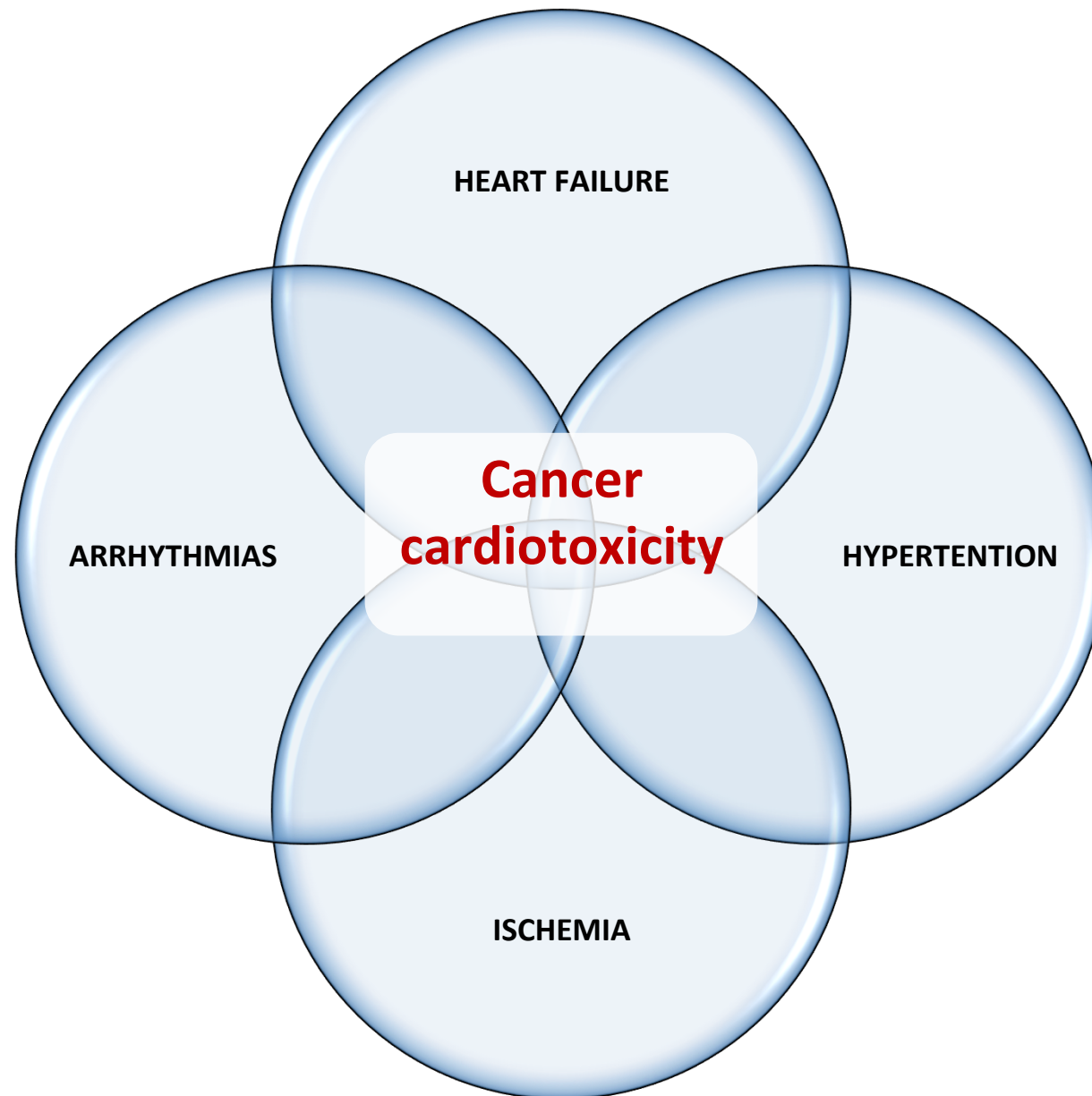


Trattamento cardiologico nei pazienti oncologici

Dott.ssa Iris Parrini
Ospedale Mauriziano di Torino





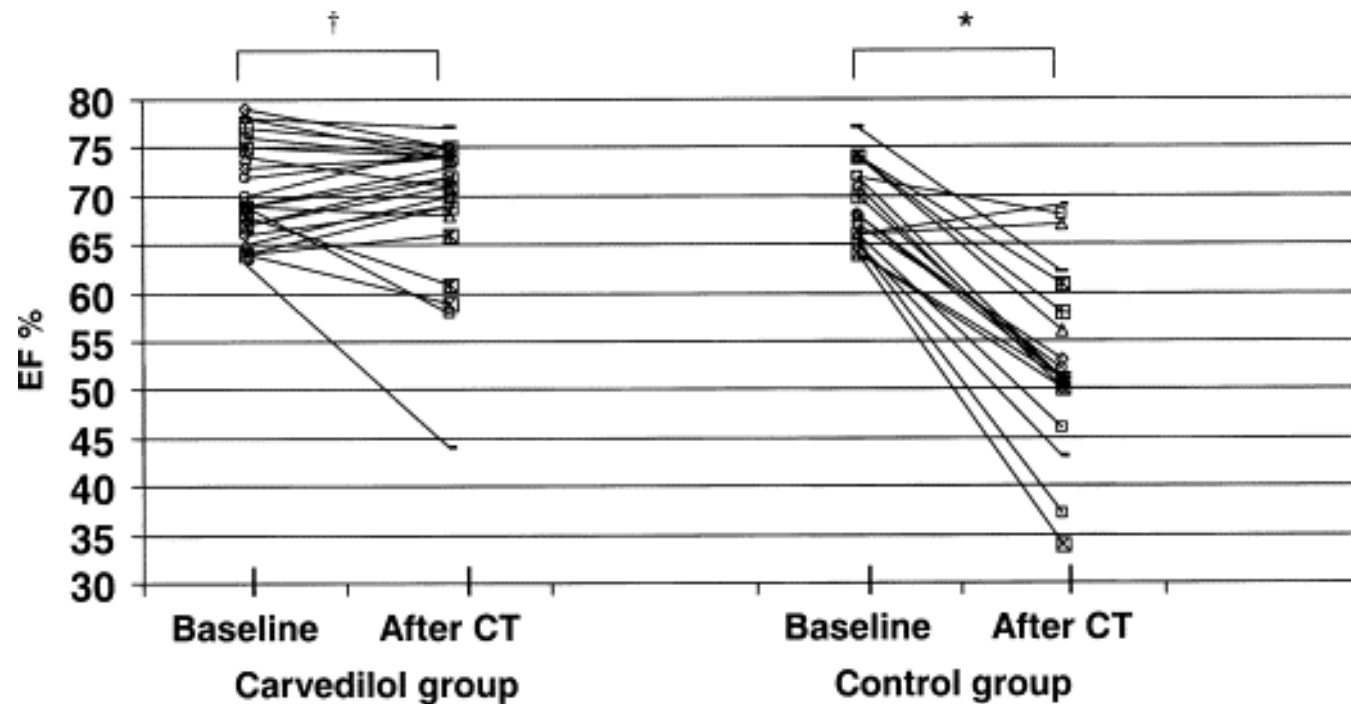
La terapia cardiologica per il
paziente che sviluppa cardiotossicità:

