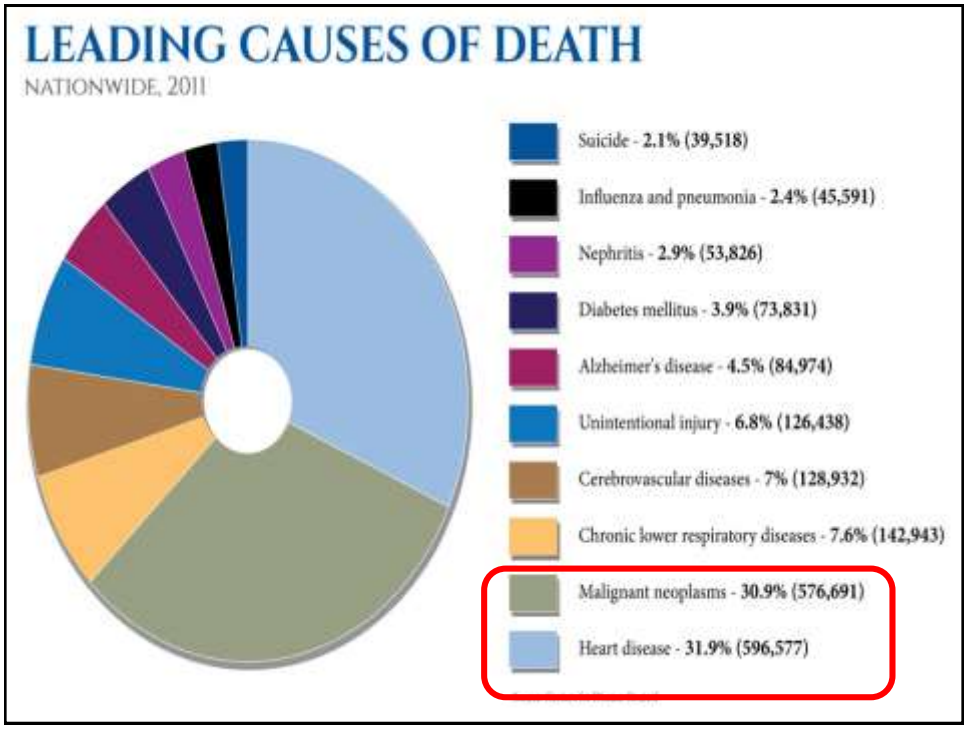
Prevention of CV complications of anti-cancer treatment

Waleed Abdou
Assistant Professor of Cardiology
Menoufia University



Improvements in longevity after cancer

Site	5 year survival 1975 (%)	2007 (%)	% increase
Overall	50	67	17
Childhood	30	79	49
Prostate	67	99	32
Breast	75	90	15
Colon	51	65	14
Lung	12	16	4

- Dramatic improvements in early detection and adjuvant therapy
- Significant survival gains
  - 13.7M cancer survivors in the US (~25M worldwide)
  - Projected 18M US cancer survivors by 2022

American Cancer Society, Surveillance Research 2012

- **After surviving cancer, patients are more likely to die of heart disease than recurrence of cancer.**
- **This has led to increasing awareness of potential damaging cardiac effects associated with cancer therapies.**
- **Emphasis on ways to diagnose and prevent these occurrences is crucial.**

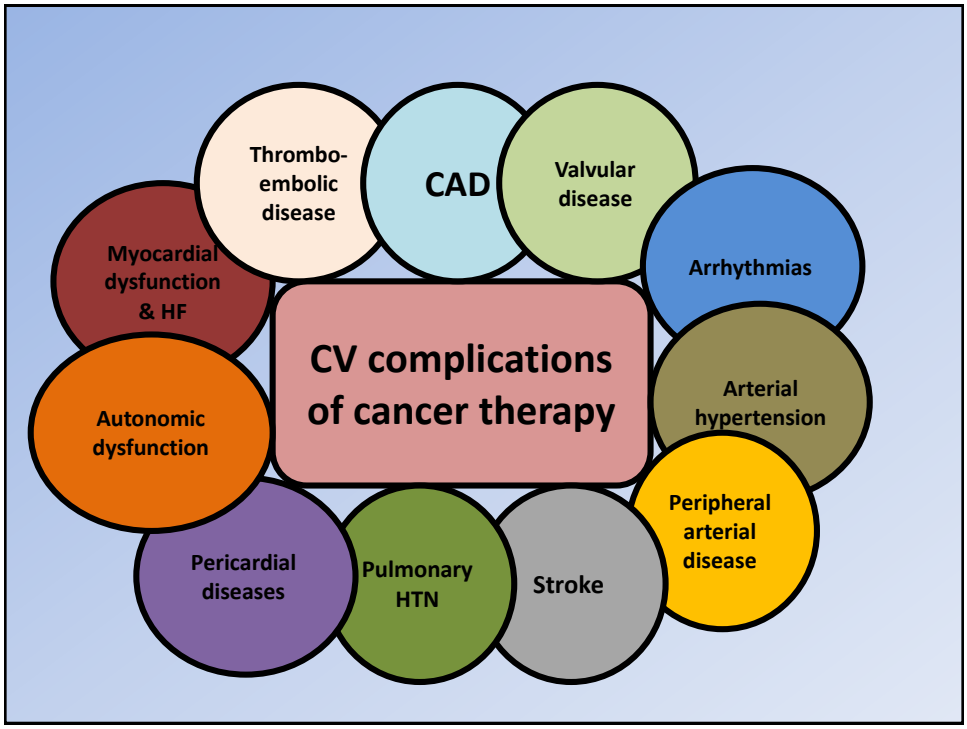
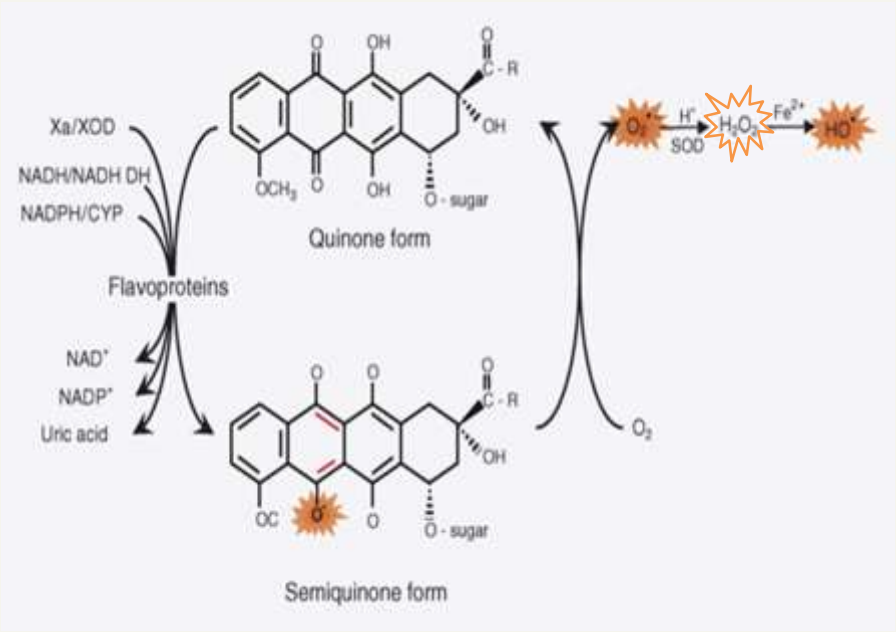


