3.2		36.3 ± 8.2	

Abbreviation: SRs: systolic strain rate.

EXPERT CONSENSUS STATEMENT

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

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(J Am Soc Echocardiogr 2014;27:911-39.)

Table 1 Characteristics of type I and II CTRCD

	Type I	Type II
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course and typical response to antiremodeling therapy (β-blockers, ACE inhibitors)	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2–4 months after interruption (reversible)
Dose effects	Cumulative, dose related	Not dose related
Effect of rechallenge	High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death	Increasing evidence for the relative safety of rechallenge (additional data needed)
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities (though not thoroughly studied)

Cancer Therapeutics-Related Cardiac Dysfunction

define CTRCD as a decrease in the LVEF of >10 percentage points, to a value <53% (normal reference value for two-dimensional (2D) echo- cardiography (2DE)

Dopo 2-3 sett

- Reversible: to within 5 percentage points of baseline
- Partially reversible: improved by ≥10 percentage points from the nadir but remaining >5 percentage points below baseline
- Irreversible: improved by <10 percentage points from the nadir and remaining >5 percentage points below baseline
- Indeterminate: patient not available for re-evaluation

- **Echocardiography** is the **method of choice** for the evaluation of patients before, during, and after cancer therapy.
- **Accurate calculation of LVEF** should be done with the **best method available** in the echo laboratory (ideally **3DE**).
- When using 2DE, the **modified biplane Simpson's technique** is the method of choice.
- LVEF should be combined with the calculation of **wall motion score index**.
- In the absence of **global longitudinal strain (GLS) by STE**, quantification of LV longitudinal function using mitral annular displacement by M-mode echocardiography (**MAPSE**) and/or peak systolic velocity (**S wave**) of the mitral annulus by pulsed-wave **DTI** is recommended.
- LVEF assessed by 2DE often fails to detect small changes in LV contractility.

DIASTOLIC FUNCTION

- Use of the **E/E' ratio** remains questionable in the oncologic setting, as E and E' velocities fluctuation in these patients could be the consequence of changes in loading conditions as a result of side effects associated with the chemotherapy (nausea, vomiting, and diarrhea)
- a **conventional assessment of LV diastolic function**, including grading of diastolic function and noninvasive estimation of LV filling pressures, should be added to the assessment of LV systolic function, per ASE and EAE recommendations

- A quantitative assessment of **RV chamber** and function should be performed because of possible RV involvement.
- **Cardiac valves** should be **carefully evaluated** in patients undergoing chemotherapy.
- Patients with baseline or **changing valvular findings** during chemotherapy should undergo **careful reevaluation** of valve structure and function on serial echocardiography during and after the course of their treatment.
- **Pericardial disease** in oncologic patients can be associated with cardiac **metastasis** or be a **consequence** of chemotherapy and/or radiotherapy.
- **Pericardial effusion should be quantified and graded** according to standard methods.
- Echocardiographic and Doppler signs of **cardiac tamponade** should be investigated,

STRAIN

- Myocardial deformation (strain) can be measured using DTI or 2D STE. The latter is favored because of a lack of angle dependency.
- GLS is the optimal parameter of deformation for the early detection of subclinical LV dysfunction.
- Ideally, the measurements during chemotherapy should be compared with the baseline value. In patients with available baseline strain measurements, a relative percentage reduction of GLS of <8% from baseline appears not to be meaningful, and those >15% from baseline are very likely to be abnormal.
- When applying STE for the longitudinal follow-up of patients with cancer, the same vendor-specific ultrasound machine should be used.

CASISTICA MOLINETTE

- **73 pazienti ♀**
- **carcinoma mammario**
- **ecocardiogramma 2D 3D Doppler prima della CHT e al F.U. 9 mesi**
- **valutazione EF e nuovi indici s-d**

