

Monitoring, Diagnosis and Mitigation of Cardiotoxicity

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Presenter Disclosure Information

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- I **will not** discuss off label use or investigational use in my presentation.
- I **have** financial relationships to disclose:
 - Research support from: Myocardial Solutions, Inc
 - Consultant (modest): AstraZeneca, BMS, OncXerna, Clementia, Eidos

How/why did Cardio-Oncology get started?

Because cardiac safety is a major concern wherever you are



The screenshot shows an MSNBC news article. The MSNBC logo is in the top left. The breadcrumb trail is 'MSNBC Home > Health > Cancer'. The main headline is 'Drug firm says cancer drug can raise heart risk' in red, with a sub-headline 'Herceptin significantly increases 'cardiotoxicity' in patients, Genentech says'. The article is attributed to 'REUTERS' and is dated 'Updated: 3:00 p.m. ET Aug. 31, 2005'. The text of the article begins with 'WASHINGTON - An early review of a recent study showed Genentech Inc.'s cancer drug Herceptin can significantly increase the risk of heart problems, the company said in a letter released by U.S. regulators Wednesday.' On the left side, there is a 'Health' sidebar with links to 'Health Library', 'Katrina's Impact', 'Women's Health', 'Diet & Fitness', 'Men's Health', 'Cancer', 'Children's Health', 'Infectious Diseases', and 'Aging'. On the right side, there is a 'Q & A LIBRARY' section with the heading 'Click on a topic to learn more:' and a list of topics: 'Breast cancer', 'Colon cancer', 'Melanoma', 'Ovarian cancer', and 'Prostate cancer'. At the bottom right, there is a 'RELATED STORIES' section with a link to 'What's this?'.

Increased Risk Of Fatal Side Effects From 3 'Targeted' Cancer Drugs

Medical News Today

Treatment with three relatively new "targeted" [cancer](#) drugs has been linked to a slightly elevated chance of fatal side effects, according to a new analysis led by scientists at Dana-Farber Cancer Institute.

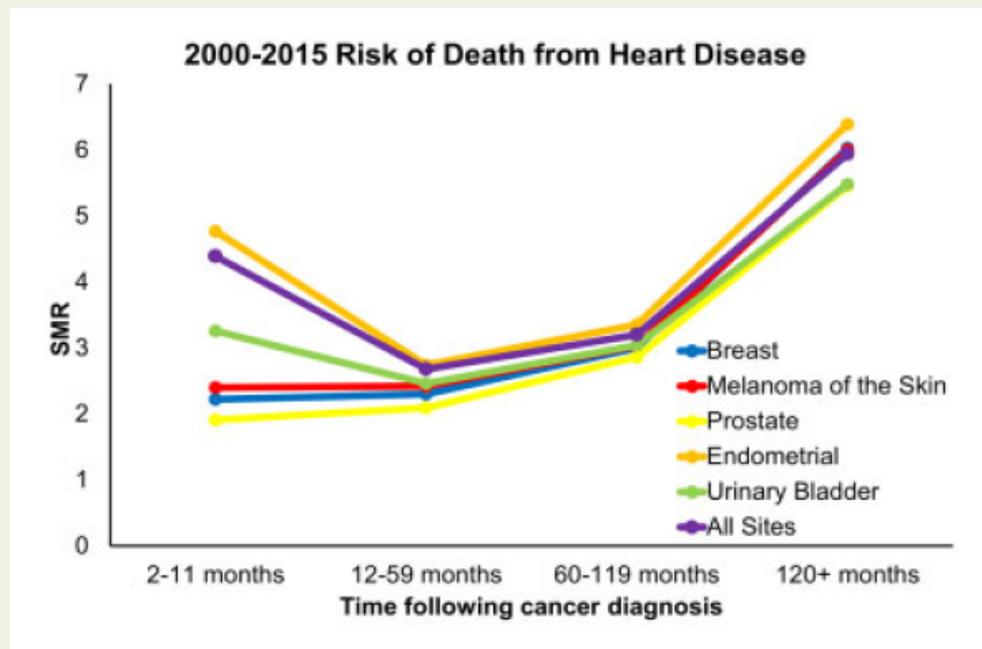
<http://www.medicalnewstoday.com/releases/241256.php>

A population-based study of cardiovascular disease mortality risk in US cancer patients

Kathleen M. Sturgeon^{1†}, Lei Deng^{2†}, Shirle Daniel M. Trifiletti³, Changchuan Jiang⁴, Scot

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Take home figure Standardized mortality ratios for cancer sites with both $\leq 30\%$ risk of death from the index-cancer and $\geq 20\%$ risk of mortality from heart disease were calculated and binned by follow-up time. Cancers sites with at least 1000 person years of risk for death from heart disease between 2000 and 2015 were displayed.

Just look at the developments over the last 45 years.....