Table 1 Incidence of left ventricular dysfunction associated with chemotherapy drugs[10–21]

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m² 550 mg/m² 700 mg/m²	 3–5 7–26 18–48
Idarubicin (>90 mg/m²)	5–18
Epirubicin (>900 mg/m²)	0.9–11.4
Mitoxanthone >120 mg/m²	2.6
Liposomal anthracyclines (>900 mg/m²)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide <10 g/m² 12.5–16 g/m²	 0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1
Monoclonal antibodies	
Trastuzumab	1.7–20.1[28a]
Bevacizumab	1.6–4[14b]
Pertuzumab	0.7–1.2

Pathogenesis:



Free radicals (H_2O_2, HO):

- Highly reactive and damaging to tissues such as proteins, lipids and nucleic acids, leading to modifications that affect the nucleus, the sarcoplasmic reticulum and the mitochondria.
- The heart is predisposed to oxidative stress because of relatively low levels of antioxidant enzymes.

European Heart Journal Advance Access published August 26, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

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

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

Authors/Task Force Members: Jose Luis Zamorano* (Chairperson) (Spain), Patrizio Lancellotti* (Co-Chairperson) (Belgium), Daniel Rodriguez Muñoz (Spain), Victor Aboyans (France), Riccardo Asteggiano (Italy), Maurizio Galderisi (Italy),

Prevention of myocardial dysfunction

1. Screening for CV risk factors.
2. Dose limitation.
3. Dosing Schedules modification.
4. Use different forms of anthracyclines that cause less cardiotoxicity.
5. Use cardioprotective agent (Dexrazoxane).
6. Use agents to prevent the cardiotoxicity.

1- Screening for CV risk factors

- Identify and treat CV risk factors.
- Treat comorbidities (CAD, PAD).
- LVEF assessment:
  1. ≤ 30% → Don't give anthracyclines.
  2. 30%–50%
  3. ≥ 50%

  Give with monitoring of LVEF & Repeat evaluation at 250–300 mg/m^2 and again at 450 mg/m^2 cumulative dose.

10% decrease in LVEF or a drop from ≥ 50% to < 50%.
Drop from 30%–50% to < 30%.
→ Stop anthracyclines

2- Dose limitation

keep the total lifetime cumulative dose below the recommended threshold:

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m^2 550 mg/m^2 700 mg/m^2	 3–5 7–26 18–48
Idarubicin (>90 mg/m^2)	5–18
Epirubicin (>900 mg/m^2)	0.9–11.4
Mitoxanthone >120 mg/m^2	2.6
Liposomal anthracyclines (>900 mg/m^2)	2

3- Dosing Schedules

It should be as possible in:

