

Cardiovascular Oncology

From the perspective of an oncologist

Susan Dent, BSc, FRCPC

Medical Oncologist

The Ottawa Hospital Cancer Center

Professor of Medicine, University of Ottawa

February 22nd, 2017

17th Annual Benjamin Schuster, MD Colloquium



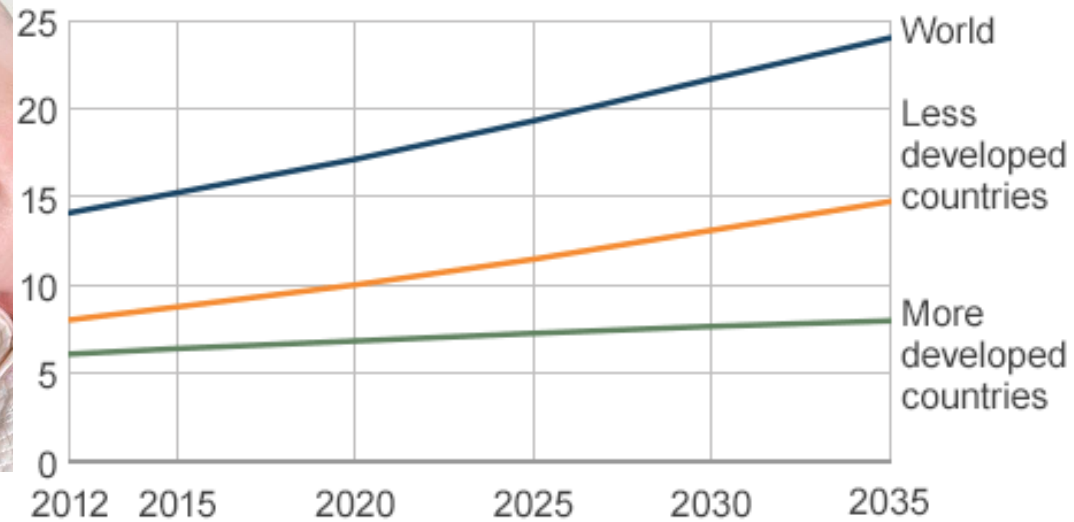
Objectives

- To discuss the impact of cancer treatments on the heart
- To discuss strategies to optimize cardiac health in cancer patients
- To discuss the benefits of a multidisciplinary approach in management of these patients

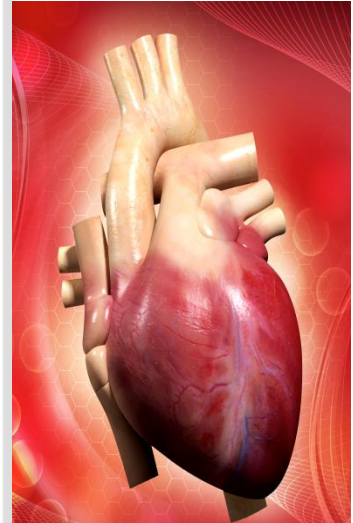


Predicted global cancer cases

Cases (millions)