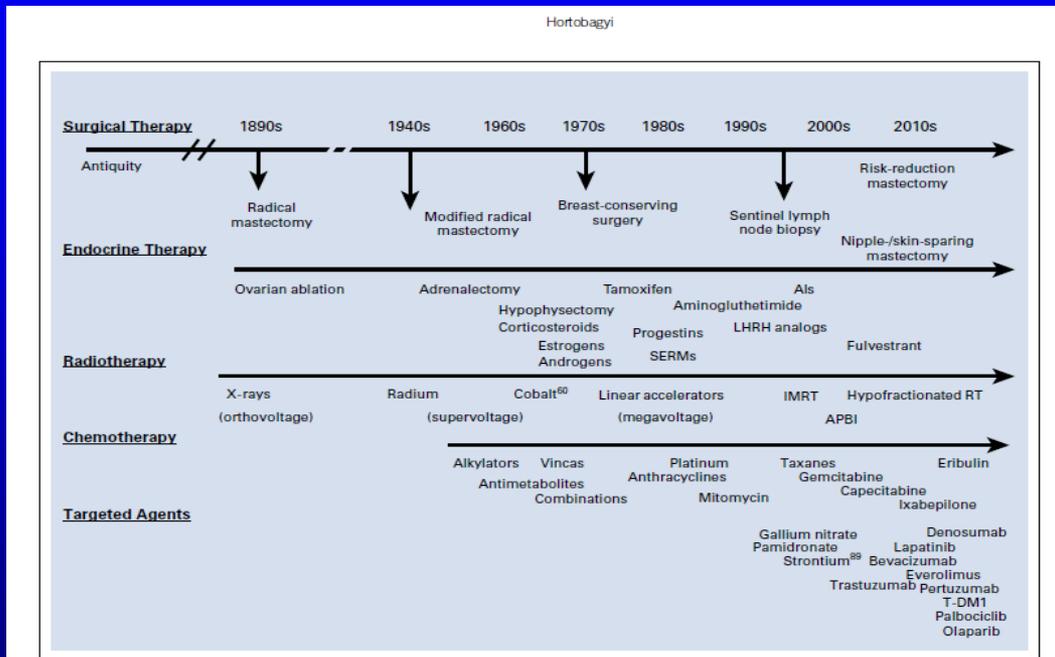
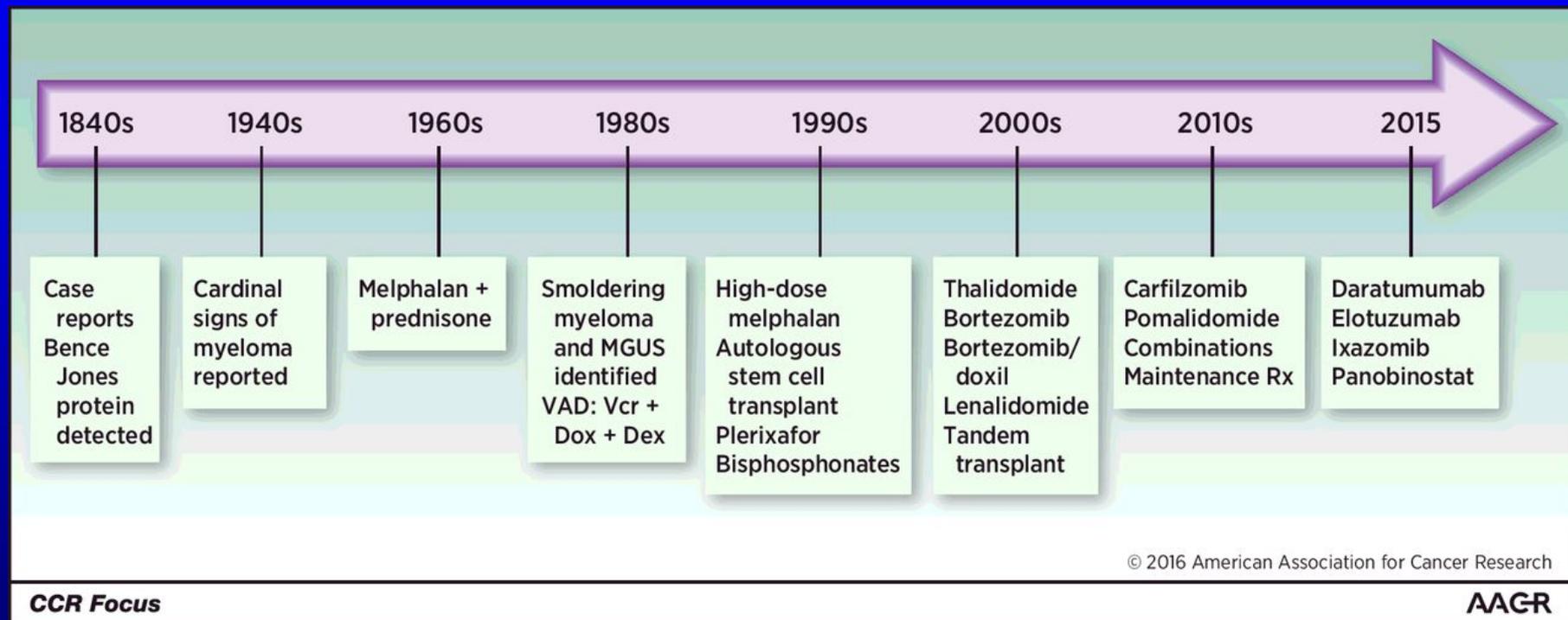


FIG 1. History of breast cancer treatment: Timeline. Integration of various discoveries that led to changes in the standard of care. Discoveries are displayed by approximate year of incorporation into practice. AI, aromatase inhibitor; APBI, accelerated partial breast irradiation; IMRT, intensity-modulated radiotherapy; LHRH, luteinizing hormone-releasing hormone; RT, radiotherapy; SERM, selective estrogen receptor modulator; T-DM1, trastuzumab emtansine.