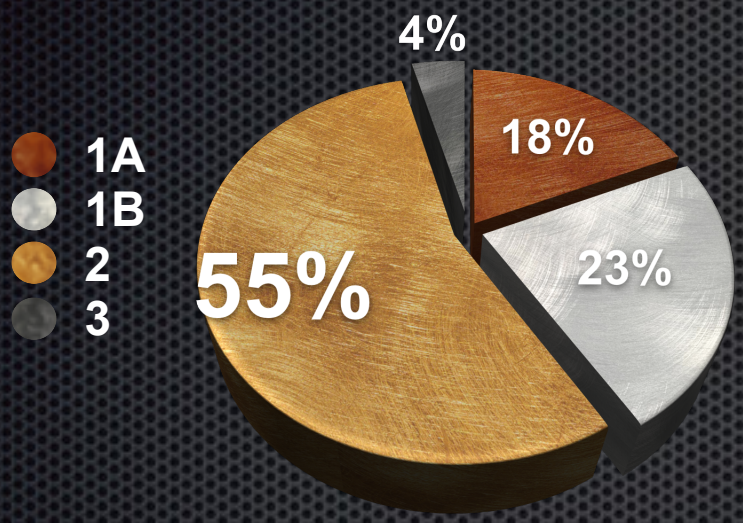
S.C. Cardiologia 2 Marra: M. Giorgi, G. Alunni, A. Fava, F. Astegiano
COES Ciuffreda: M. Donadio, M. Mistrangelo

VARIABILITÀ INTEROPERATORE

EF	t -	p value
2D	2,07	0,04
3D Triplano	2,04	0,04
3D Full	2,1	0,03

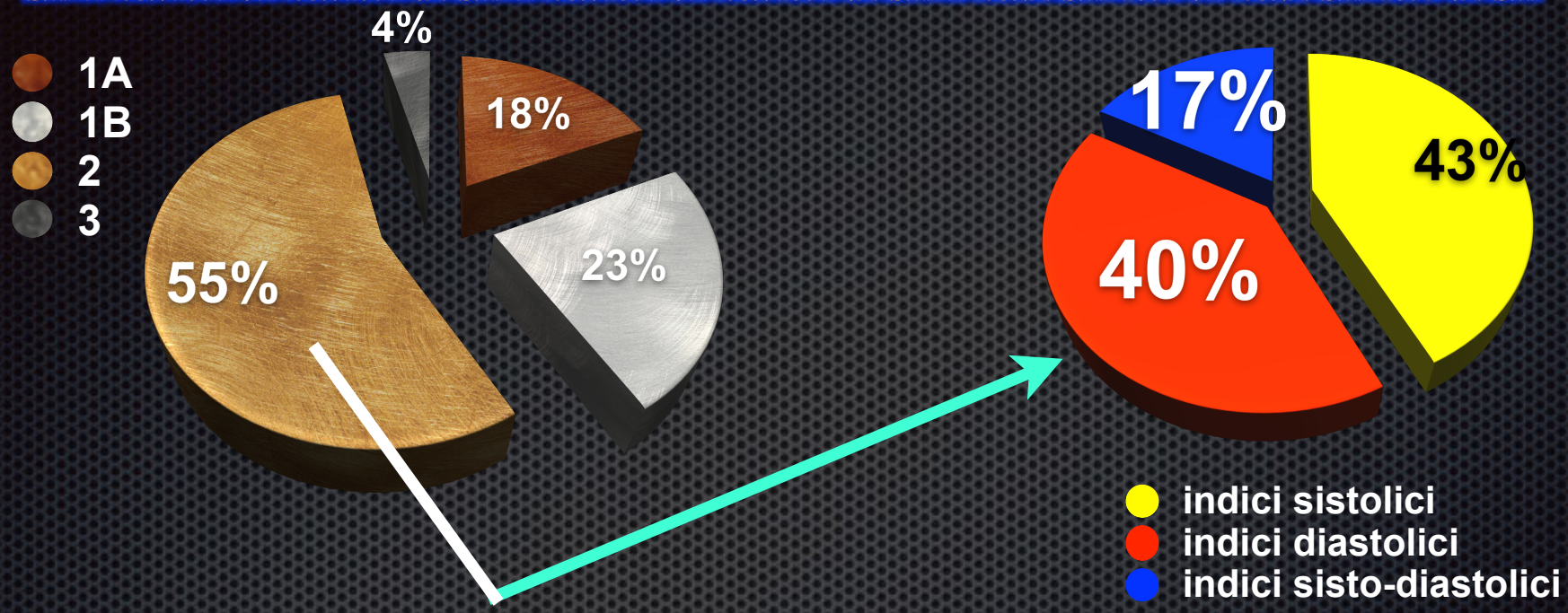
L' ECHO 3D full-volume si è dimostrata la metodica con maggior riproducibilità