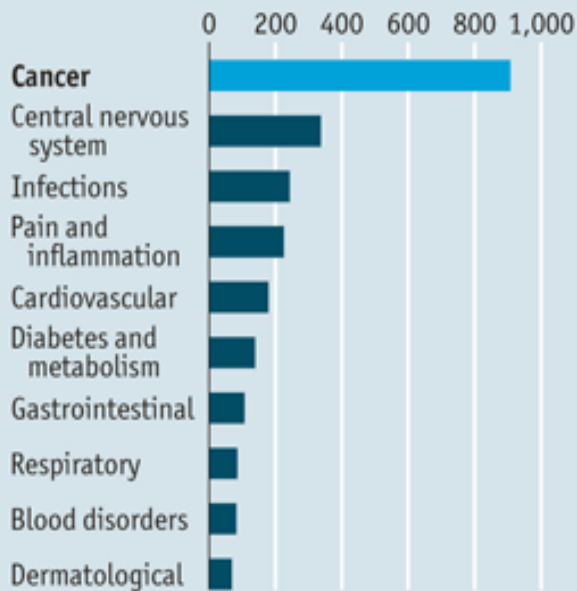


Source: WHO GloboCan



The big C

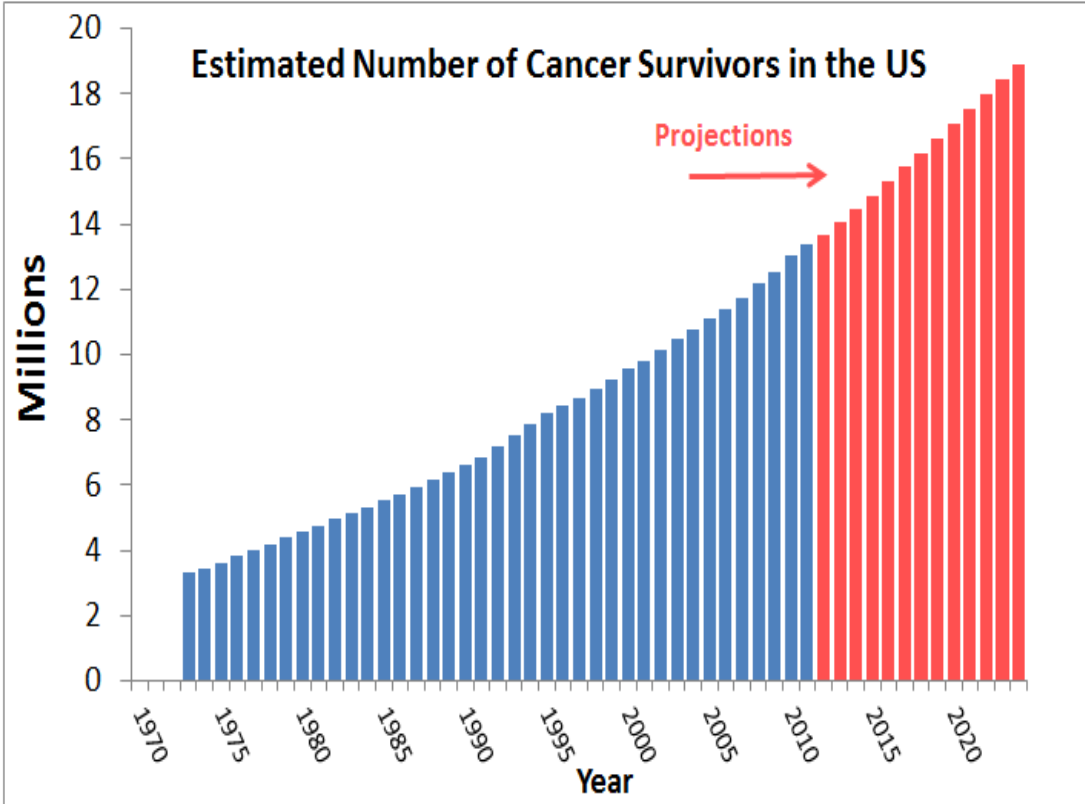
Drugs in development*, 2010



*Top ten therapeutic areas for the world's big pharmaceutical firms, includes drugs in Phase I, II, III or awaiting FDA approval

Source: Medco, R&D Directions

Estimated Number of Cancer Survivors in the US



¹ DeSantis C, Chunchieh L, Mariotto AB, et al. (2014). Cancer Treatment and Survivorship Statistics, 2014. CA: A Cancer Journal for Clinicians. In press.



Canadian Cardiac
Oncology Network

cardiaconcolgy.ca

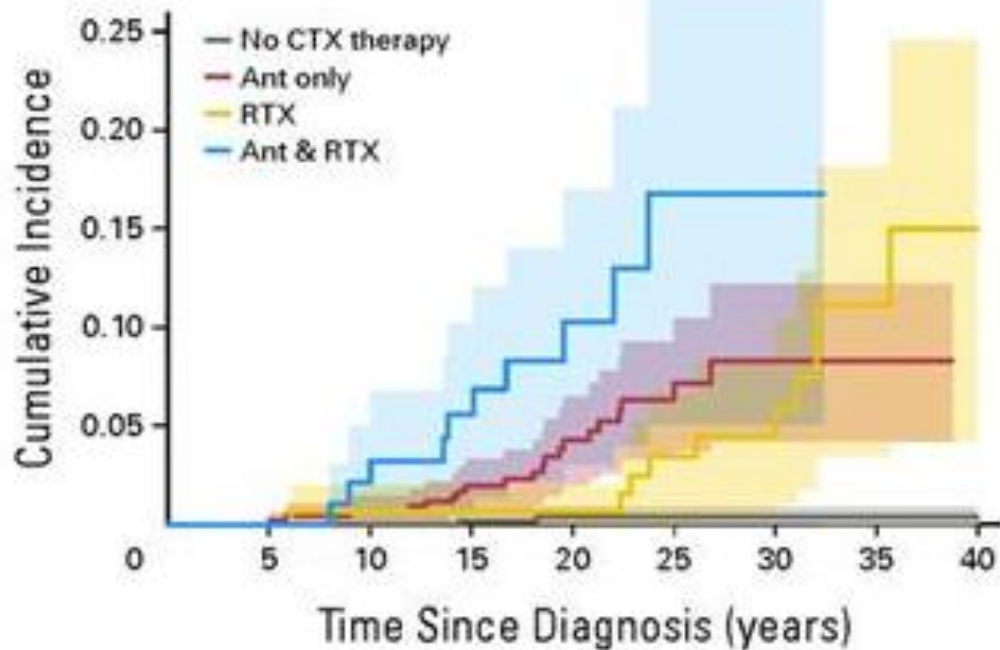


“The cured cancer patient of today does not want to become the heart failure patient of tomorrow.”