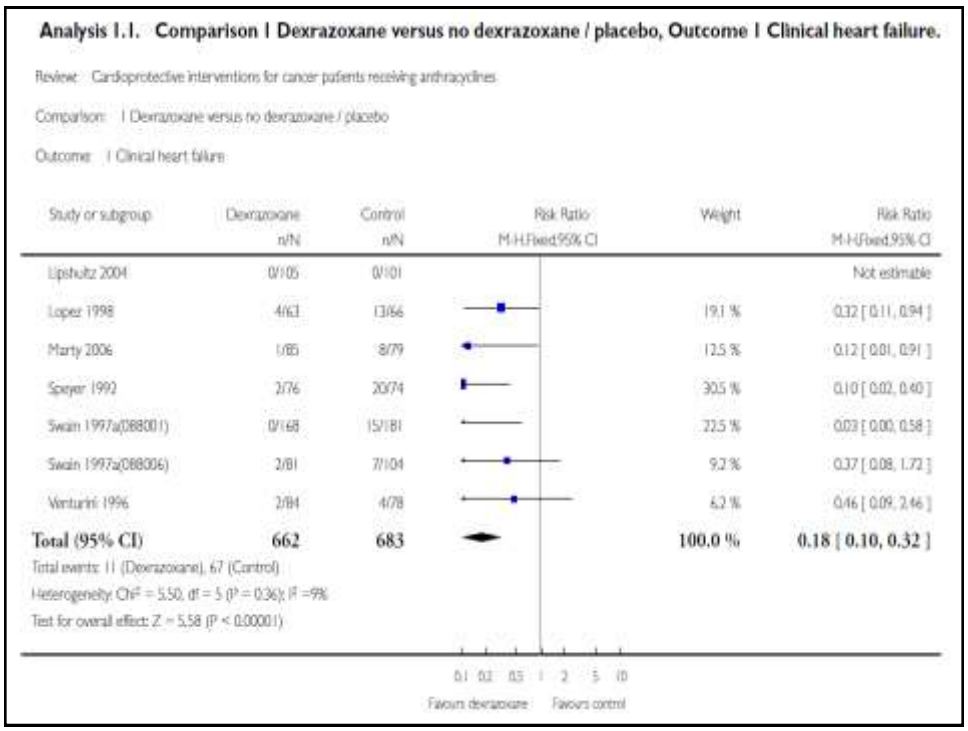
- Smaller, frequent dosing.
- Weekly doses.
- Continuous infusion.

4- Use different forms of anthracyclines that cause less cardiotoxicity

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m² 550 mg/m² 700 mg/m²	 3–5 7–26 18–48
Idarubicin (>90 mg/m²)	5–18
Epirubicin (>900 mg/m²)	0.9–11.4
Mitoxanthone >120 mg/m²	2.6
Liposomal anthracyclines (>900 mg/m²)	2

5- Use cardioprotective agent (Dexrazoxane)

- Dexrazoxane is an oral iron chelator.
- It prevents the role of iron in production of free radicals.
- It has been tested in many clinical trials and has been shown to reduce cardiac toxicity
- The recommended dosage ratio of dexrazoxane to doxorubicin is 10:1; doxorubicin should be given within 30 minutes of giving dexrazoxane.



Analysis 1.1. Comparison 1 Dexrazoxane versus no dexrazoxane / placebo, Outcome 1 Clinical heart failure.

Review: Cardioprotective interventions for cancer patients receiving anthracyclines

Comparison: 1 Dexrazoxane versus no dexrazoxane / placebo

Outcome: 1 Clinical heart failure

Study or subgroup	Dexrazoxane n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lipshultz 2004	0/105	0/101			Not estimable
Lopez 1998	4/63	13/66		19.1 %	0.32 [0.11, 0.94]
Marty 2006	1/85	8/79		12.5 %	0.12 [0.01, 0.91]
Speyer 1992	2/76	20/74		30.5 %	0.10 [0.02, 0.40]
Swain 1997a(088001)	0/168	15/181		22.5 %	0.03 [0.00, 0.58]
Swain 1997a(088006)	2/81	7/104		9.2 %	0.37 [0.08, 1.72]
Venturini 1996	2/84	4/78		6.2 %	0.46 [0.09, 2.46]
Total (95% CI)	**662**	**683**		**100.0 %**	**0.18 [0.10, 0.32]**

Total events: 11 (Dexrazoxane), 67 (Control)

Heterogeneity: $Chi^2 = 5.50$, $df = 5$ ($P = 0.36$); $I^2 = 9\%$

Test for overall effect: $Z = 5.58$ ($P < 0.00001$)

0.1 0.2 0.5 1 2 5 10

Favours dexrazoxane Favours control

6- Drugs to prevent cardiotoxicity

These include

1. **Angiotensin-converting enzyme (ACE) inhibitors.**
2. **Angiotensin II receptor blockers (ARBs).**
3. **Beta blockers.**
4. **Statins.**

European Heart Journal Advance Access published February 21, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw022