Year	Stage		
	Localized	Regional	Distant
1973 ⁵⁶	85	53	< 10
2019 ¹	99	85	27

FIG 3. Five-year relative survival rates for breast cancer: 1973-2019. Numbers represent 5-year relative survival figures. The change between 1973 and 2019 reflects the progress in detection and treatment. Data are given as percent 5-year survival.

Timeline of pivotal events in the development of myeloma therapeutics.



Susan E. Bates Clin Cancer Res 2016;22:5418

CENTRAL ILLUSTRATION Priorities Identified for Advancing the Field of Cardio-Oncology



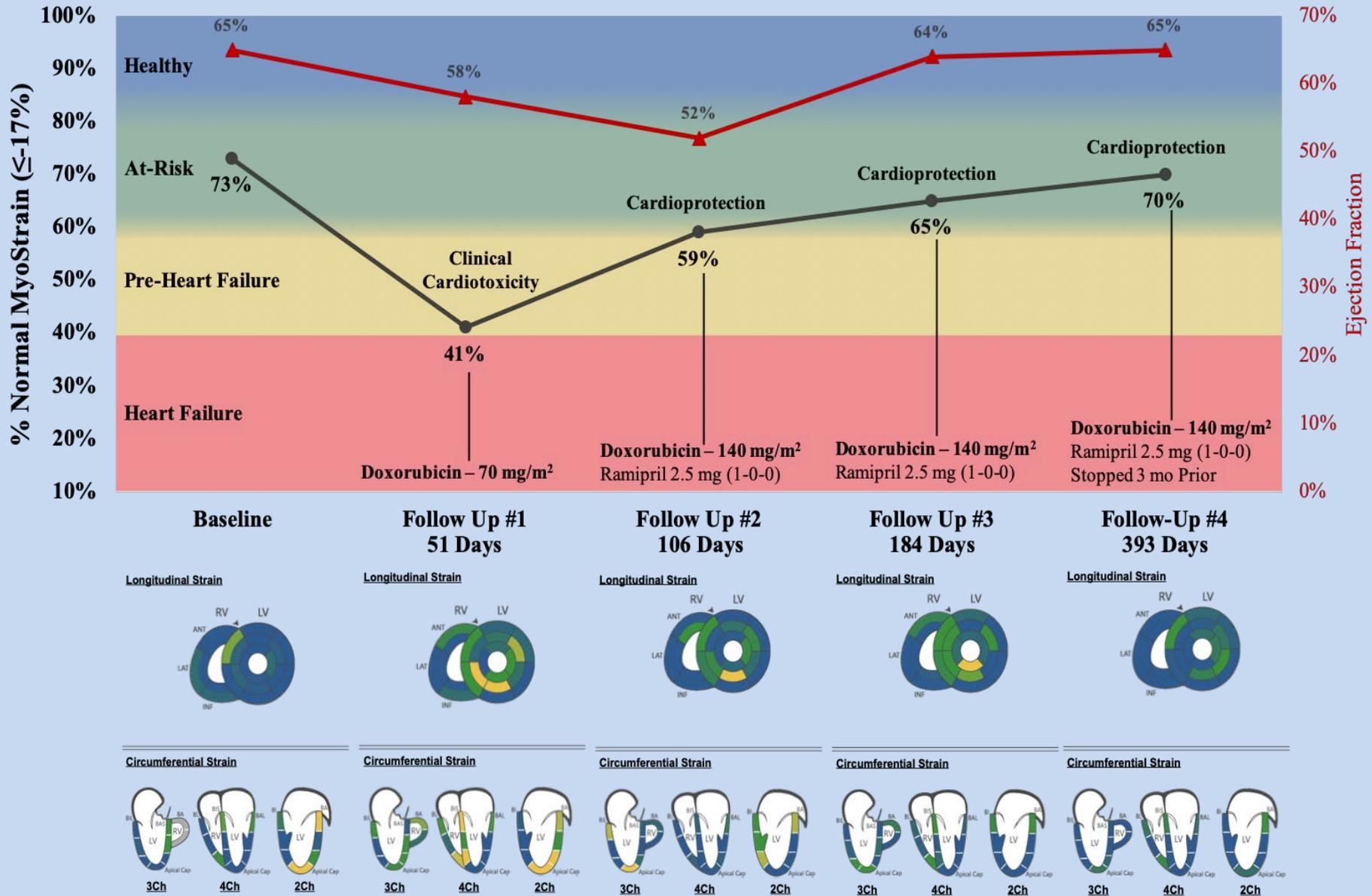
Lerihan, D.J. et al. *J Am Coll Cardiol CardioOnc.* 2019;1(2):256-72.