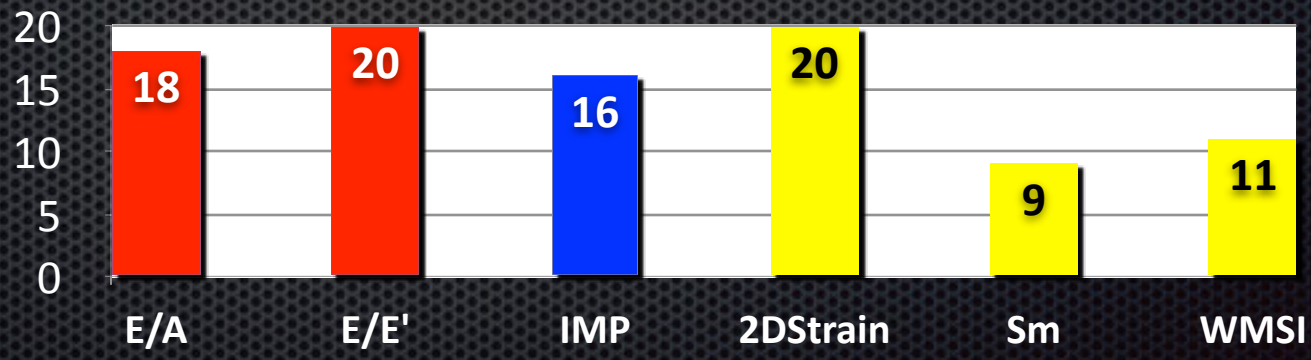
RISULTATI



- **GRUPPO 1A**: 13 pazienti (18%) senza alterazioni dell'EF, né dei nuovi indici
- **GRUPPO 1B**: 17 pazienti (23%) con EF inalterata ed alterazioni ab initio dei nuovi indici, non progredite al follow-up
- **GRUPPO 2: 40 pazienti (55%) con EF inalterata ed alterazioni dei nuovi indici al follow-up**
- **GRUPPO 3**: 3 pazienti (4%) con alterazioni significative dell'EF

EF INVARIATA - NUOVI INDICI





RISULTATI

✓ **INDICI SISTOLICI**:

- *2D STRAIN LONGITUDINALE (**AFI**)*
  - alterazioni precoci
  - variazioni più significative
- *4D STRAIN*
  - riduzione di **tutte** le componenti (long, rad, circ)
  - più marcata la riduzione **radiale**
- *CINESI SEGMENTARIA (WMSI)*
  - tardivo e con minor frequenza
  - segmenti settali coinvolti più precocemente