AHA FASTTRACK
CLINICAL RESEARCH

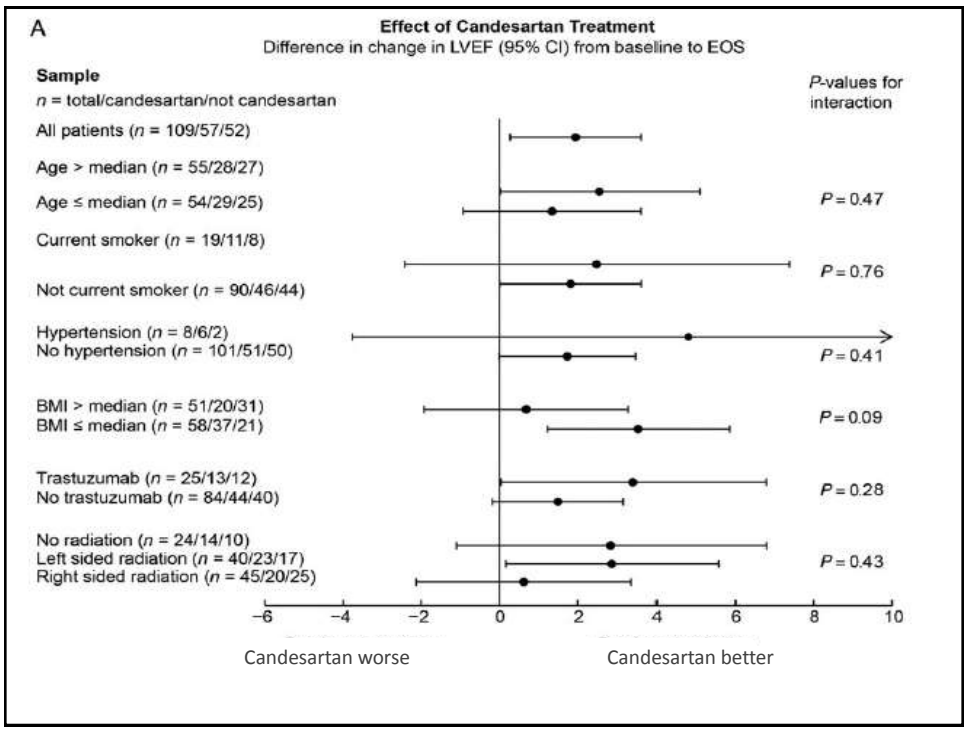
Heart failure/cardiomyopathy

Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol

Geeta Gulati[1,2†], Siri Lagethon Heck[1,2†], Anne Hansen Ree[3,4], Pavel Hoffmann[5], Jeanette Schulz-Menger[6,7], Morten W. Fagerland[8], Berit Gravdehaug[9], Florian von Knobelsdorff-Brenkenhoff[6], Åse Bratland[10], Tryggve H. Storås[11],

Table 2 Primary and secondary endpoints, estimated values from linear mixed models (intention-to-treat analysis)

	n	Baseline	EOS	Change from baseline to EOS	Between-group difference in change from baseline to EOS	*P*-value
LVEF						
No candesartan	60	63.2 (62.0, 64.4)	60.6 (59.4, 61.8)	−2.6 (−3.8, −1.5)	1.9 (0.2, 3.5)[a]	0.026
Candesartan	60	62.1 (61.0, 63.3)	61.4 (60.2, 62.6)	−0.8 (−1.9, 0.4)		
No metoprolol	62	62.8 (61.6, 64.0)	61.0 (59.8, 62.2)	−1.8 (−3.0, −0.7)	0.2 (−1.4, 1.9)	0.772
Metoprolol	58	62.5 (61.3, 63.7)	61.0 (59.8, 62.2)	−1.6 (−2.8, −0.4)		
RVEF						
No candesartan	60	61.3 (60.0, 62.5)	58.9 (57.6, 60.1)	−2.4 (−3.7, −1.1)	0.8 (−1.0, 2.6)	0.370
Candesartan	60	60.2 (59.0, 61.4)	58.7 (57.4, 59.9)	−1.6 (−2.8, −0.3)		
No metoprolol	62	60.4 (59.2, 61.6)	58.0 (56.8, 59.3)	−2.4 (−3.7, −1.1)	0.8 (−1.0, 2.6)	0.377
Metoprolol	58	61.1 (59.8, 62.3)	59.5 (58.3, 60.8)	−1.6 (−2.9, −0.3)		
LV GLS						
No candesartan	48	−21.6 (−22.1, −21.1)	−21.0 (−21.5, −20.5)	0.6 (0.1, 1.1)	−0.7 (−1.4, 0.1)	0.076
Candesartan	45	−21.3 (−21.8, −20.7)	−21.3 (−21.9, −20.8)	−0.1 (−0.6, 0.5)		
No metoprolol	46	−21.4 (−21.9, −20.8)	−21.0 (−21.6, −20.5)	0.3 (−0.2, 0.8)	−0.1 (−0.8, 0.7)	0.824
Metoprolol	47	−21.5 (−22.0, −21.0)	−21.3 (−21.8, −20.7)	0.2 (−0.3, 0.7)		
E/E'						
No candesartan	63	7.1 (6.6, 7.6)	7.2 (6.7, 7.7)	0.1 (−0.4, 0.5)	0.1 (−0.5, 0.8)	0.688
Candesartan	59	7.4 (6.9, 7.9)	7.6 (7.1, 8.1)	0.2 (−0.2, 0.7)		
No metoprolol	62	7.4 (7.0, 7.9)	7.2 (6.7, 7.7)	−0.3 (−0.7, 0.2)	0.8 (0.2, 1.5)	0.009
Metoprolol	60	7.1 (6.6, 7.5)	7.6 (7.1, 8.1)	0.6 (0.1, 1.0)		



(*Circulation*. 2006;114:2474-2481.)

Heart Failure

Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

Daniela Cardinale, MD; Alessandro Colombo, MD; Maria T. Sandri, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Maurizio Civelli, MD; Giovanni Martinelli, MD; Fabrizio Veglia, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