The priorities identified for the discipline of cardio-oncology from the Global Cardio-Oncology Summit 2019 meeting serve as a focus for our collective efforts to advance the field. CV – cardiovascular; TKI – tyrosine kinase inhibitor.

Top 10 Priorities for Cardio-Oncology:

- **Knowing the Reproducible Predictors of Cardiotoxicity**
- **Better define Cardioprotective Strategies in patients with Cancer**
- **Describe the Optimal Management of Thromboembolic Events in patients with Cancer**
- **Improve the CV Outcomes in Stem Cell Transplant**
- **Personalization of Cardiovascular Interventions**

MRI Strain can improve detection



PROTECT study, JCO Aug 2019, JCO1900231

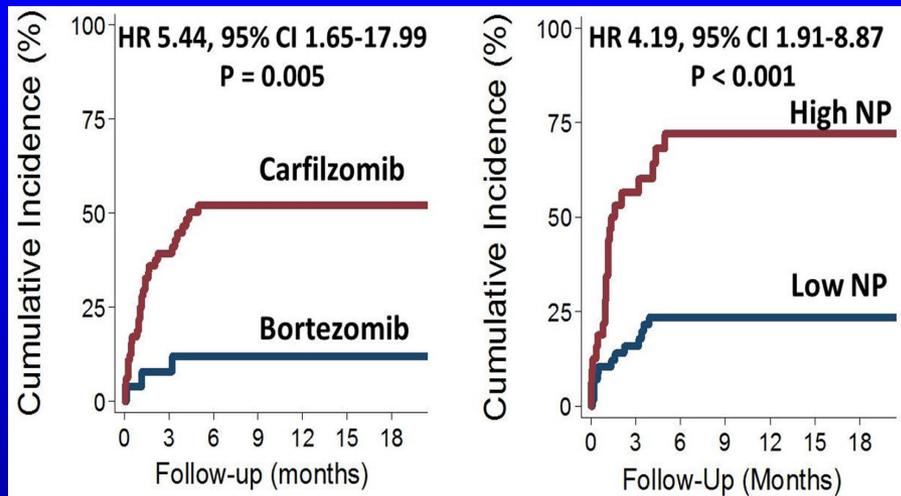
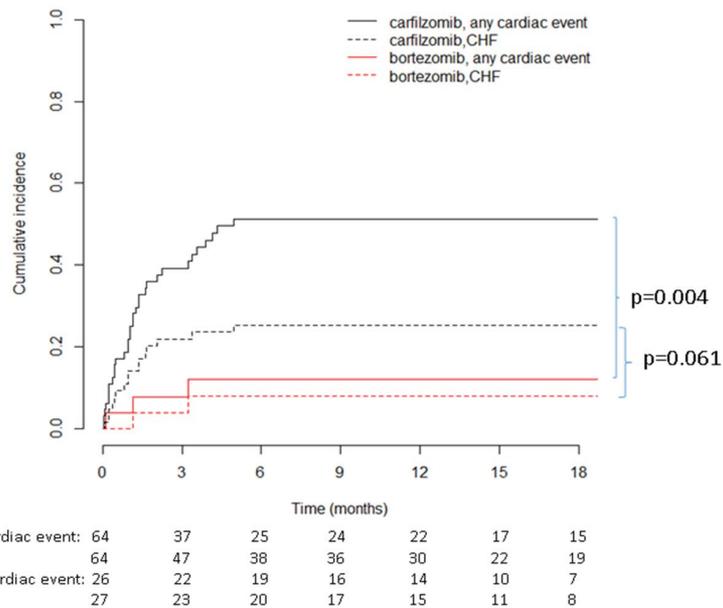
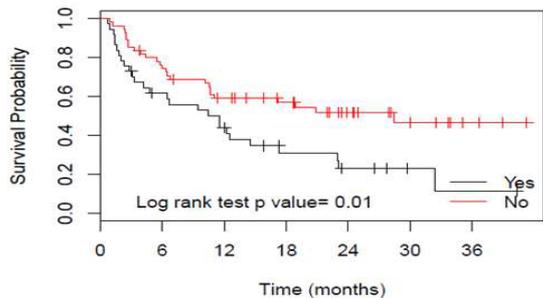
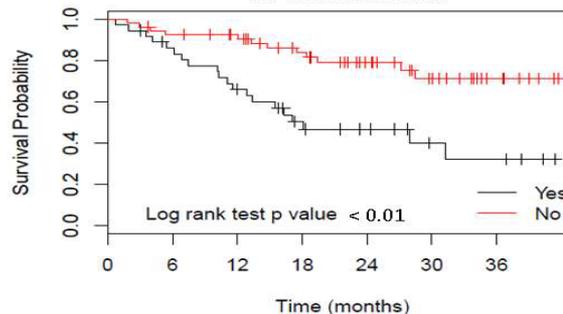