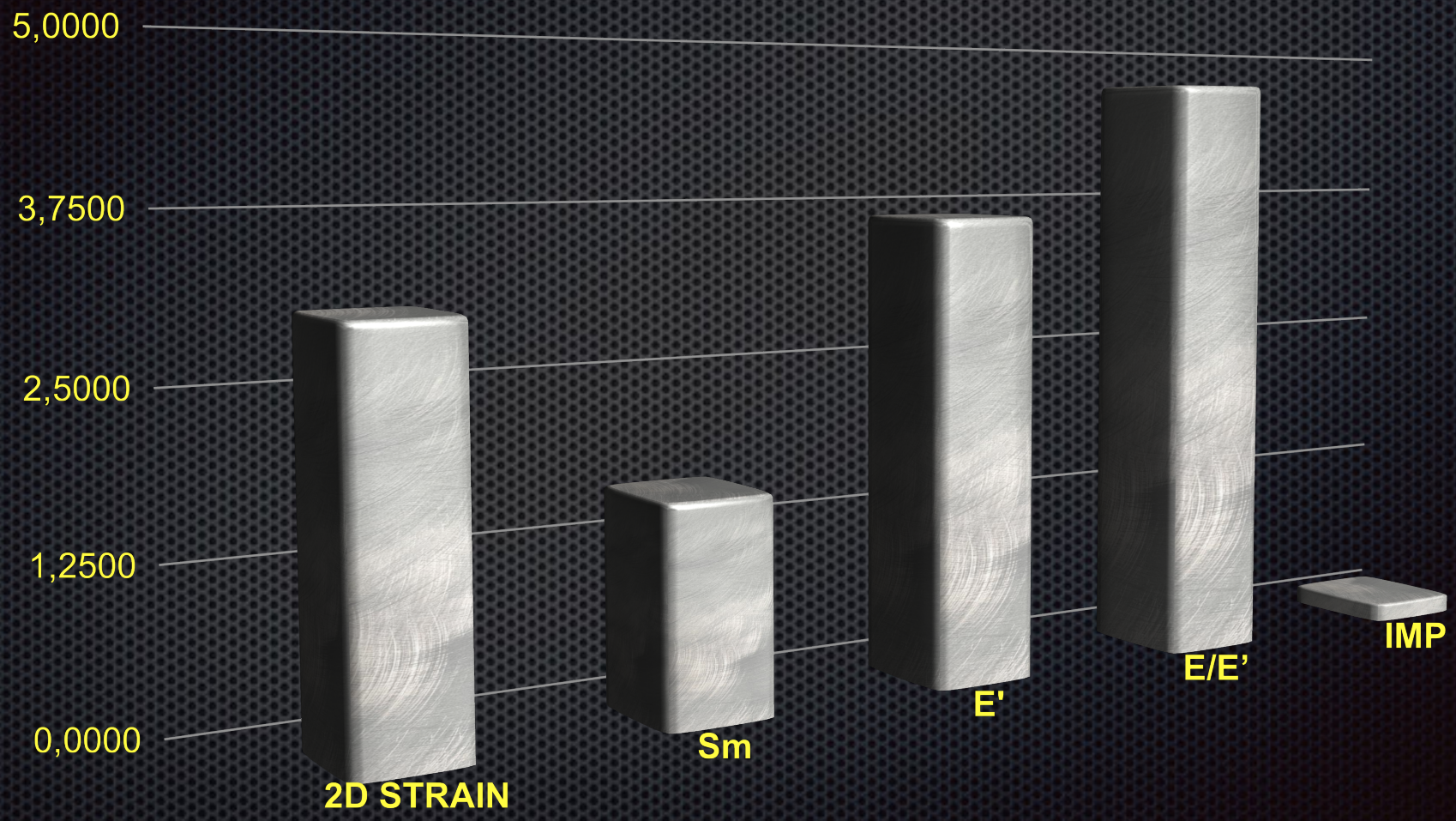
✓ **INDICI DIASTOLICI**

- variazioni precoci di **E'/A'**, del rapporto **E/E'** e dell'**onda E**

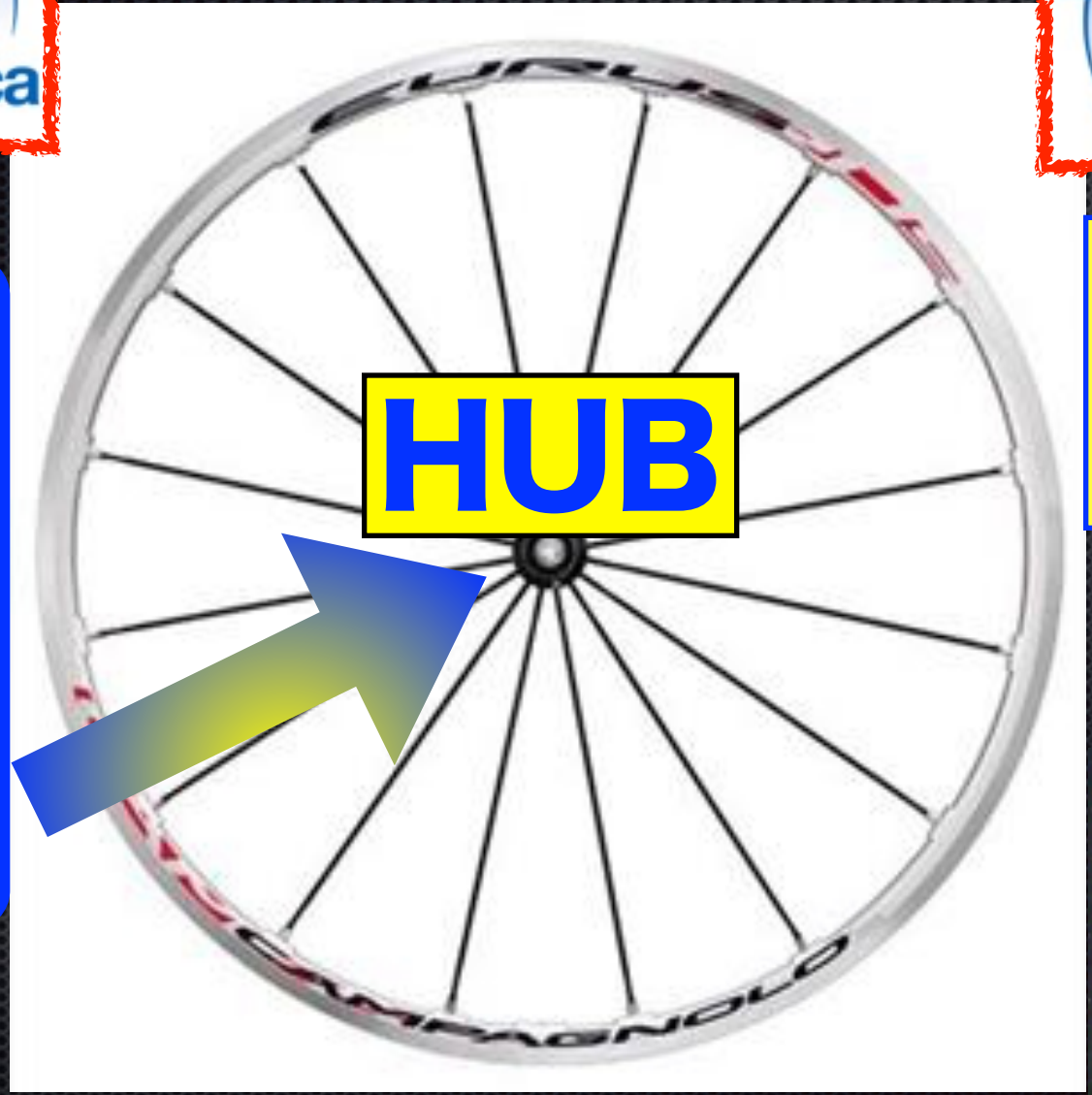
✓ **INDICI SISTODIASTOLICI (IMP / TEI index)**