Eschenhagen T et al. Eur J of Heart Fail 2011; 3:1-10

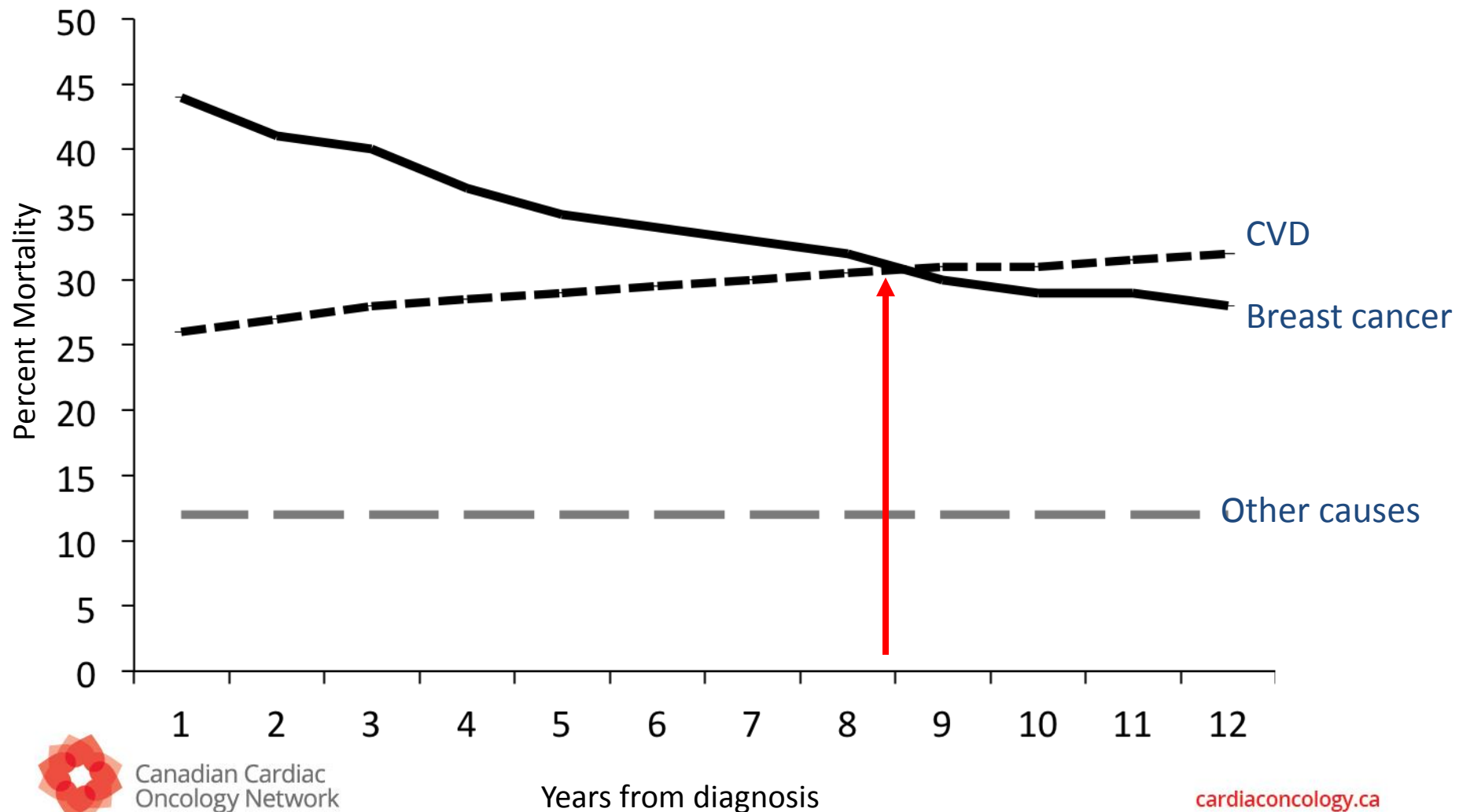
Cardiovascular events in cancer survivors

Incidence of cardiac events in pediatric cancer survivors



Helena J. van der Pal et al. JCO 2012

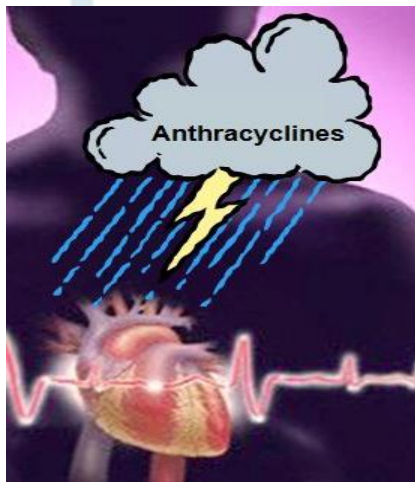
Cardiovascular Disease: Important cause of mortality in early breast cancer



Cardiotoxicity of Chemotherapy Drugs

Table 1 Systemic cancer drugs with important cardiovascular side effects; selected indications

	Class/drug	Selected indications	Important CV side effects	
Cytostatic chemotherapeutics	Anthracyclines/analouges			
	Doxorubicin	Lymphoma	Cardiac dysfunction/heart failure	
	Daunorubicin	Leukaemia		
	Epirubicin	Breast cancer		
		Ovarian cancer		
		Sarcoma		
	Mitoxantrone	Leukaemia		
		Multiple sclerosis		
	Pyrimidine analogues			
	Fluorouracil (5-FU)	Colorectal cancer	Coronary spasms/ischaemia	
Capecitabine	Breast cancer			
Alkylating agents				
Cyclophosphamide	Breast cancer	Myocarditis (rare)		
Cisplatin	Genitourinary cancer			
Antimicrotubule agents				
Paclitaxel	Breast cancer	Bradycardia		
	Colorectal cancer			