Figure 2

Impact of Cardiac Event on Progression Free Survival



Impact of Cardiac Event on Overall Survival



Cardioprotection improved survival

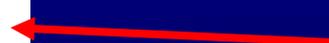


TABLE 5. Cardiovascular Drugs Showing a Prophylactic Effect Against Anthracycline/Trastuzumab-Induced Cardiotoxicity in Adult Cancer Populations

STUDY	STUDY DESIGN/ FOLLOW-UP	NO. OF PATIENTS	CANCER TYPE	DRUGS	INTERVENTION	RESULTS
ACEI Cardinale 2006 ¹³⁷	RCT/12 mo	114	Various	HD CT	Enalapril	No LVEF↓; MACE incidence↓
ARB Nakamae 2005 ¹³⁸	RCT/7 d	40	NHL	AC	Valsartan	No LVEDD↑; no BNP and ANP↑; no QT↑
Cadeddu 2010 ¹³⁹	RCT/18 mo	49	Various	AC	Telmisartan	No peak strain rate↓; no interleukin 6↑
Aldosterone antagonists Akpek 2015 ¹⁴⁰	RCT/6 mo	83	Breast cancer	AC	Spironolactone	No LVEF↓; no TNI and BNP↑
Beta-blockers Kalay 2006 ¹⁴¹	RCT/6 mo	50	Various	AC	Carvedilol	No LVEF↓
Kaya 2013 ¹⁴²	RCT/6 mo	45	Breast cancer	AC	Nebivolol	No LVEF and NT-proBNP↑
Seicean 2013 ¹⁴³	Retrospective/5 y	318	Breast cancer	AC, TRZ	Beta-blockers	HF↓
ACEI + beta-blockers Bosch 2013 ¹⁴⁴	RCT/6 mo	90	Hematological	AC	Enalapril + carvedilol	No LVEF↓; death↓; HF↓
Statin Acar 2011 ¹⁴⁵	RCT/6 mo	40	Hematological	AC	Atorvastatin	No LVEF↓
Seicean 2012 ¹⁴⁶	Retrospective/5 y	67	Breast cancer	AC	Statins	HF↓

↓, decrease; ↑, increase; ACEI, angiotensin-converting enzyme inhibitor; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; HD CT, high-dose chemotherapy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; HF, heart failure; MACE, major adverse cardiac events; NHL, non-Hodgkin lymphoma; NT-proBNP, N-terminal-probrain natriuretic peptide; QT, QT interval; RCT, randomized controlled trial; TNI, troponin I; TRZ, trastuzumab.

Top 10 Priorities for Cardio-Oncology:

- **Build the Cardio-Oncology Community**
- **Define and detect the Adverse Cardiac Events in Immunotherapy**
- **Understanding of Mechanisms of Multi-Targeted Tyrosine Kinase Inhibitors**
- **Improvements in Survivorship Care**
- **How do we move forward?**