- minor variazione nel tempo (parametro tardivo)

ANALISI della VARIANZA



MANAGEMENT

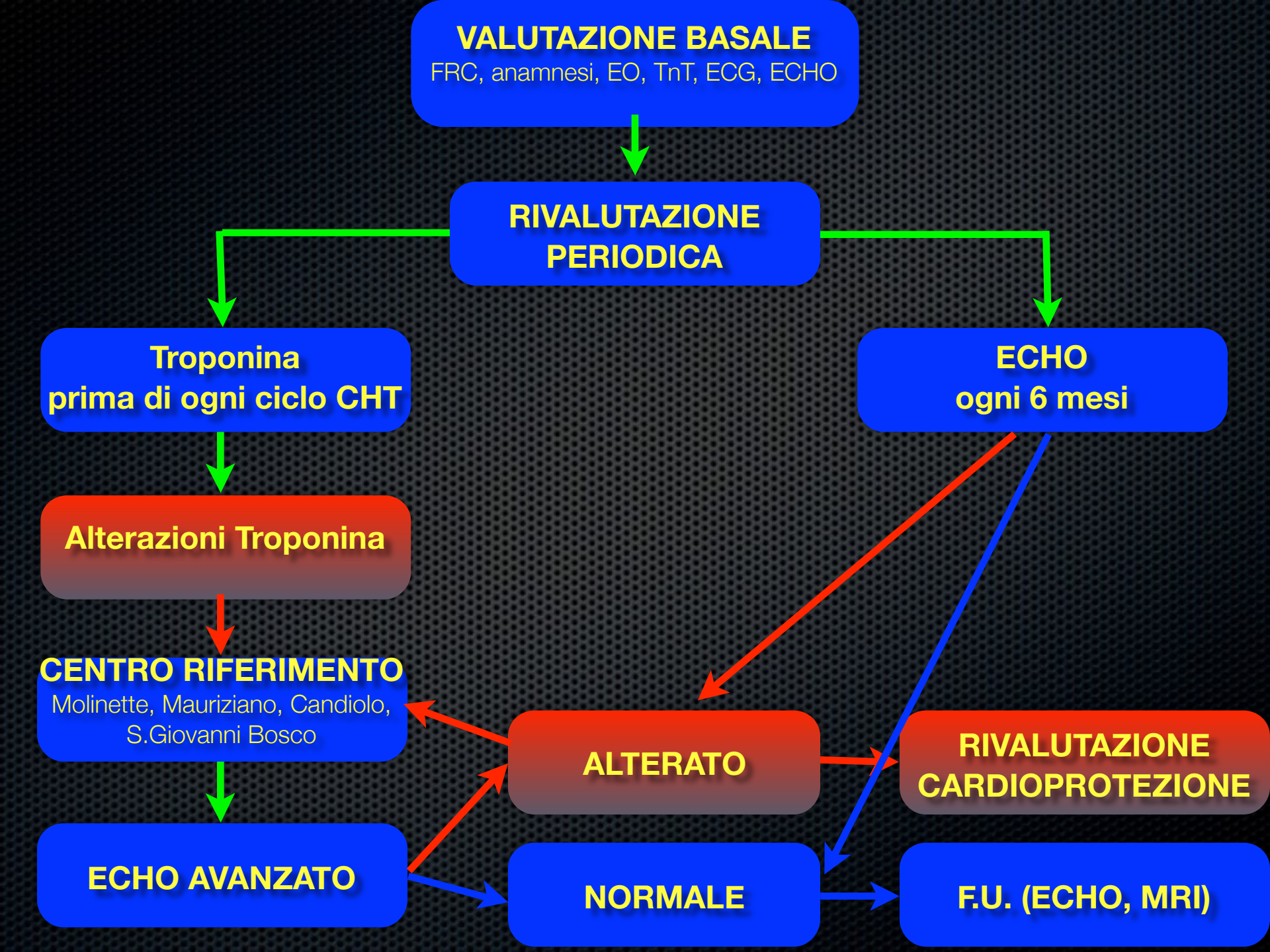


Oncologia
Ematologia

Cardiologia
osp/amb

SPOKE

- Molinette
- Mauriziano
- GiovanniBosco
- Candiolo
- Orbassano


VALUTAZIONE BASALE
FRC, anamnesi, EO, TnT, ECG, ECHO
RIVALUTAZIONE PERIODICA
Troponina prima di ogni ciclo CHT
ECHO ogni 6 mesi
Alterazioni Troponina
CENTRO RIFERIMENTO
Molinette, Mauriziano, Candiolo, S.Giovanni Bosco
ALTERATO
RIVALUTAZIONE CARDIOPROTEZIONE
ECHO AVANZATO
NORMALE
F.U. (ECHO, MRI)

STEP 1 - VALUTAZIONE BASALE

- **Anamnesi - Individuazione dei FRC**
- **Visita / esame obbiettivo**
- **Profilo biochimico completo** *(funzionalità renale ed epatica, assetto lipidico, HbA1C)*
- **ECG**
- **Troponina**
- **ECHO**

MINIMUM DATA SET ECHO 1°

- Diametri e spessori M-mode (Teicholz) - *NO FS!*
- FUNZIONE SISTOLICA: EF (v.n. > 55%)
- FUNZIONE DIASTOLICA - IMP
- Ventricolo destro: TAPSE (>18 mm), S2 (>12 cm/s -TDI)
- Area/Volumetrie atriali: area < 18 cm^2, AS < 28 ml/m^2
- Aorta ascendente (inner-to-inner edge)
- Vena cava (v.n. < 20 mm, normocollabente)
- Apparati valvolari e flussimetria Doppler
- Stima PAPs (da IT o AcT)
- Pericardio: misura e localizzazione eventuale versamento

FUNZIONE SISTOLICA

- M-mode (Teicholz: spessori e diametri td e ts)
- Frazione d'eiezione: SIMPSON BIPLANO (v.n. > 55%)
- MAPSE (v.n. > 12 mm)
- dP/dt: v.n. > 1200 mmHg/s *(quando fattibile per IM)*
- Cinesi segmentaria: WMSI

Se disponibili:

- *Onda S2 al TDI (v.n. ≥ 8 cm/s)*
- *3D-ECHO (triplano e full-volume)*
- *STRAIN (GLPSavg = Global Longitudinal Peak Systolic):*
  - ➡ ***2D-strain longitudinale: v.n. < -18%*** *(b.l. < -16%)*
  - ➡ ***4D-strain:*** *longitudinale, circonferenziale, area, radiale*

RIVALUTAZIONE ECHO PERIODICA

- **FUNZIONE SISTOLICA**
- **CINESI SEGMENTARIA**
- **FUNZIONE DIASTOLICA**
- **FOCUSED ECHO**: mirato alla rivalutazione di eventuali parametri alterati di base (es. versamento)