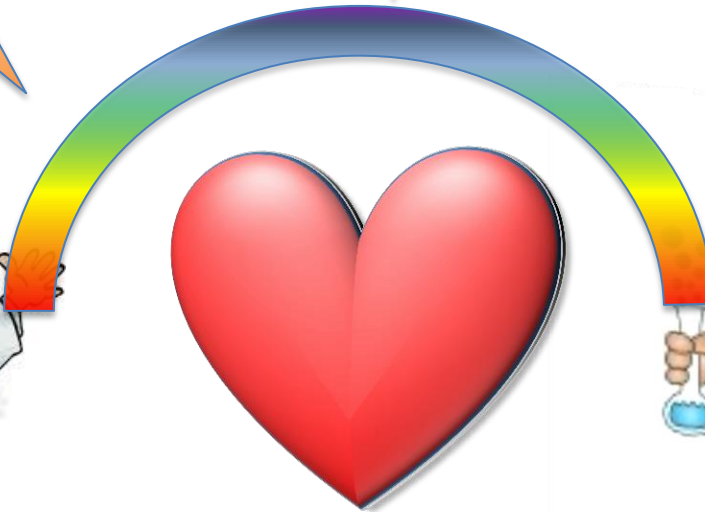


Suter and Ewer. Eur Heart Journal, 2013

Anthracyclines

Targeted
Agents

Radiotherapy

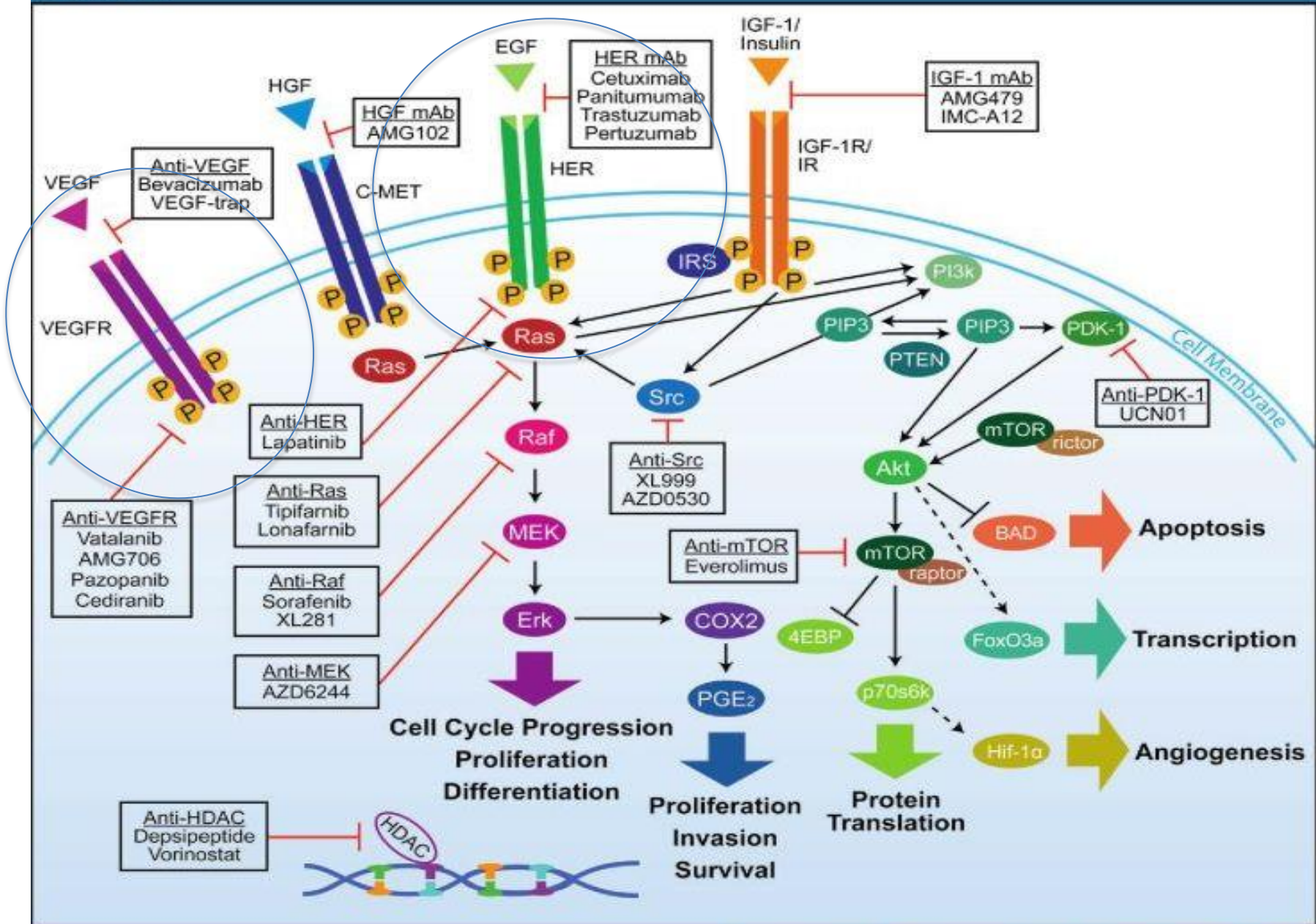


Cardiotoxicity not new!
Why the interest now ?



Canadian Cardiac
Oncology Network

cardiaconology.ca



Cardiotoxicity of Targeted Agents

Table 1 Systemic cancer drugs with important cardiovascular side effects; selected indications

	Class/drug	Selected indications	Important CV side effects
Signalling inhibitors	Anti-HER2		
	Trastuzumab	Breast cancer	Cardiac dysfunction
	Lapatinib	Gastric cancer	
	Angiogenesis inhibitors/anti-VEGF		
	Bevacizumab	Gastrointestinal cancer	Hypertension
	Sunitinib	Renal cell carcinoma	Endovascular damage
	Sorafenib	Hepatocellular carcinoma	
	BCR-ABL inhibitors		
	Imatinib	Leukaemia	Oedema, cardiac dysfunction (rare)
	Dasatinib	Gastric cancer	QTc prolongation
	Nilotinib		

Suter et al. Eur Heart Journal, 2013



Cardiotoxicity with VEGF inhibitors

TABLE 3. Rates of Hypertension With Selected Angiogenesis Inhibitors

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

GIST, gastrointestinal stromal tumor; NA, not available.