cosa cambia, se cambia?

in funzione del trattamento
chemioterapico e/o della malattia
oncologica

HEART
FAILURE

Prevenzione primaria

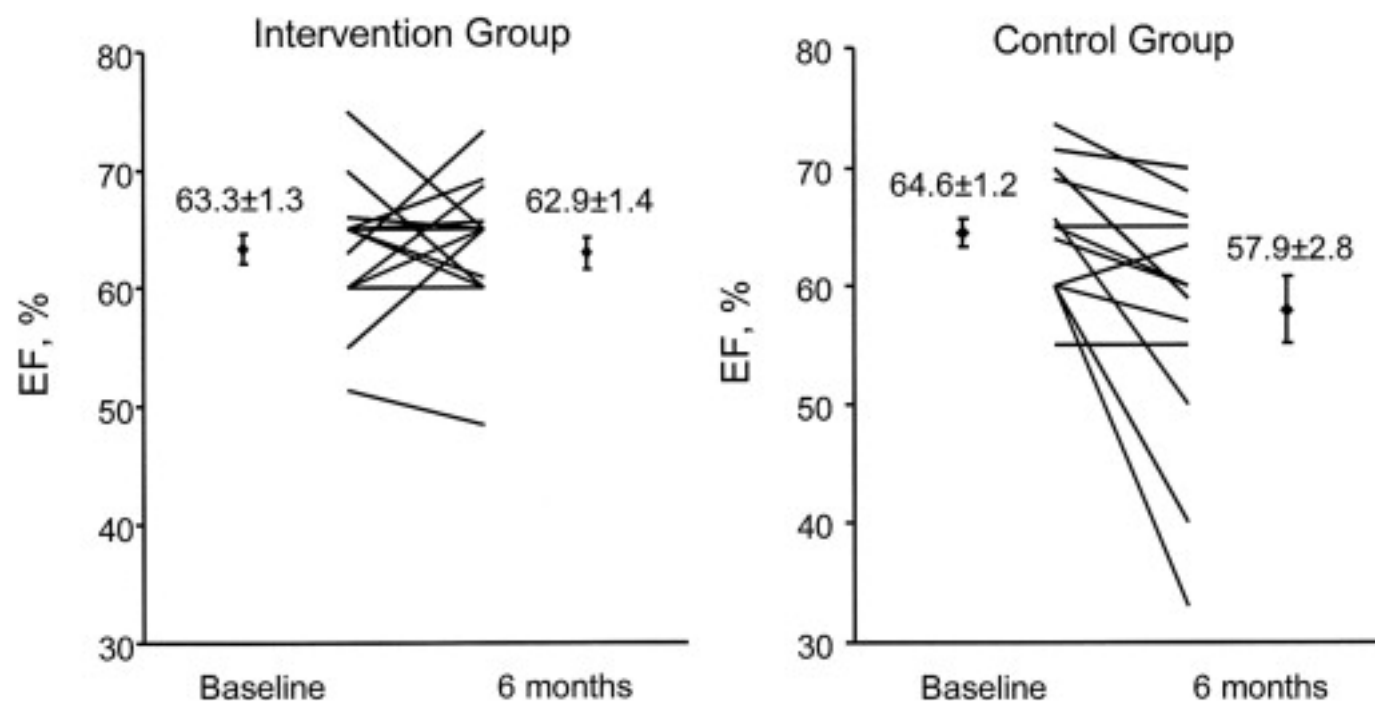


protective effect of carvedilol in anthracycline (ANT)-induced cardiomyopathy (CMP).

HEART
FAILURE

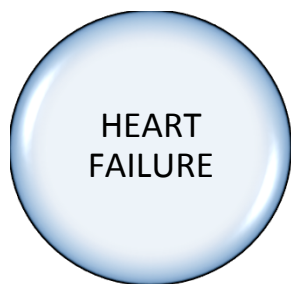
Prevenzione primaria

Overcome Trial



Combined treatment with enalapril and carvedilol may prevent LVSD in patients with malignant hemopathies.

Xavier Bosch et al, Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies: The OVERCOME Trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies; Journal of the American College of Cardiology, Volume 61, Issue 23, 2013, 2355–2362