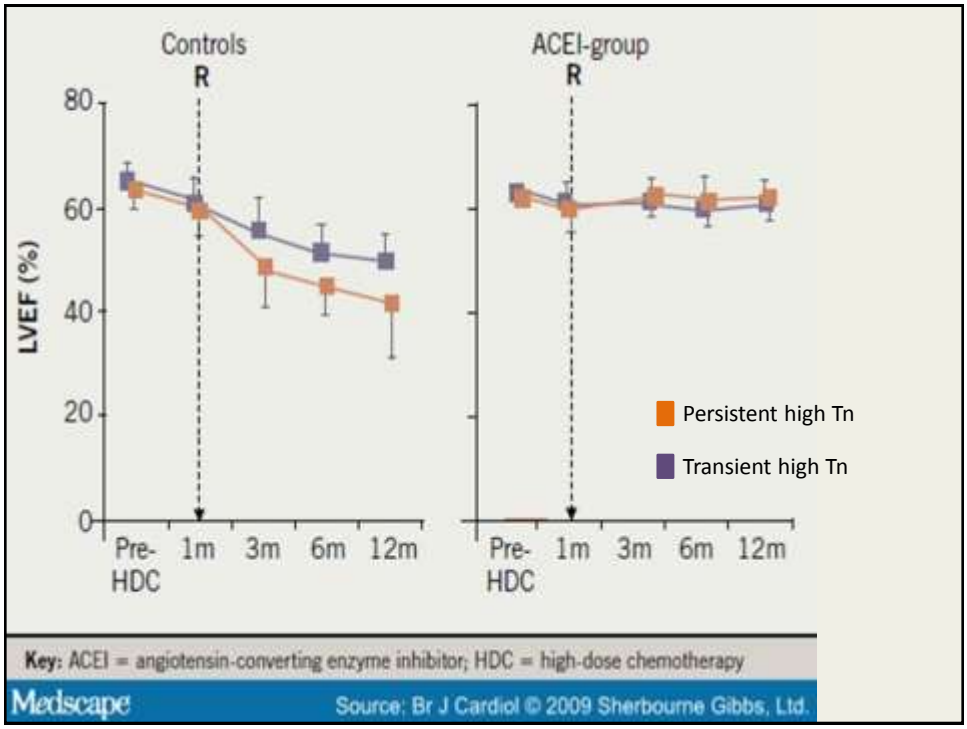
Background—An increase in troponin I soon after high-dose chemotherapy (HDC) is a strong predictor of poor cardiological outcome in cancer patients. This finding has important clinical implications and provides a rationale for the development of prophylactic strategies for preventing cardiotoxicity. Angiotensin-converting enzyme inhibitors slow the progression of left ventricular dysfunction in different clinical settings, but their role in the prevention of cardiotoxicity has never been investigated.

Methods and Results—Of the 473 cancer patients evaluated, 114 (72 women; mean age, 45±12 years) who showed a

TABLE 4. Cardiac Events in the Study Groups

	Total (n=114), n (%)	ACEI Group (n=56), n (%)	Control Subjects (n=58), n (%)	*P*
Sudden death	0 (0)	0 (0)	0 (0)	1.0*
Cardiac death	2 (2)	0 (0)	2 (3)	0.49*
Acute pulmonary edema	4 (3)	0 (0)	4 (7)	0.07*
Heart failure	14 (12)	0 (0)	14 (24)	<0.001
Arrhythmias requiring treatment	11 (10)	1 (2)	10 (17)	0.01
Cumulative events	31	1	30	<0.001

*Fisher exact test.



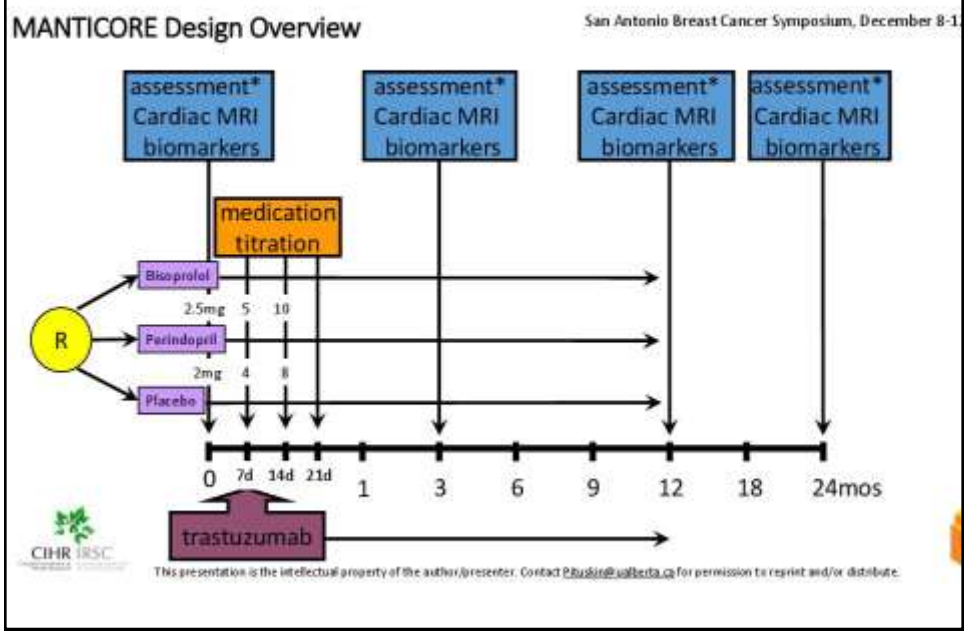
DOI 10.1002/cncr.21478
Published online 24 October 2005 in Wiley InterScience (www.interscience.wiley.com).

Notable Effects of Angiotensin II Receptor Blocker, Valsartan, on Acute Cardiotoxic Changes after Standard Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone

Valsartan significantly reduced changes in the left ventricular end-diastolic diameter, the QTc interval and QTc dispersion on the ECG. Future long-term studies are necessary to judge whether ARBs have a potential to prevent the chronic or late-onset types of doxorubicin-induced cardiotoxicity.