Cardiotoxicity and Tyrosine Kinase Inhibitors (CML)

Multitargeted tyrosine kinase inhibitors	Drug	Targeted Kinases	Cardiotoxicity
	Dasatinib	ABL, ABL mutants (except T315I), and other kinases; SRC, KIT, PDGFR, EGFR, BRAF, DDR1, DDR2, ephrin receptors	Pulmonary hypertension, vascular events, prolongation of QT interval corrected for heart rate
	Nilotinib	ABL, ABL mutants (except T315I), and other kinases; ABL2 (also called ARG), KIT, DDR1, NQO2	Coronary, cerebral, and peripheral vascular events, hyperglycemia, prolongation of QT interval corrected for heart rate
	Ponatinib	ABL, ABL mutants (including T315I), and other kinases; FGFR, VEGFR, PDGFR, ephrin receptors, SRC, KIT, RET, TEK (also called TIE2), FLT3	Coronary, cerebral, and peripheral vascular events



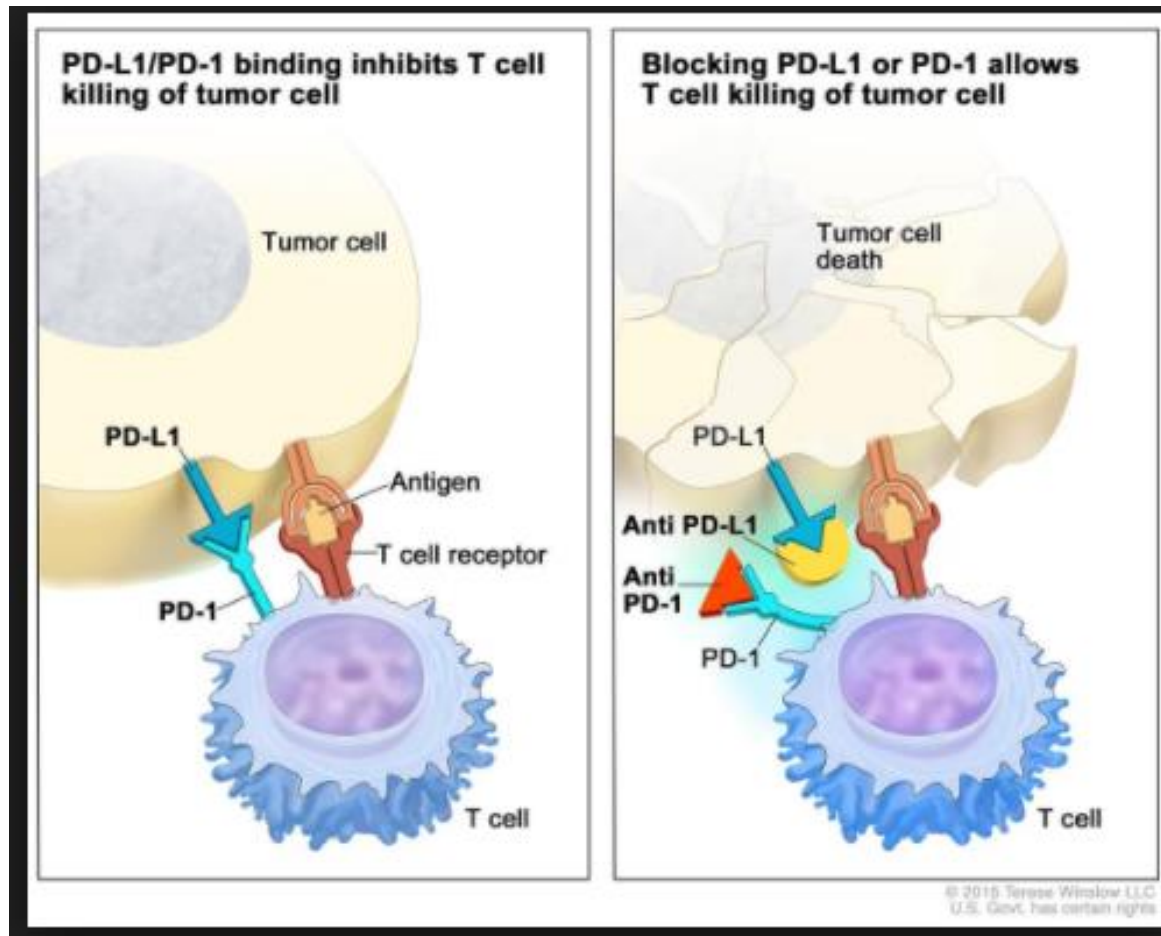
CML Patients on TKI

Annual Rate of Arterial Event (95 percent C.I.)