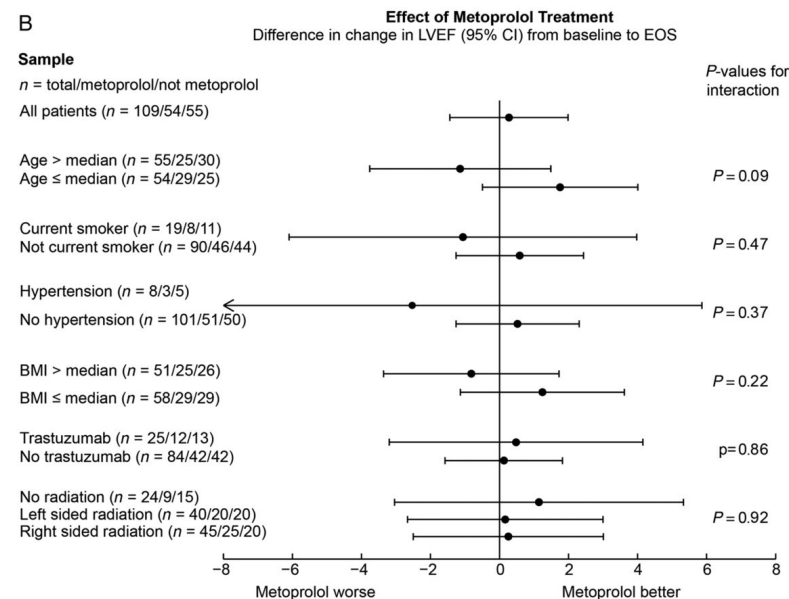
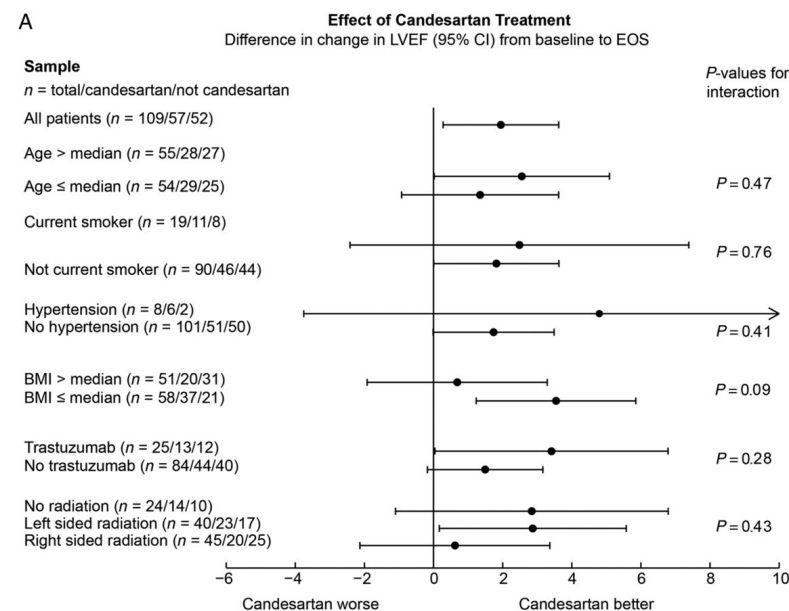


Prevenzione primaria

Prada Trial

Effect of candesartan and metoprolol on left ventricular ejection fraction during adjuvant therapy for early breast cancer.

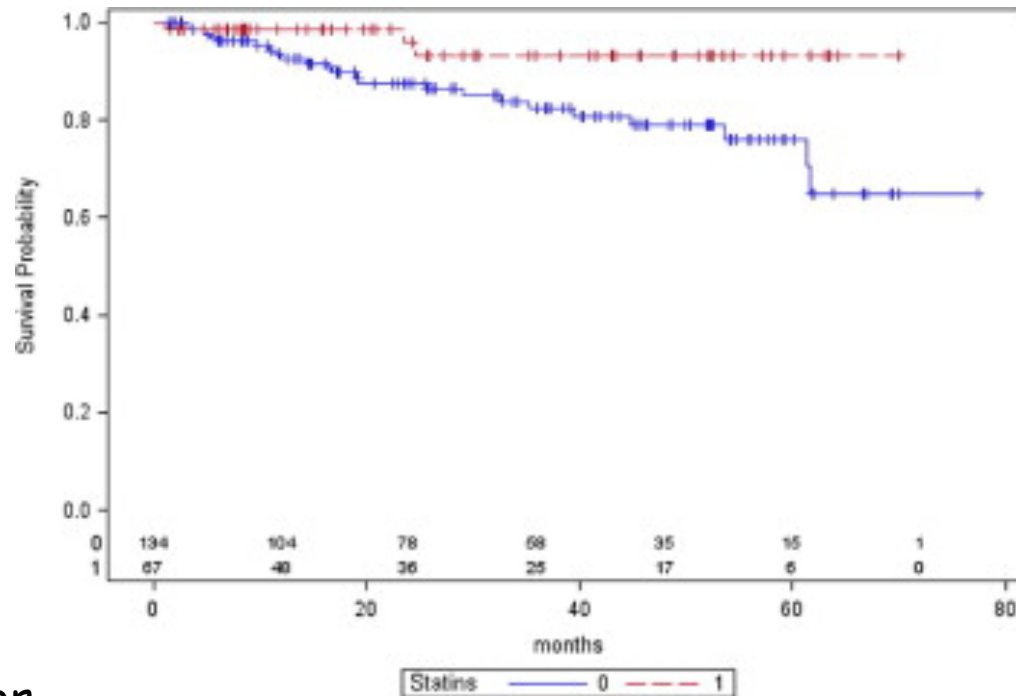
Concomitant therapy with **candesartan** alleviated the decline in left ventricular ejection fraction(A). No effect of **metoprolol** on the mean left ventricular ejection fraction was observed (B).



HEART
FAILURE

Prevenzione primaria

Statin use is
associated with
↓ risk of HF and
cardiac related
mortality



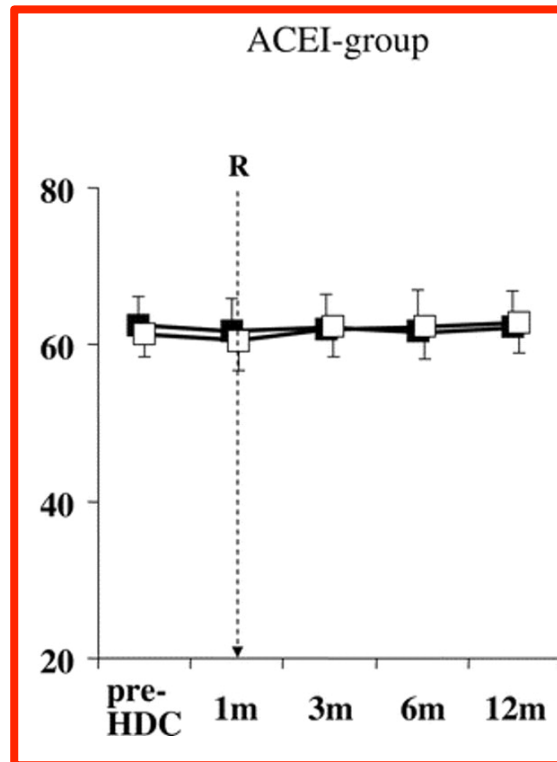
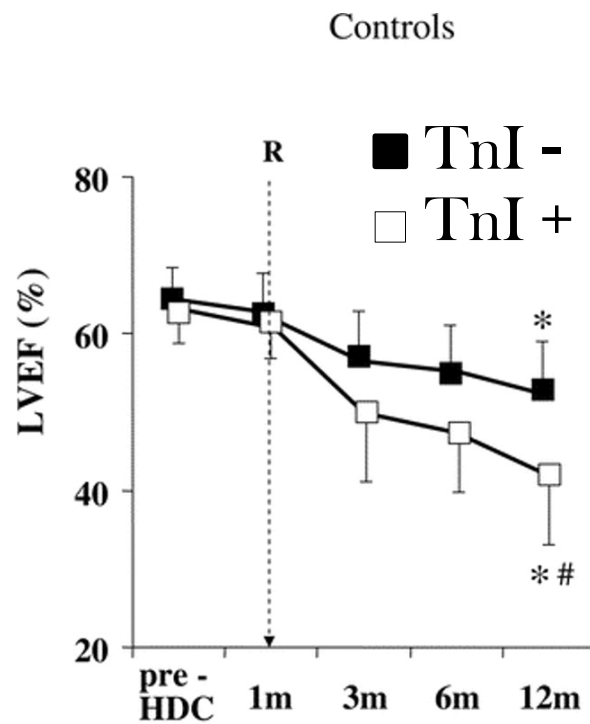
Consider a lower threshold for initiating statins in individuals at risk for CVD (10-year CV risk > 5%) who are being treated with cardiotoxic drugs.