SAN ANTONIO BREAST CANCER SYMPOSIUM 2015

Prophylactic beta blockade preserves left ventricular ejection fraction in breast cancer patients receiving trastuzumab: primary results of MANTICORE randomized controlled trial



San Antonio Breast Cancer Symposium, December 8-12, 2015

Results – Cardiac MRI

	Placebo (N=30)	Perindopril (N=33)	Bisoprolol (N=31)	ANOVA P value
Pre LVEDVi (ml/m²)	76 ± 13*	67 ± 14	69 ± 10	**< 0.01**
Post LVEDVi (ml/m²)	79 ± 12	74 ± 16†	76 ± 14†	**0.27**
Δ LVEDVi from baseline	+4 ± 11	+7 ± 14	+8 ± 9	**0.36**
Pre LVEF (%)	61 ± 5	62 ± 5	62 ± 4	**0.55**
Post LVEF (%)	56 ± 4*†	59 ± 6†	61 ± 4	**0.0001**
Δ LVEF from baseline	-5 ± 5	-3 ± 4	-1 ± 5*	**0.001**
Trastuzumab interruptions due to drop in LVEF	8*	1	1	**0.002**

* P < 0.05 compared to other groups, † P < 0.05 from baseline

Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 48, No. 11, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.07.052

Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy

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

Kayseri, Turkey

OBJECTIVES The aim of this study was to determine the protective effect of carvedilol in anthracycline (ANT)-induced cardiomyopathy (CMP).

BACKGROUND Despite its broad effectiveness, ANT therapy is associated with ANT-induced CMP. Recent animal studies and experimental observations showed that carvedilol prevented development of CMP due to chemotherapeutics. However, there is no placebo-controlled clinical trial concerning prophylactic carvedilol use in preventing ANT-induced CMP.

METHODS Patients in whom ANT therapy was planned were randomized to administration of carvedilol or placebo. We enrolled 25 patients in carvedilol and control groups. In the carvedilol group, 12.5 mg once-daily oral carvedilol was given during 6 months. The patients were evaluated with echocardiography before and after chemotherapy. Left ventricular ejection fraction (EF) and systolic and diastolic diameters were calculated.

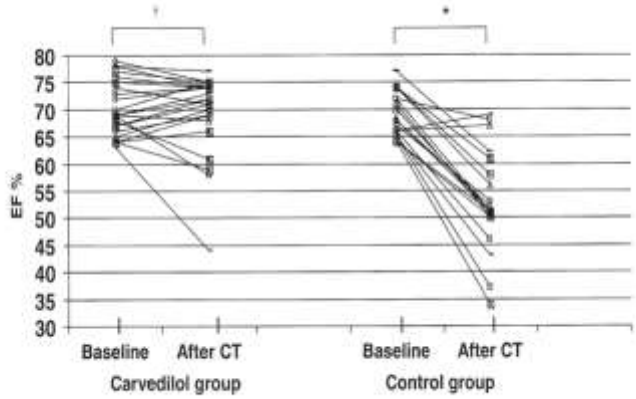
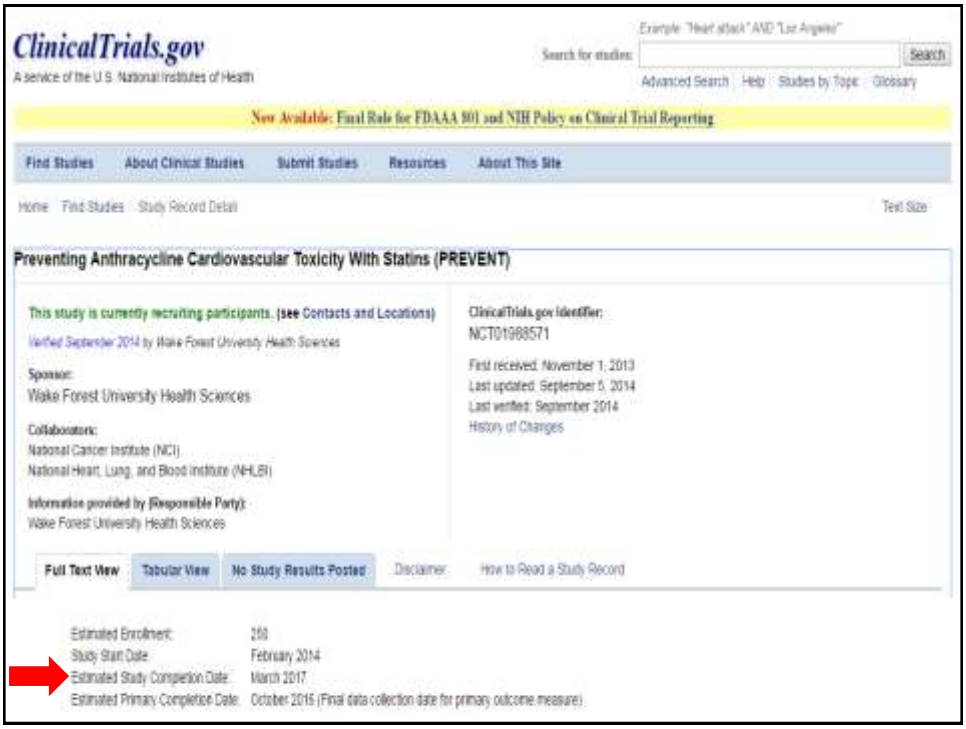
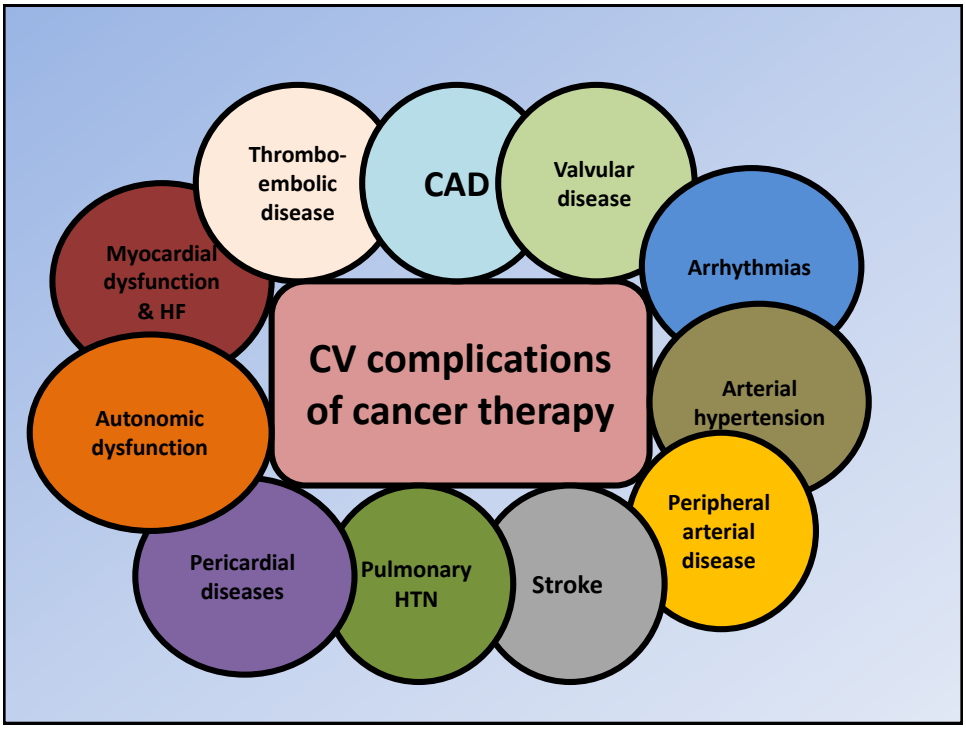