Combination checkpoint inhibitors may have important cardiac effects

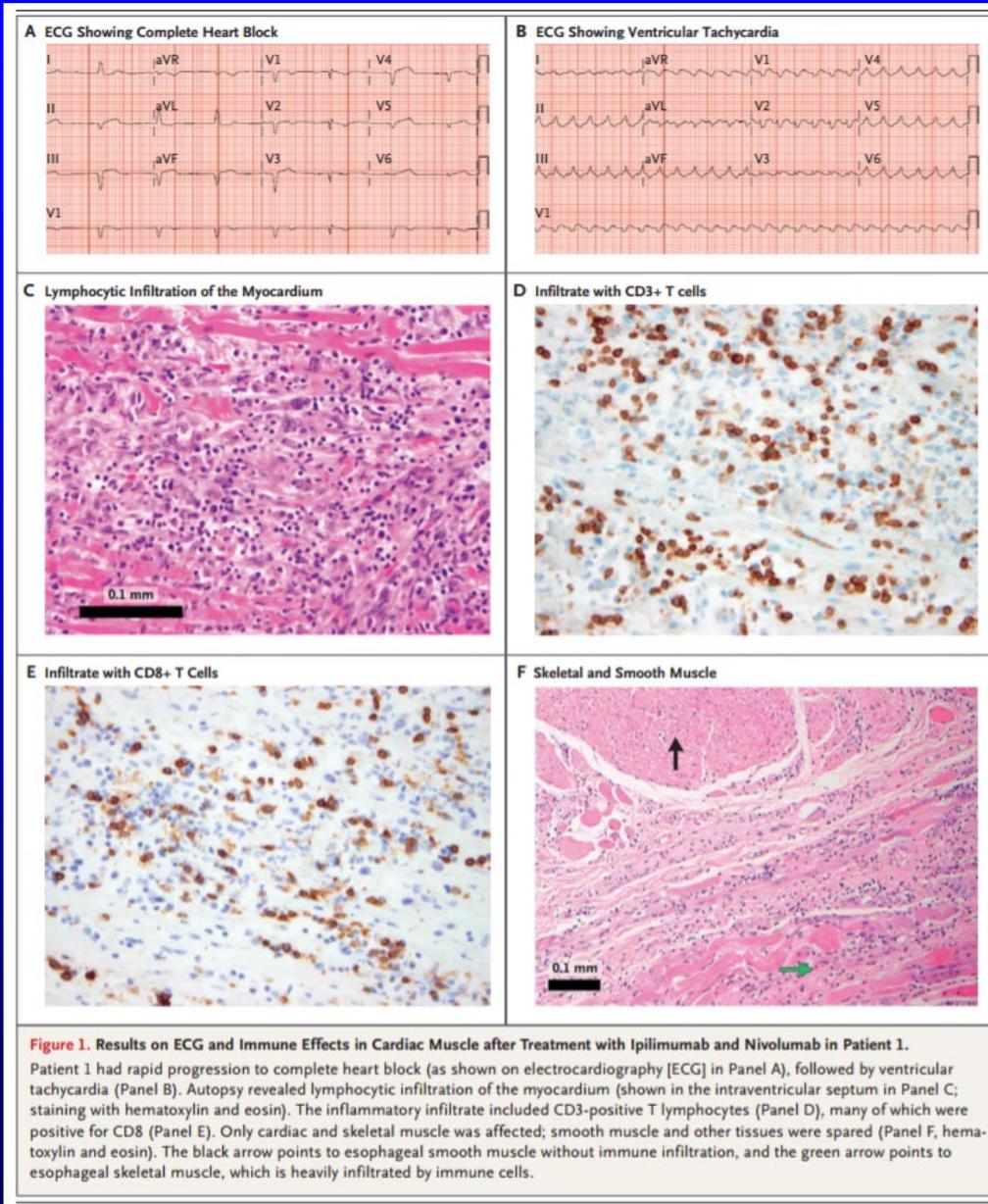


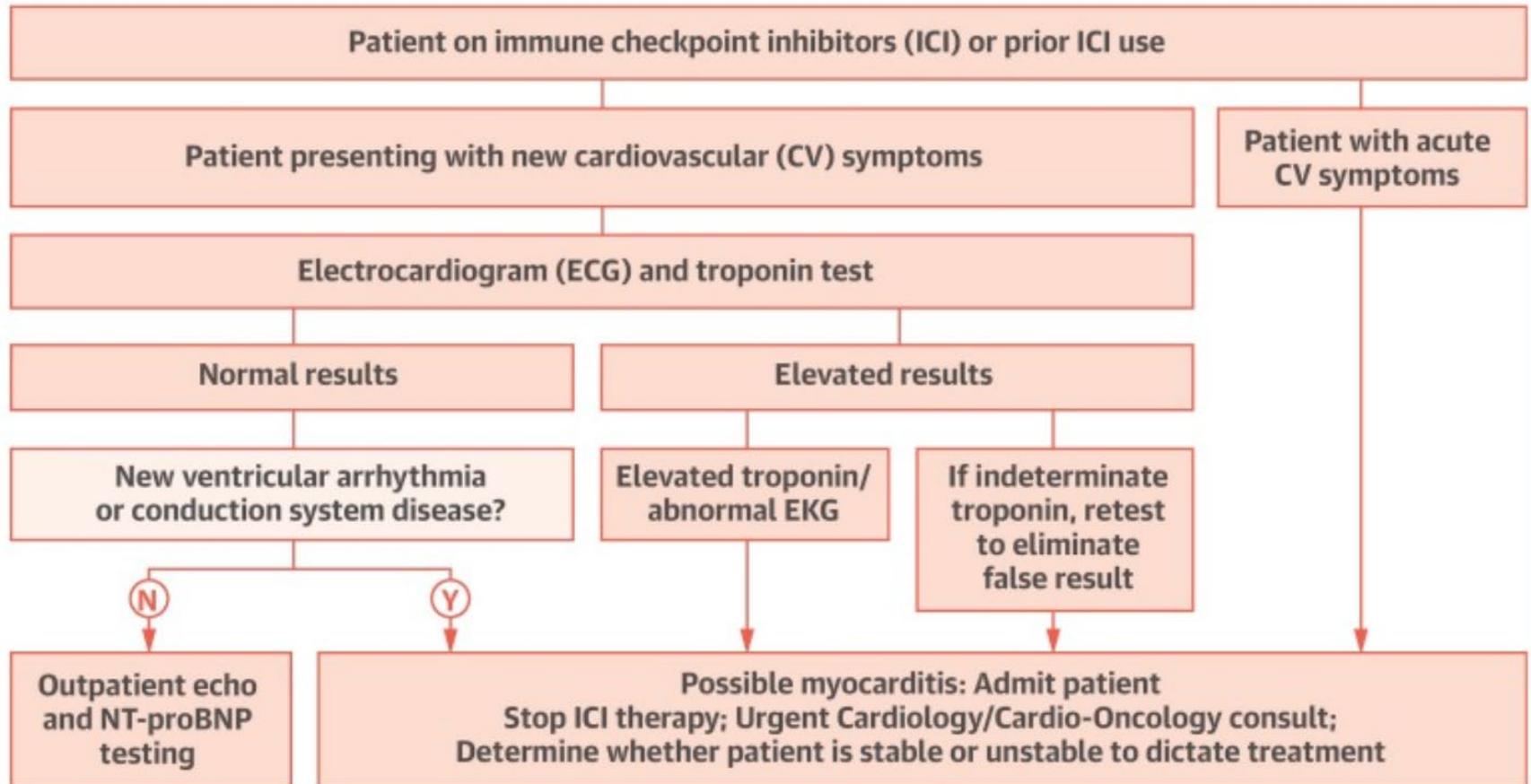
Table 1. Incidence of Myocarditis and Myositis in Patients Receiving Nivolumab or Ipilimumab plus Nivolumab.