Rev Esp Cardiol. 2007;60(5):476-85

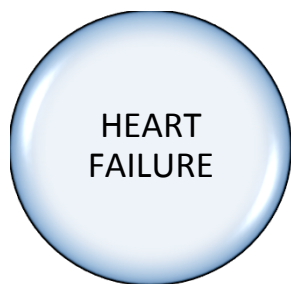
Sinziana Seicean, et al, Effect of Statin Therapy on the Risk for Incident Heart Failure in Patients With Breast Cancer Receiving Anthracycline Chemotherapy: An Observational Clinical Cohort Study; Jacc, 2012,

HEART
FAILURE

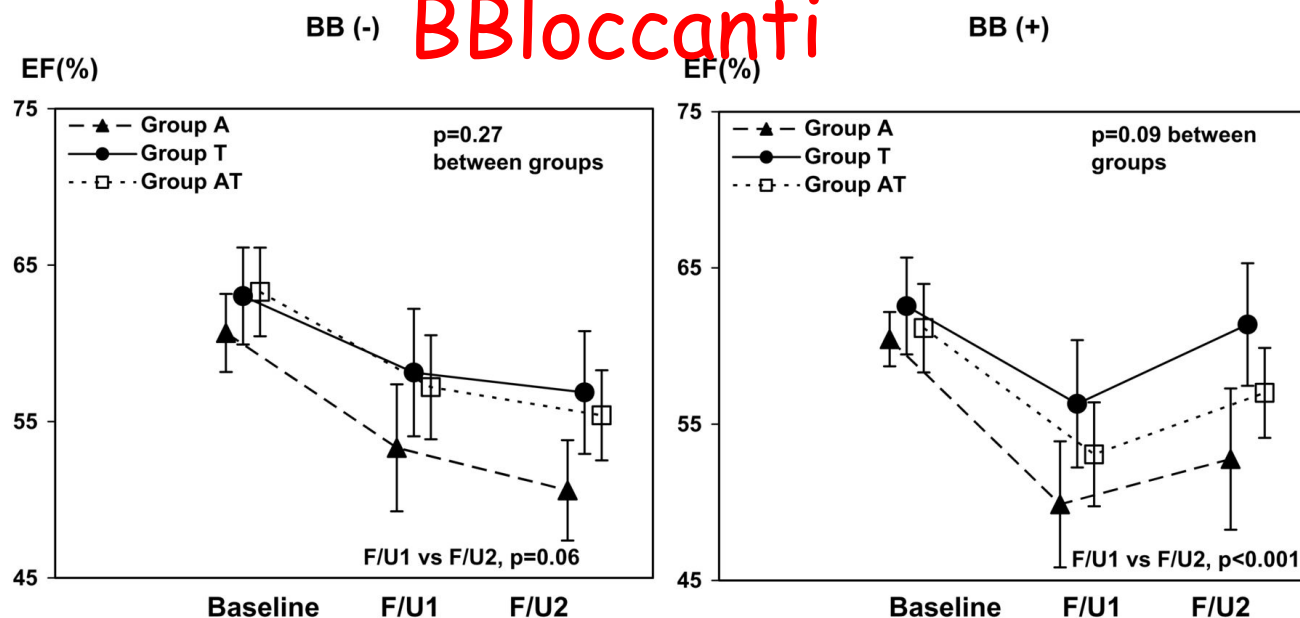
Effetto cardioprotettivo ACE inibitori



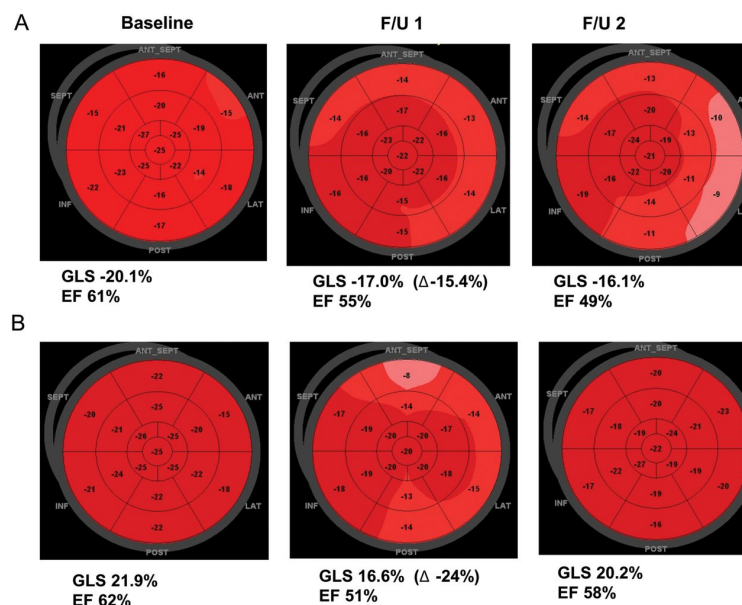
Enalapril
treatment in
TnI + patients
with normal EF
decreases the
risk of HF