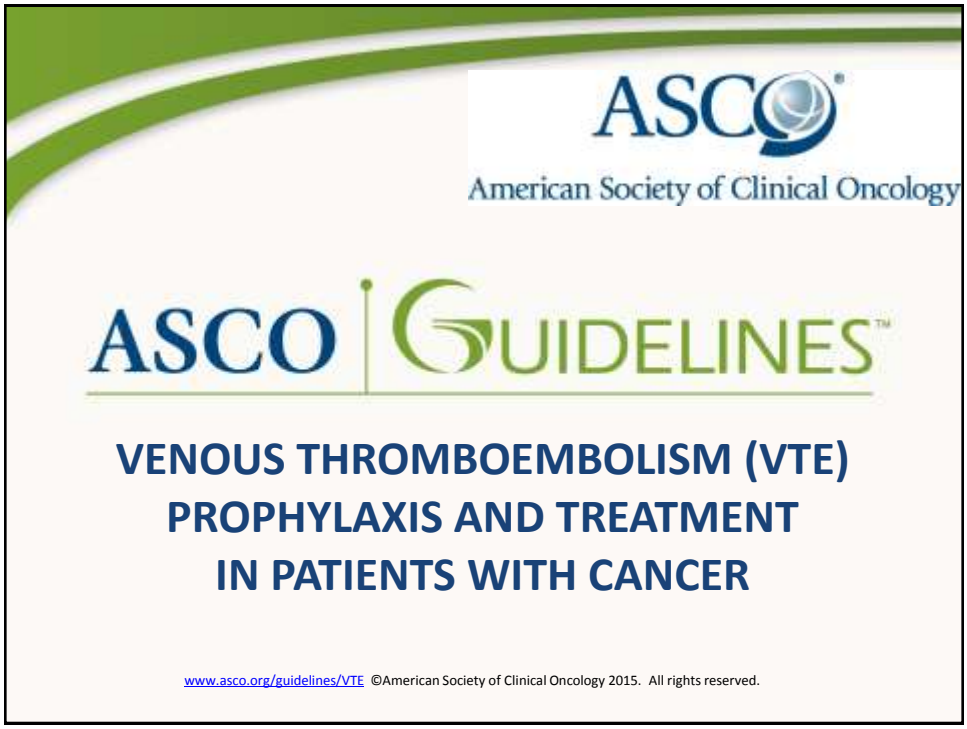
Figure 2. Individual systolic function data at baseline and after chemotherapy (CT) in the 2 groups. *p < 0.001; †p = 0.3. EF = ejection fraction.





Scope of the problem:

- Among patients with malignancy, VTE is one of the leading causes of mortality.
- Up to 50% of cancer patients may have evidence of asymptomatic DVT/PE.
- The risk of VTE in cancer patients undergoing surgery is 3-5 folds higher than those without cancer.
- Patients with cancer have higher risk of bleeding on anticoagulants.