Characteristic	Nivolumab (N=17,620)	Nivolumab plus Ipilimumab (N=2974)
		no. (%)
Myocarditis		
Any*	10 (0.06)	8 (0.27)
Fatal events	1 (<0.01)	5 (0.17)
Myositis		
Any	27 (0.15)	7 (0.24)
Fatal events	2 (0.01)	1 (0.03)

* The number of patients with myocarditis includes six patients with concurrent myocarditis and myositis.

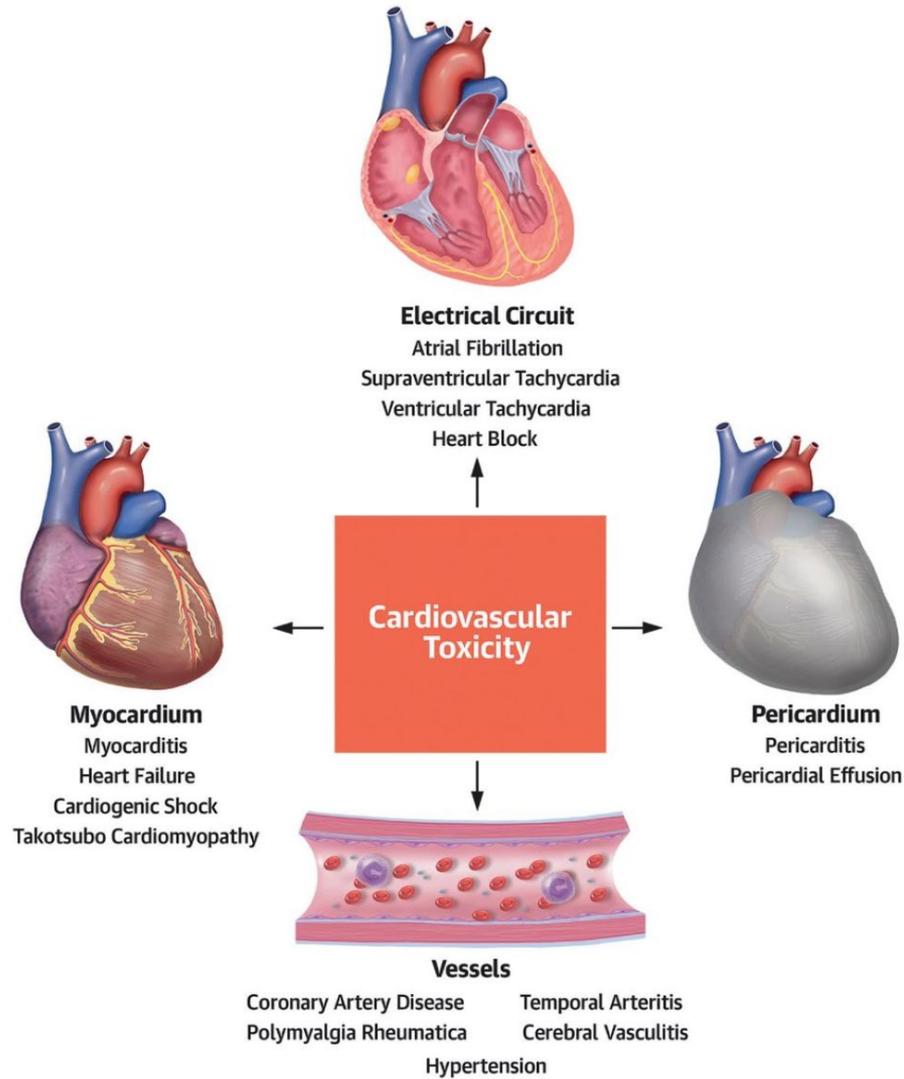
N Engl J Med 2016;375:1749-55.
 DOI: 10.1056/NEJMoa1609214

CENTRAL ILLUSTRATION: Algorithm for Work-Up and Management of Immune-Mediated Myocarditis



Mahmood, S.S. et al. *J Am Coll Cardiol.* 2018;71(16):1755-64.