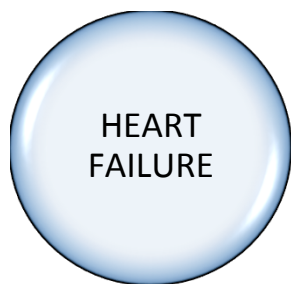


Effetto cardioprotettivo dei BBloccanti



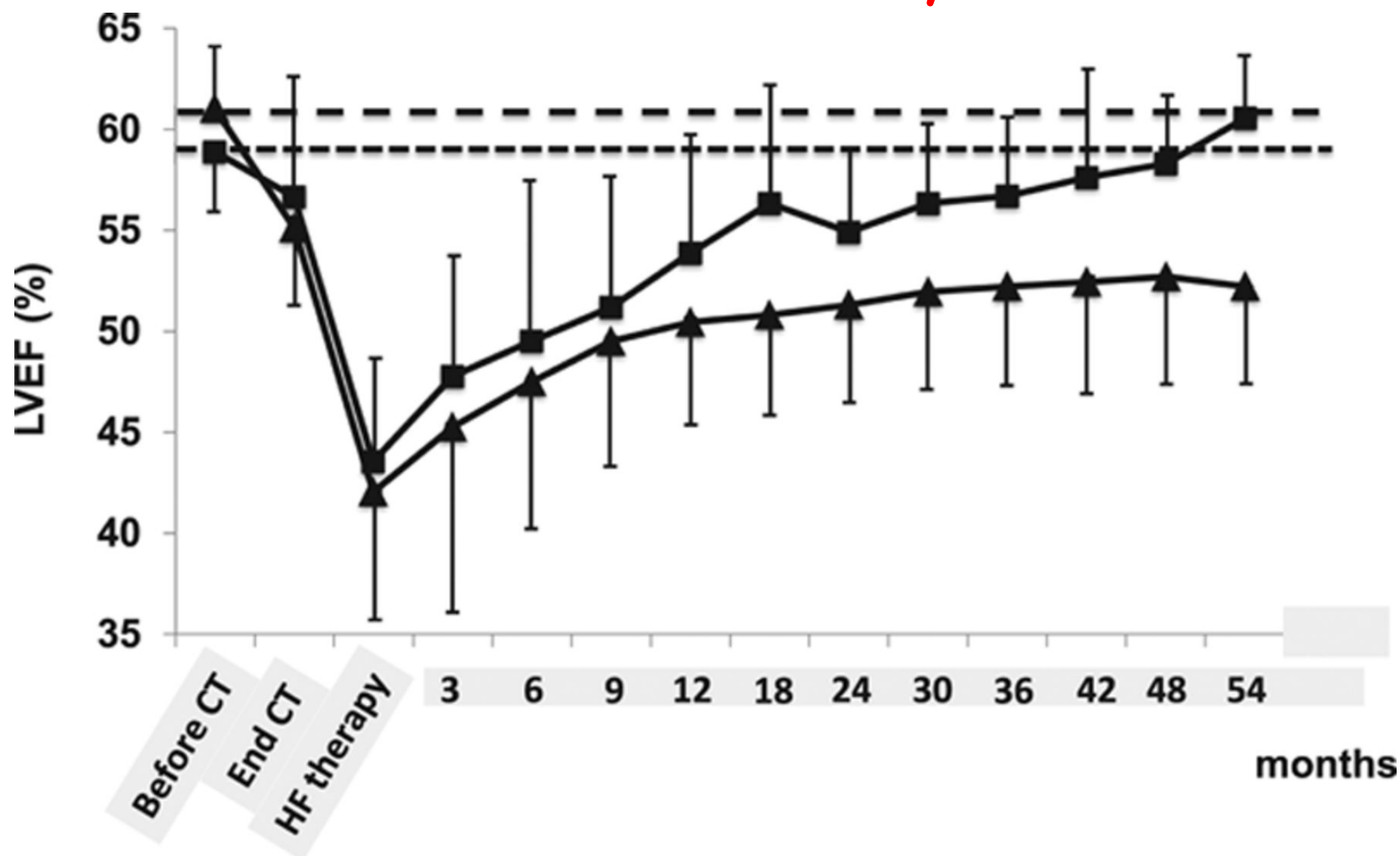
Cardioprotective
effect of B-blockers
in patients with
▼ GLS>11%

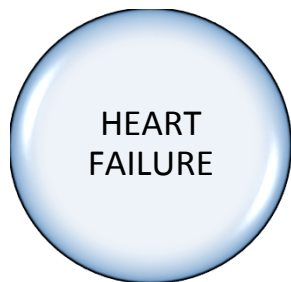




Left ventricular ejection fraction (LVEF) in patients with cardiotoxicity and with partial (triangle) or full (square) recovery with heart failure therapy.

Recovery





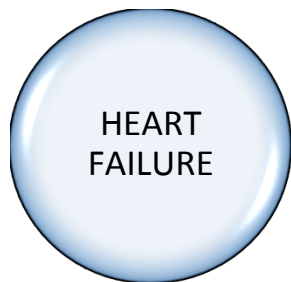
HEART
FAILURE

Disfunzione ventricolare sinistra asintomatica da antracicline o TKI

Considera alternative terapeutiche
(antracicline liposomiali, TKI meno cardiotossici)

Avviare terapia con ACE-inibitori e/o sartani e/o
Betabloccanti e controllo dopo un mese

- a) **Recupera**: possibile **rechallenge** con monitoraggio
ecocardiografico prima di ogni somministrazione
- b) **Non recupera**: cerca alternative terapeutiche



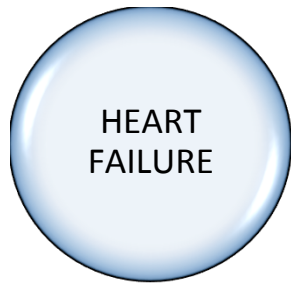
Disfunzione ventricolare sinistra asintomatica da trastuzumab