	PVD	CAD	CVA
Ponatanib	3.9% (2.4-5.3%)	6% (4.2-7.8%)	2.9% (0-4.1%)
Nilotinib	1.3% (0.8-1.8%)	1.4% (1-1.6%)	0.3% (0.1-0.4%)
Dasatinib	0.2% (0.1-0.3%)	0.6% (0.3-0.8%)	0.7% (0.4-1.0%)
Bosotinib	0.1% (0-0.3%)	0.3% (0-0.7%)	0.1% (0-0.4%)
Imatinib	0.1% (0-0.1%)	0.1% (0-0.1%)	0.1% (0-0.1%)

Chai-Adisaksopha et al Leukemia & Lymphoma 2015

Immune checkpoint inhibitors



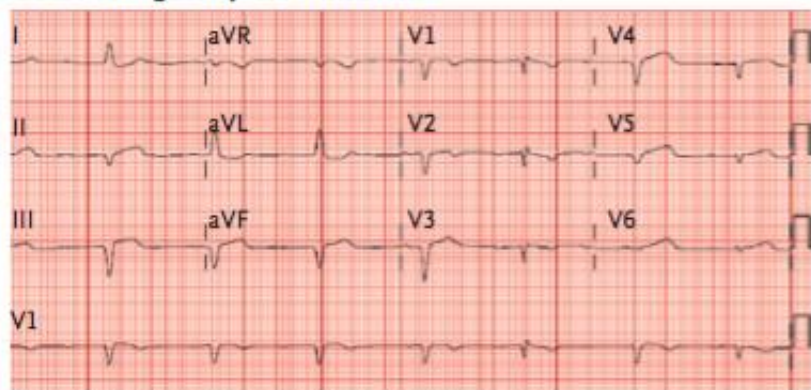
BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

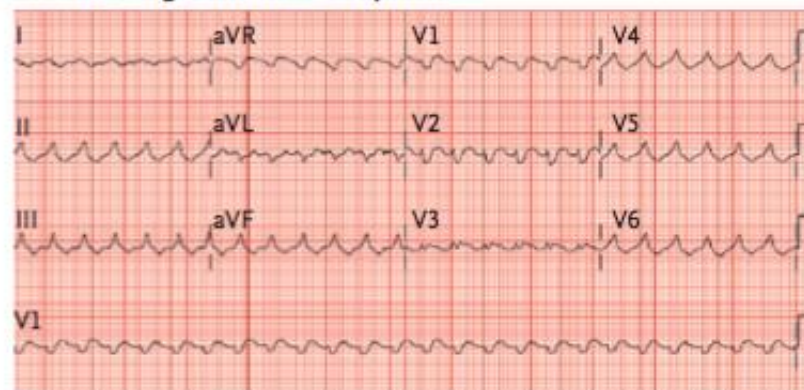
Douglas B. Johnson, M.D., Justin M. Balko, Pharm.D., Ph.D., Margaret L. Compton, M.D., Spyridon Chalkias, M.D., Joshua Gorham, B.A., Yaomin Xu, Ph.D., Mellissa Hicks, Ph.D., Igor Puzanov, M.D., Matthew R. Alexander, M.D., Ph.D., Tyler L. Bloomer, M.D., Jason R. Becker, M.D., David A. Slosky, M.D., Elizabeth J. Phillips, M.D., Mark A. Pilkinton, M.D., Ph.D., Laura Craig-Owens, M.D., Nina Kola, M.D., Gregory Plautz, M.D., Daniel S. Reshef, M.D., M.P.H., Ph.D., Jonathan S. Deutsch, M.D., Raquel P. Deering, Ph.D., Benjamin A. Olenchock, M.D., Ph.D., Andrew H. Lichtman, M.D., Dan M. Roden, M.D., Christine E. Seidman, M.D., Igor J. Koralnik, M.D., Jonathan G. Seidman, Ph.D., Robert D. Hoffman, M.D., Ph.D., Janis M. Taube, M.D., Luis A. Diaz, Jr., M.D., Robert A. Anders, M.D., Jeffrey A. Sosman, M.D., and Javid J. Moslehi, M.D.

A 65-year-old woman with metastatic melanoma was admitted to the hospital with atypical chest pain, dyspnea, and fatigue 12 days after receiving her first doses of nivolumab (1 mg per kilogram of body weight) and ipilimumab (3 mg per kilogram).

A ECG Showing Complete Heart Block



B ECG Showing Ventricular Tachycardia

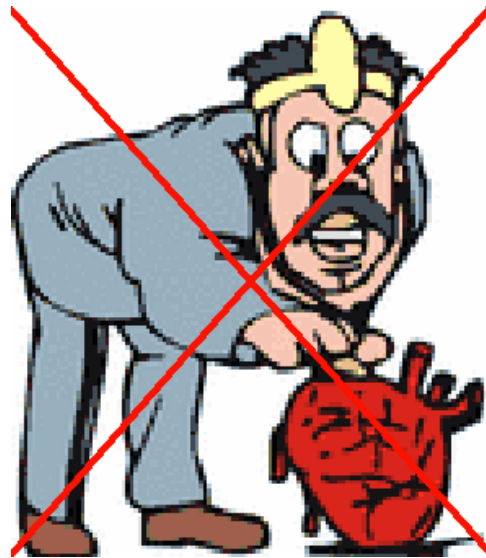


A clinical scenario

- 65 y.o. female with node positive breast cancer – ER +, PR +, HER2 +
- Oncologist recommends adjuvant anthracycline-based chemotherapy (FEC-D) and Trastuzumab
- History of hypertension and diabetes
- 30 pack year smoking history
- Echocardiogram: EF = 40 %
- **What now ?**