	WALL DYNAMICS (STRAIN) e DIASTOLE	
	NORMALE	ALTERATO
EF NORMALE		*iniziale disfunzione*
EF ALTERATA		

No risk factors

Evaluation	BASELINE	3 months	6 months	12 months	Every 6 months	Every 12 months
Physical examination§	X	X	X	X	X	
LDL, HDL, TAG	X	X	X	X		X
Uric acid, creatinine, K, Mg, glucose	X	X	X	X		X
BP	X	X	X	X	X	
ECG	X	(X if clinically indicated)				
Echocardiogram	X	(X if clinically indicated)				

§ Inclusi polsi periferici

1-3 Risk factors

Evaluation	BASELINE	3 months	6 months	12 months	Every 6 months	Every 12 months
Physical examination‡	X	X	X	X	X	
LDL, HDL, TAG	X	X	X	X		X
Uric acid, creatinine, K, Mg, glucose	X	X	X	X		X
BP	X	X	X	X	X	
ECG	X			X		X
Echocardiogram	X		(X if clinically indicated)			
HbA1c (in pts with DM)	X	X	X	X	X	
Edinburgh Claudication Questionnaire+	X			X		X (24 mesi)

>3 Risk factors

Evaluation	BASELINE	3 months	6 months	12 months	Every 6 months	Every 12 months
Physical examination‡	X	X	X	X	X	
LDL, HDL, TAG	X	X	X	X		X
Uric acid, creatinine, K, Mg, glucose	X	X	X	X		X
BP	X	X	X	X	X	
ECG*	X		X	X	X	
Echocardiogram*	X		(X if clinically indicated)			
HbA1c (in pts with DM)	X	X	X	X	X	
Edinburgh Claudication Questionnaire+*	X			X		X
Carotid ultrasound (Doppler) scan†*	X			X		X

‡ Physical examination should include: peripheral pulses
+ ABI if positive Edinburgh; Vascular surgeon referral if ABI < 0.9
† Vascular surgeon referral if positive Carotid ultrasound (Doppler) scan
* Within the context of a referral to a cardiovascular specialist

RIDUZIONE EF e CARDIOPROTEZIONE

- EF > 50% e ⬇ EF ≥ 10 p.% rispetto al basale: proseguire CHT (antracicline) o transtuzumab
- EF < 50% : rivalutazione dopo 3 settimane --> se confermata, sospensione trattamento
- EF < 40%: stop CHT e considerare regimi CHT alternativi

In tutti iniziare CARDIOPROTEZIONE con:

- ACEinibitori (*ramipril*) **e/o sartani** (*val-,telmisartan*)

- Beta-bloccanti (*bisoprololo, carvedilolo*)