Stop per un mese

a) Recupera: rechallenge con controllo eco prima di ogni ciclo

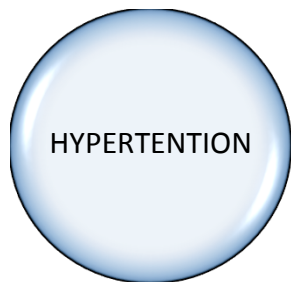
b) Non recupera: avviare terapia con ACE-inibitori e/o sartani e/o Betabloccanti e controllo dopo un mese

- a) Recupera: rechallenge
- b) Non recupera: stop trastuzumab
- c) Recupera ma peggiora dopo rechallenge: stop oppure allunga gli intervalli



Disfunzione ventricolare sinistra sintomatica

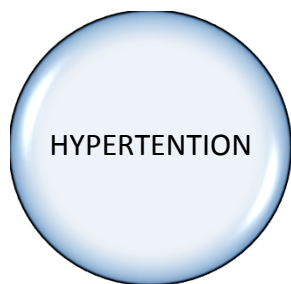
- **Stop chemioterapia**
- **Avviare terapia**
con ACE-inibitori e/o sartani e/o Betabloccanti $\pm$
antialdosteronici, diuretici, ivabradina
- **Controllo eco dopo un mese**
Se recupera, controllo a due mesi
Se non recupera (o non del tutto) adegua la terapia
- **Rechallenge** solo se indispensabile, con controlli stretti



Ipertensione arteriosa

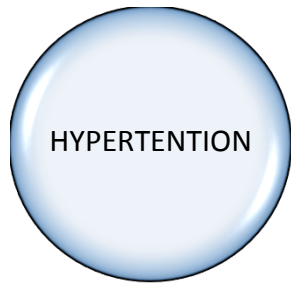
Più frequente e severa

- Con anti-VEGF diretti:
 - ✓ Bevacizumab 35%: spesso dura pochi giorni dopo l'infusione.
 - ✓ Emivita 20 gg, ma range 10-50 gg: possibile effetto cumulativo
 - ✓ TKI: Axitinib (40%), Pazopanib (40%), Sunitinib (35%), Cabozatinib (33%), Sorafenib (25%), everolimus (10%)
 - ✓ Solitamente compare e regredisce rapidamente
- In pazienti già ipertesi
- In pazienti con insufficienza renale



Scegliere la terapia anti-ipertensiva in base alla terapia antineoplastica

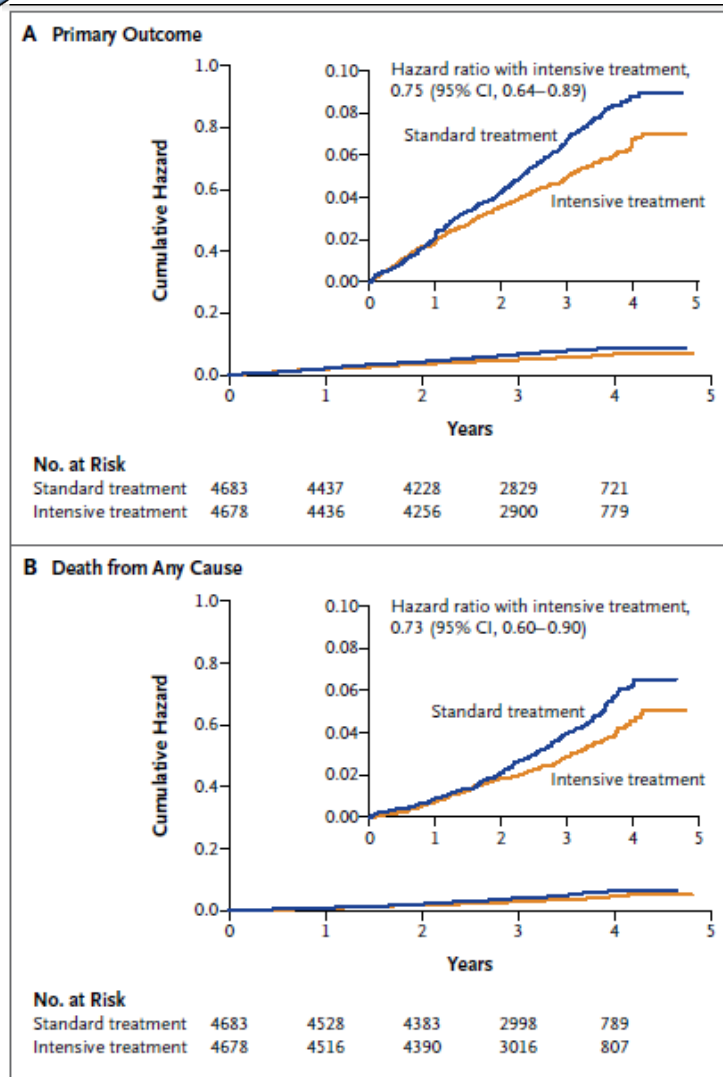
Antracicline, Herceptin... disfunzione ventricolare	ACE-inibitori, Sartani, Betabloccanti effetto cardioprotettivo
Fluoropirimidine vasospasmo, ischemia, bradicardia	Calcioantagonisti attivi anche per ischemia (amlodipina, nifedipina) effetto anti-spastico su coronarie
Bevacizumab ipertensione	Nebivololo, ACE-inibitori, Sartani, Betabloccanti, Diuretici
TKI disfunzione ventricolare, ipertensione. (CytP450!)	ACE-inibitori, Sartani, Atenololo, Diuretici, Clonidina? MA: attenzione a bradicardia (sunitinib). NO CALCIOANTAGONISTI per rischio interferenza
Taxani tachicardia, edemi	Betabloccanti, diuretici NO CALCIOANTAGONISTI (edemi)



Terapia dell'ipertensione correlata ad anti VEGF

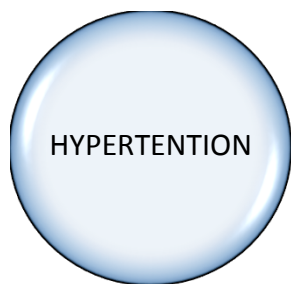
- **ACE inibitori o sartani:** Ramipril o losartan, valsartan, candesartan, irbesartan e telmisartan sono usati in alternativa o in associazione con CCB. **Attenzione ai pazienti con insufficienza renale**
- **Calcio-antagonisti:** sono particolarmente efficaci ma possono essere usate solo amlodipina e nifedipina. **Calcio antagonisti non-diidropiridinici** (es: diltiazem e verapamil) **non dovrebbero essere usati in combinazione con gli antiVEGF per l'interazione con l'isoenzima CYP3A4**, concorrendo all'aumento dei livelli ematici del sorafenib, sunitinib, o di altri farmaci.
- **Beta-bloccanti** principalmente il nebivololo può essere usato da solo o in associazione con altri farmaci. **Attenzione agli effetti collaterali** bradicardia, astenia, asma.
- **Diuretici tiazidici** possono essere usati **attenzione agli effetti collaterali** come l'ipercalcemia, ipokalemia, e QT lungo.