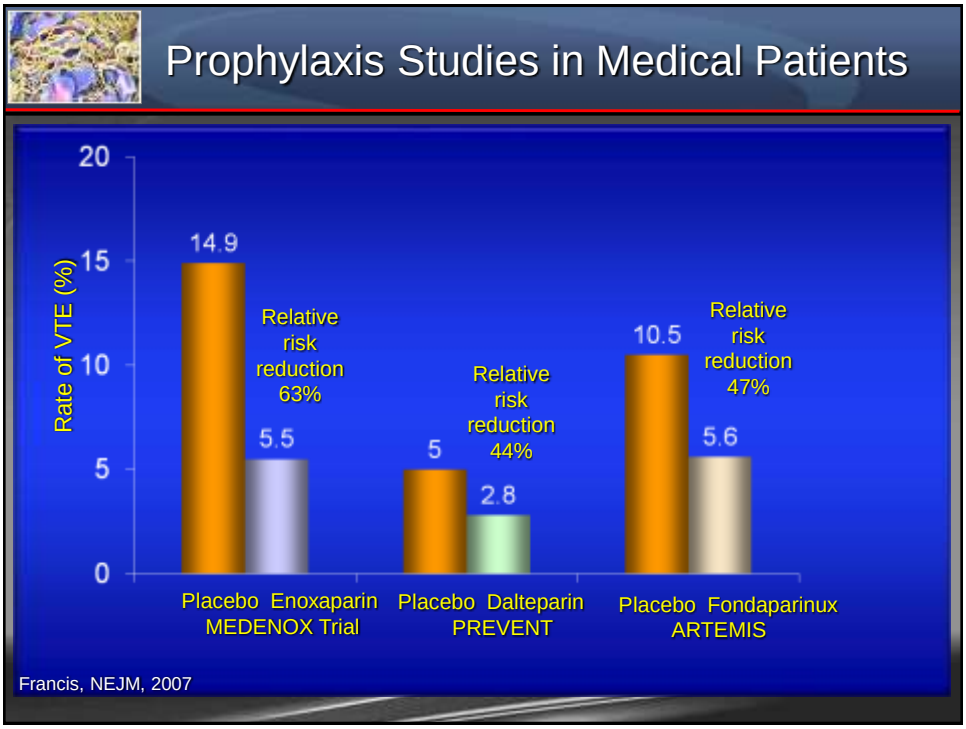
Should ambulatory outpatients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy ?

- Routine pharmacologic thromboprophylaxis is not recommended in cancer outpatients.
- Based on limited RCT data, clinicians may consider LMWH prophylaxis on an individual basis in high risk selected outpatients with solid tumors receiving chemotherapy.

Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis ?

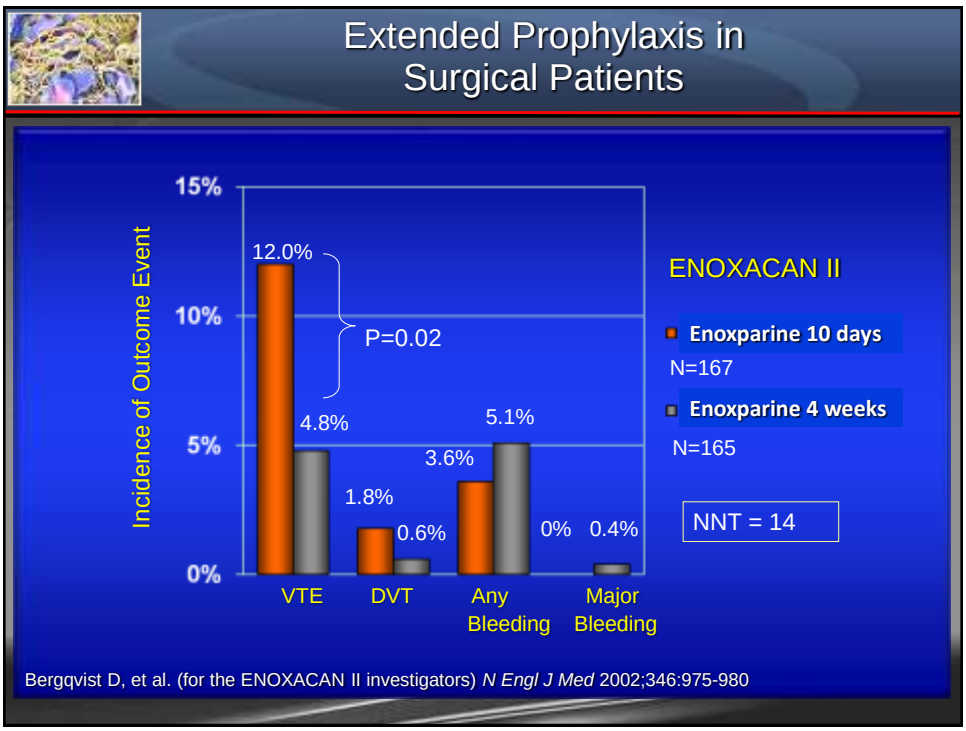
- Hospitalized patients who have active malignancy with acute medical illness or reduced mobility should receive pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications

- Data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion.



Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?

- All patients with malignant disease undergoing major surgical intervention should receive thromboprophylaxis with either UFH or LMWH unless contraindicated .
- A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients.
- Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7-10 days.
- Extended prophylaxis with LMWH for up to 4 weeks postoperatively should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE.



Take home message

- Cancer chemotherapy can cause short & long term cardiovascular complications.
- The Cardiovascular complications from cancer chemotherapy are considered the chief threats to the cancer patient's survival.
- A collaborative effort among specialists involved in the treatment of patients with cancer is critical to prevent and manage cardiotoxicity without compromising cancer care, to maximize the patient's overall outcome.