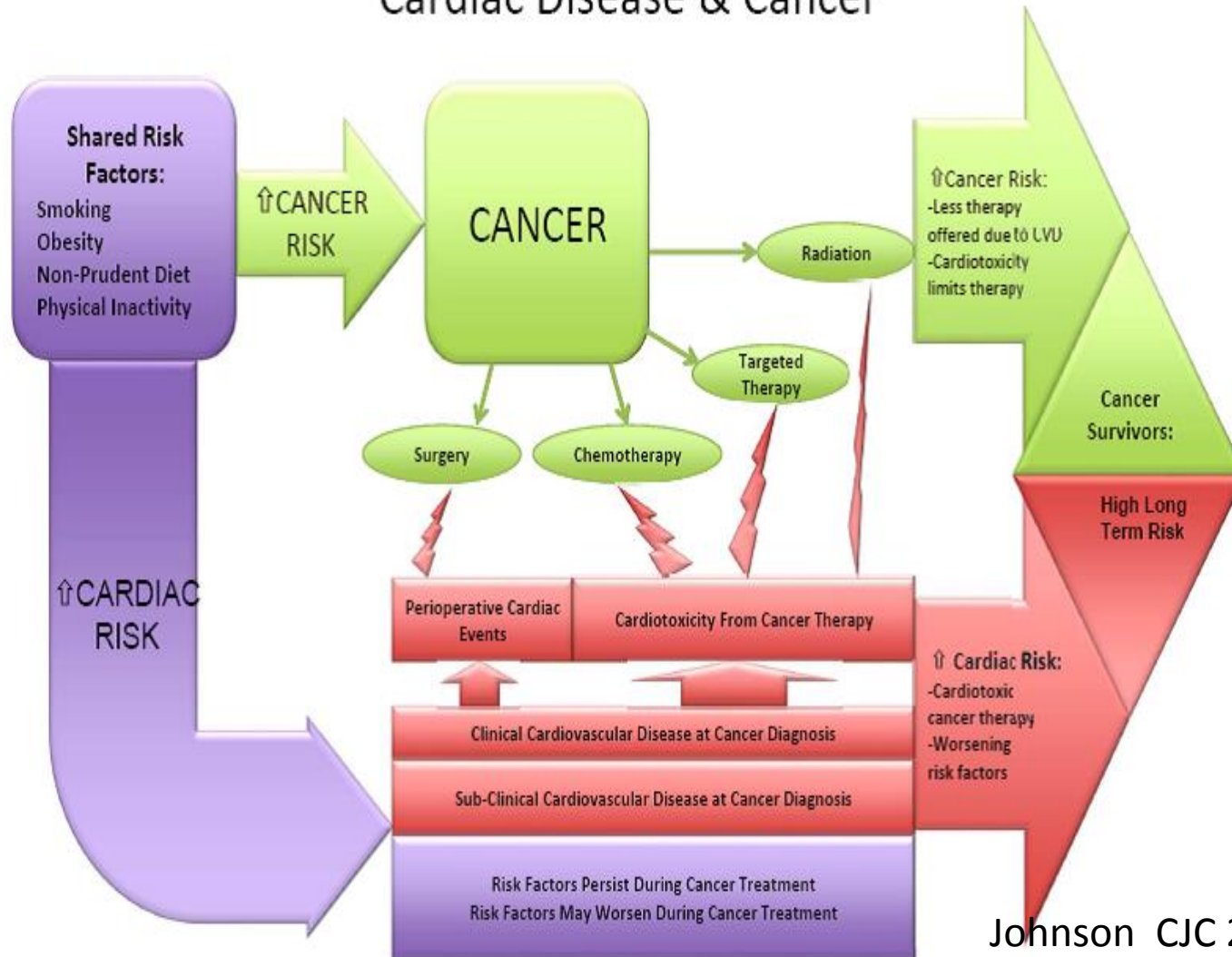
But We Are not Cardiologists!



Canadian Cardiac
Oncology Network

cardiaconcology.ca

Figure 1: Interaction Between Shared Risk Factors, Cardiac Disease & Cancer

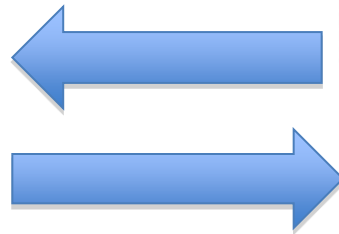


Johnson CJC 2016 (in press)