The SPRINT Research Group, a Randomized Trial of Intensive versus Standard Blood-Pressure Control



a systolic blood-pressure target of **less than 120 mm Hg** (intensive treatment) or a target of less than 140 mm Hg (standard treatment without diabetes)

Shown are the **cumulative hazards for the primary outcome** (a composite of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) (Panel A) **and for death from any cause** (Panel B).



Take home messages: controllare l'ipertensione

prima

- Ottimizzare la terapia prima della chemioterapia
- Utilizzare farmaci a basso rischio di interazione con i TKI
- Raccomandare uno stile di vita sano

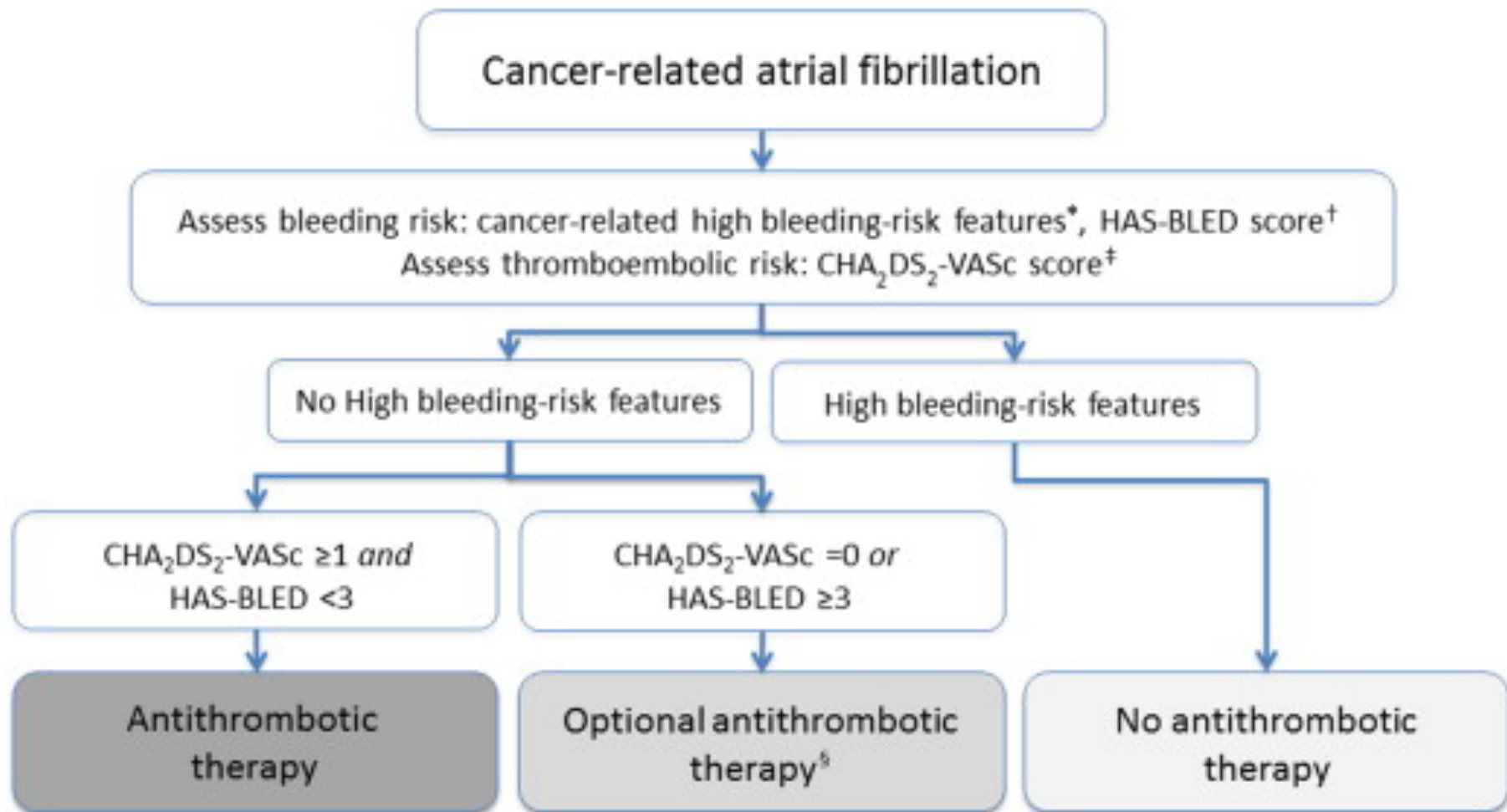
Table 3 Definitions and classification of office blood pressure levels (mmHg)^a

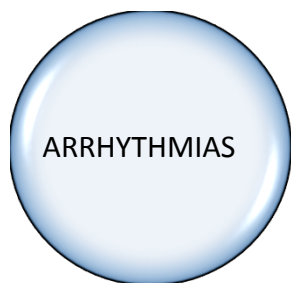
Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

dopo

- Far controllare la PA a domicilio e riportare le misure a ogni visita
- Oncologo: chiedere consulenza cardiologica se PAO di difficile controllo
- Adeguare prontamente la terapia (evitare crisi ipertensive)

Algorithm for Antithrombotic Therapy in Cancer-Related Atrial Fibrillation





QTc intervallo correlato al grado di tossicità

QTc prolongation Grade	Definition
Grade I	QTc >450 – 470 ms
Grade II	QTc >450–500 ms or > 60 ms above baseline
Grade III	QTc >500 ms
Grade IV	QTc >500 ms; life-threatening signs or symptoms (syncope, shock, hypotension, arrhythmia, heart failure)
Grade V	Death

Common terminology criteria for adverse events v3.0 (CTCAE), QT prolongation

QTc >470 milliseconds o variazione >60 milliseconds
rispetto al basale:

sono i comuni criteri utilizzati quale indice di cardiotossicità

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: The clinical evaluation of QT/QTc prolongation and pro-arrhythmic potential for non-antiarrhythmic drugs: E14. Geneva, Switzerland:

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: 2005. Available at: <http://www.ich.org/LOB/media/MEDIA1476.pdf>. Last accessed July 22, 2010.