CENTRAL ILLUSTRATION: Spectrum of Cardiovascular Toxicities With Immune Checkpoint Inhibitors

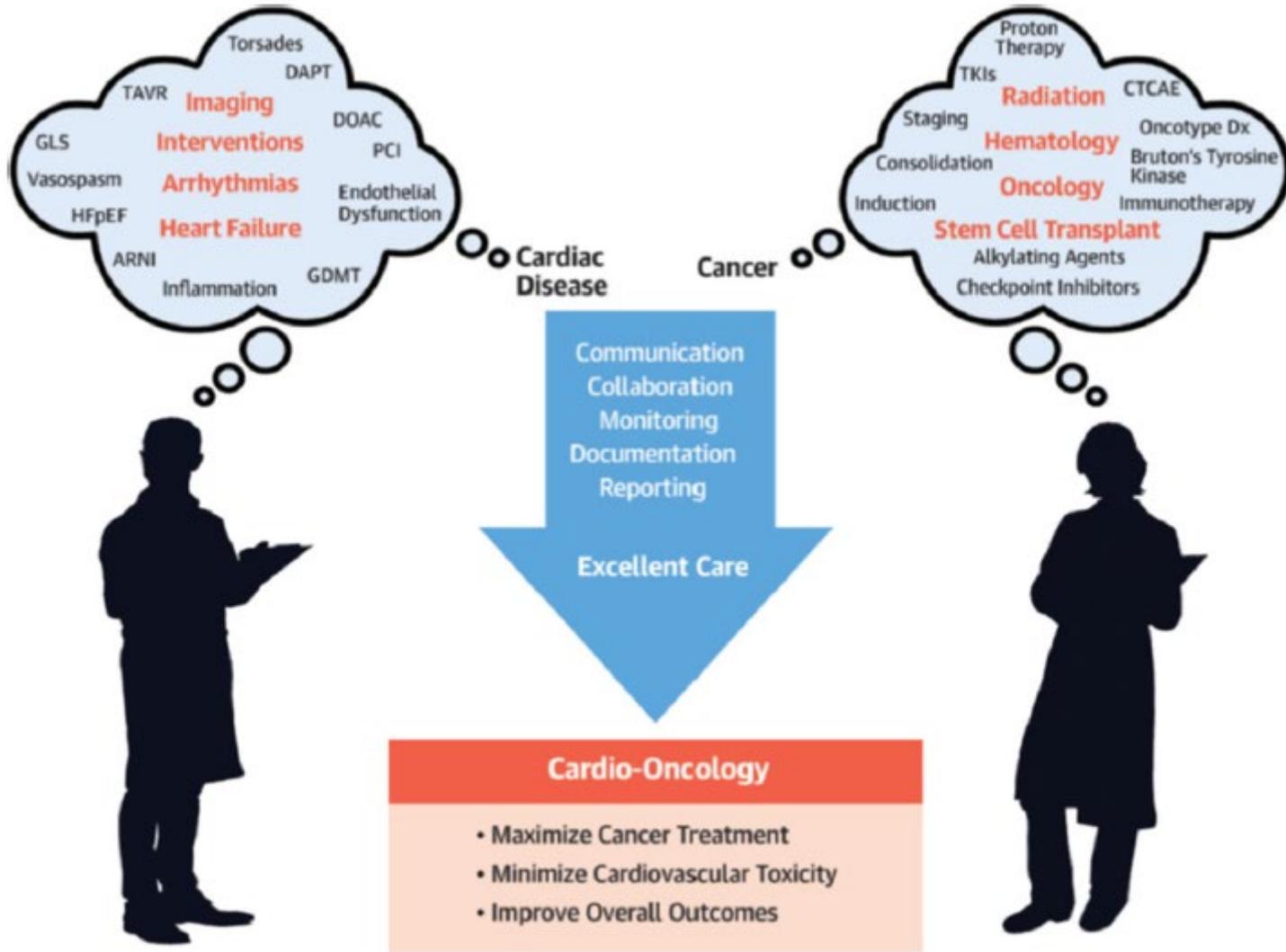


Ball, S. et al. J Am Coll Cardiol. 2019;74(13):1714-27.

SPECIAL ARTICLE

Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations

¹³ G. Curigliano^{1,2†}, D. Lenihan^{3†}, M. Fradley⁴, S. Ganatra⁵, A. Barac⁶, A. Blaes⁷, J. Herrmann⁸, C. Porter⁹, A. R. Lyon¹⁰, P. Lancellotti¹¹, A. Patel¹², J. DeCara¹³, J. Mitchell¹⁴, E. Harrison¹⁵, J. Moslehi¹⁶, R. Witteles¹⁷, M. G. Calabro¹⁸, R. Orecchia¹, E. de Azambuja¹⁹, J. L. Zamorano²⁰, R. Krone²¹, Z. Iakobishvili²², J. Carver²³, S. Armenian²⁴, B. Ky²⁵, D. Cardinale¹, C. Cipolla¹, S. Dent²⁶ & K. Jordan²⁷ on behalf of the ESMO Guidelines Committee*





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