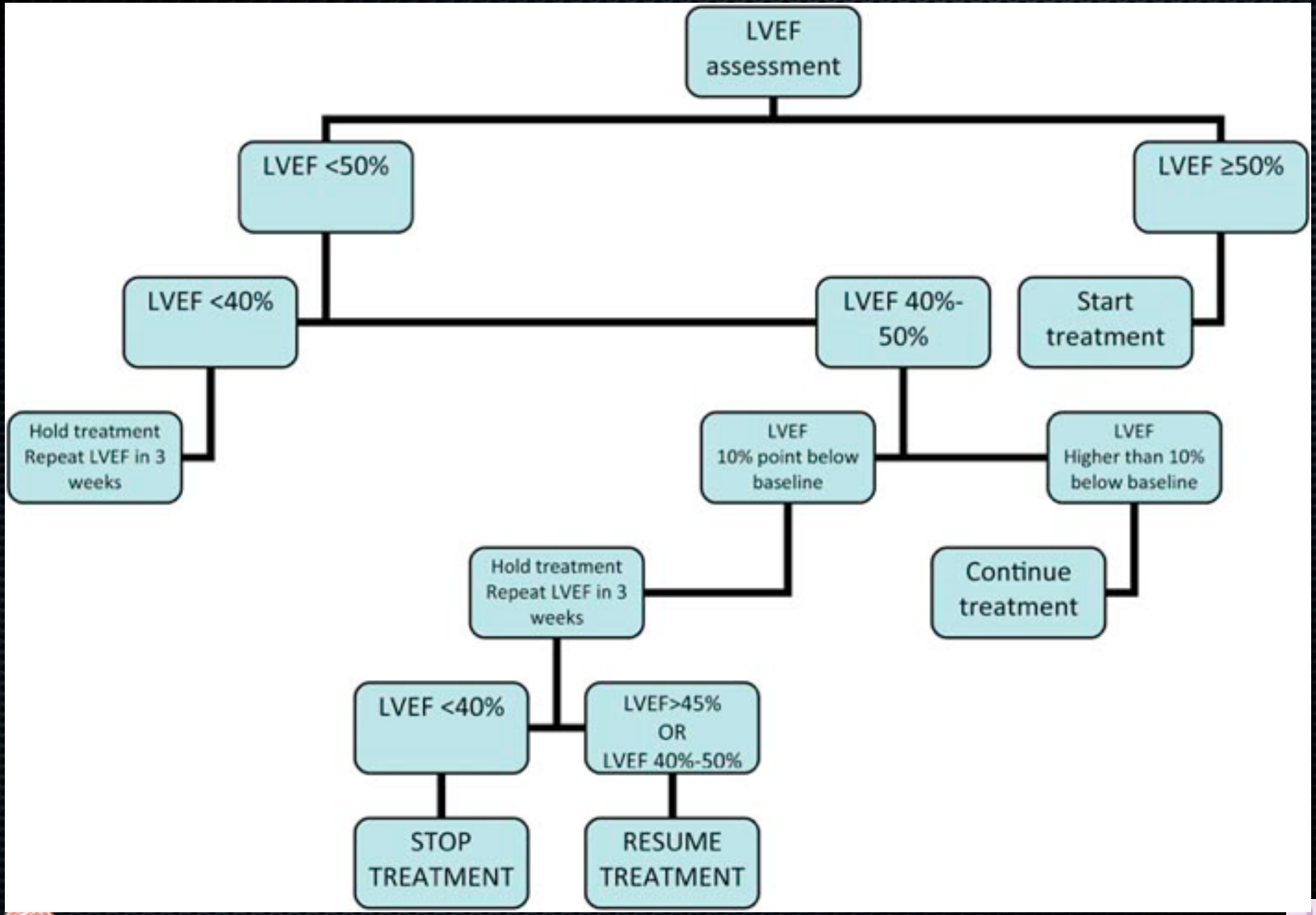
- Ivabradina? - Cardioxane? - Ranolazina?

TERMINE CHT e F.U. 6 MESI:
VISITA, ECG, ECHO

F.U. 1 ANNO:
VISITA + ECG; *ECHO se indicato*

F.U. 5 ANNI:
VISITA, ECG, ECHO

F.U. 10 ANNI:
VISITA, ECG, ECHO


LVEF assessment
LVEF <50%
LVEF ≥50%
LVEF <40%
LVEF 40%-50%
Start treatment
Hold treatment Repeat LVEF in 3 weeks
LVEF 10% point below baseline
LVEF Higher than 10% below baseline
Hold treatment Repeat LVEF in 3 weeks
Continue treatment
LVEF <40%
LVEF>45% OR LVEF 40%-50%
STOP TREATMENT
RESUME TREATMENT

FOLLOW UP: CAVEAT

1) Per **TUTTI** (cardiologi, oncologi, internisti, mdf): **variazioni** dello stato clinico
   - anamnesi: *comparsa di sintomi*
   - esame obiettivo
   - ECG: *aritmie, BBS*

2) **ECOCARDIOGRAFISTI**: **"minimum data set"**, in particolare alterazioni diastole, EF, strain

FOLLOW UP

- **A chi?** *Tutti i Pts, solo alto rischio, giovani?*
- **Quando e con che cadenza?** *6 m, ogni 1-3-5 aa?*
- **Chi?** *Oncologo, cardiologo, internista, medico di famiglia?*
- **Dove?** *Centralizzato o periferico?*
- **Come?** *Solo visita, + markers, +ECG, + ECHO?*

PROBLEMATICHE del F.U.

- Controlli troppo assidui in Pts “guariti” *(ansia)*
- Rischio di “drop out” dei Pts *(giovani)*
- Sottovalutazione del problema CTX
- Sovraccarico degli Echo-Lab
- Importanza della precisione delle misure

Cardiologo ospedaliero, Cardiologo territoriale,
Oncologo, Ematologo, Internista,
Medico di famiglia - Paziente

PATTO di COLLABORAZIONE Tra MEDICO e PAZIENTE

Grazie per l'attenzione

Grazie per l'attenzione !