Aritmie ventricolari da allungamento del QT: prevenzione

Farmaci potenzialmente a rischio di prolungare l' intervallo QT.

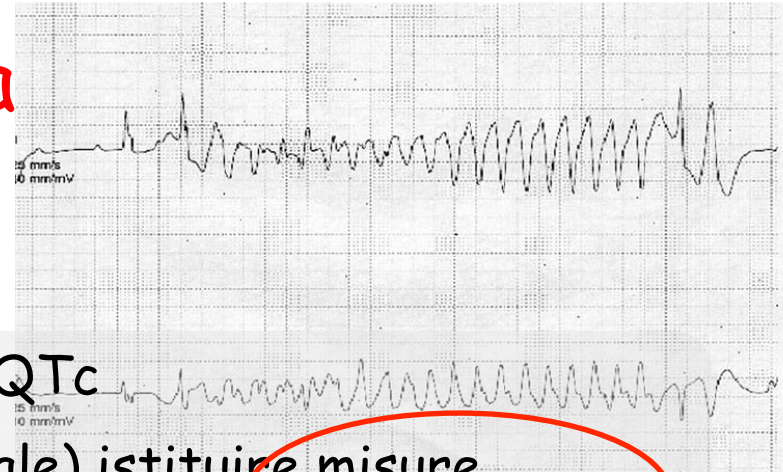
Farmaci cardiovascolari	Farmaci SNC		Farmaci respiratorio	Farmaci antivirali	Farmaci decongestionanti nasali e antistaminici
Amiodarone	Aloperidolo	Olanzapina	Salbutamolo	Amantidina	Fenilefrina
Chinidina	Amitriptilina	Paroxetina	Salmeterolo	Foscarnet	Fenilpropanolamina
Disopiramide	Citalopram	Quetiapina	Terbutalina		Pseudoefedrina
Dobutamina	Cloralio idrato	Risperidone		Farmaci antiparassitari	Terfenadina
Dopamina	Clorpromazina	Sertindolo		Cloroquina	
Efedrina	Clomipramina	Sertralina	Farmaci antibatterici	Meflochina	Altri farmaci
Epinefrina	Droperidolo	Tioridazina	Azitromicina	Pentamidina	Alfuzosina
Flecainide	Felbamato	Tizanidina	Ciprofloxacina		Octreotide
Ibutilide	Fluoxetina	Trimipramina	Claritromicina	Farmaci antimicotici	Sibutramina
Indapamide	Galantamina	Venlafaxina	Eritromicina	Fluconazolo	Tacrolimus
Isradipina	Imipramina	Farmaci GI	Levofloxacina	Itraconazolo	Tamoxifene
Midodrina	LevomEPROMAZINA	Dolasetron	Moxifloxacina	Ketoconazolo	Vardenafil
Norepinefrina	Litio	Domperidone	Ofloxacina	Voriconazolo	
Sotalolo	Metadone	Granisetron	Cotrimossazolo		
	Metilfenidato	Ondansetron			
	Nortriptilina				

- deidratazione, denutrizione

ellaneous

Ascorbic trioxide

Perché il QT lungo ci fa paura ?

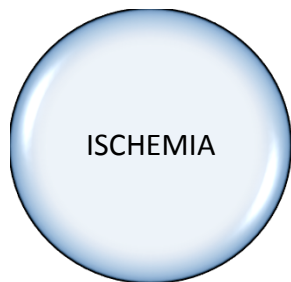


- ECG basale a 12 derivazioni con QTc
- QTc > 470 msec (o > 60 risp. basale) istituire misure correttive

- controllo creatinina, magnesio, calcio, sodio e potassio
- correggere elettroliti ($K^+ > 4 \text{ meq/l}$, $Mg^{2+} > 1,8 \text{ mg/dl}$)
- sospendere farmaci concomitanti che possono determinare l'allungamento del QT



- rivalutare QTc
- rischio / beneficio



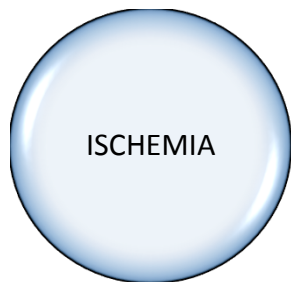
Tossicità severa da fluopiriridine 5FU- capecitabine

- **STOP** farmaco
- Ricovero, prevalentemente in presenza di gravi alterazioni ECG o aritmie

Terapia

- ✓ Nitrati
- ✓ Calcio antagonisti (diltiazem forse maggiormente efficace ?)
- ✓ Nebivololo?

➤ associazione di farmaci



Rechallenge dopo tossicità?

Alto rischio di recidiva: nessuna terapia protettiva al 100%

- Evitare il rechallenge se possibile
- Se indispensabile:
 - ✓ Ridurre dose e/o durata di somministrazione (boli settimanali o infusioni di 24-36 ore invece che 3-5 gg; 1 settimana on/1 off per capecitabina)
 - ✓ Associare nitrati e Ca-antagonisti (diltiazem, amlodipina)
 - ✓ Monitoraggio ECG quotidiano se possibile (+ Holter e/o stress test)
- Considerare alternative:
 - ✓ Raltitrexed
 - ✓ Tegafur

Thromboembolism

Predictive Model for Chemotherapy-Associated Venous Thromboembolism

VARIABLE	RISK SCORE ^a
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count $\geq 350 \times 10^9/L$	1
Hemoglobin level < 10 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count $> 11 \times 10^9/L$	1
Body mass index ≥ 35 kg/m ²	1

^aRisk categories included low risk (score 0), intermediate risk (score 1–2), and high risk (score ≥ 3). Modified from Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111:4902–4907.¹⁶⁷

The prophylactic use of LMWH may be considered for highly selected, high-risk patients only, according to the risk-assessment model validated by Khorana, in patients with scores ≥ 3 and a low bleeding risk.



Grazie dell' attenzione