Optimize Cardiac Health



Best Cancer Care



Ottawa Cardiac Oncology Clinic



Dr. Susan Dent
Medical
Oncologist



Dr. Michele Turek
Cardiologist



**Dr. Christopher
Johnson**
Cardiologist



Dr. Angeline Law
Cardiologist



Dr. Ellamae Stadnick
Cardiologist



Dr. Jeffrey Sulpher
Medical Oncologist



Dr. Olexiy Aseyev
Cardiac Oncology
Fellow



Jason Wentzell
Pharmacist



Nadine Graham
Research Assistant



Cancer Quality Council of Ontario 2013 Innovation Award



Establishing a Cardio-oncology program

THE ORGANIZATION OF CARE

Cardiac Oncology:
Improving Cardiac Safety,
Advancing Cancer Care



Burgeoning Cardio-Oncology Programs

Challenges and Opportunities for
Early Career Cardiologists/Faculty Directors

Tochi M. Okwuosa, DO,* Ana Barac, MD, PhD†

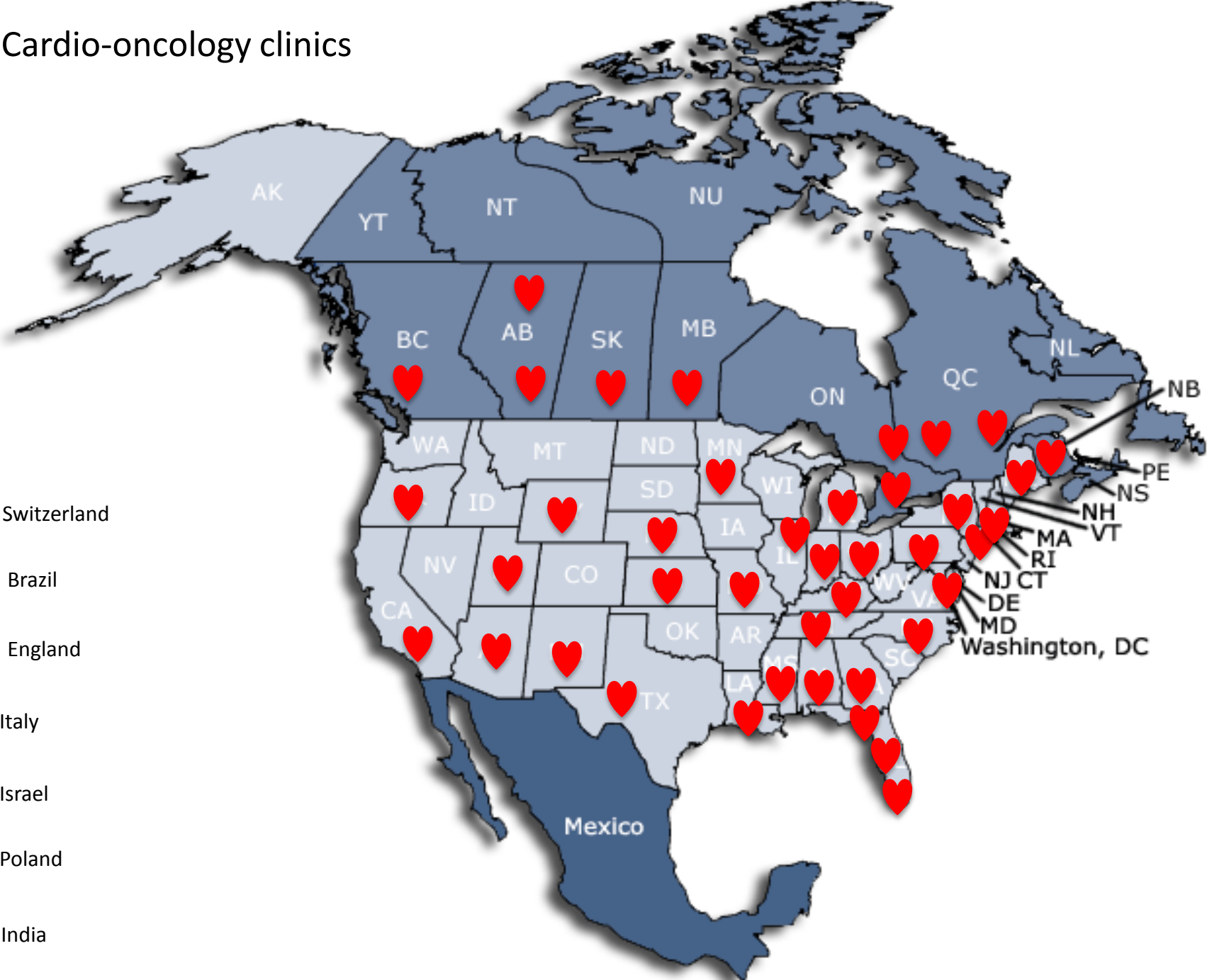
JACC, volume 66, No. 10, 2015



Sulpher et al, 2014-2015 Report Card on
Cancer in Canada

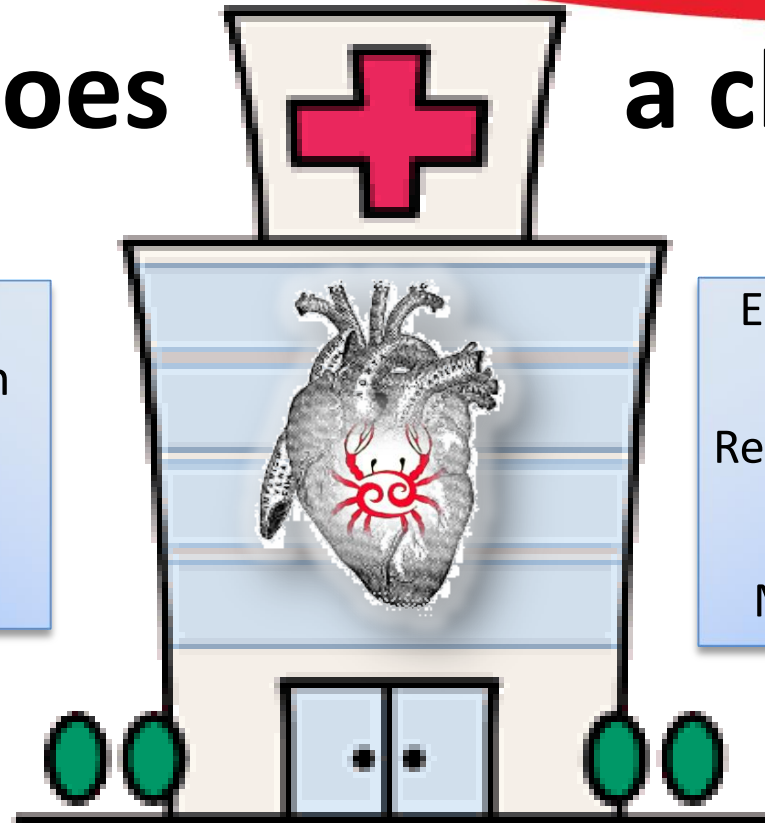
Cardio-oncology clinics

- Switzerland
- Brazil
- England
- Italy
- Israel
- Poland
- India



What does

a clinic offer ?



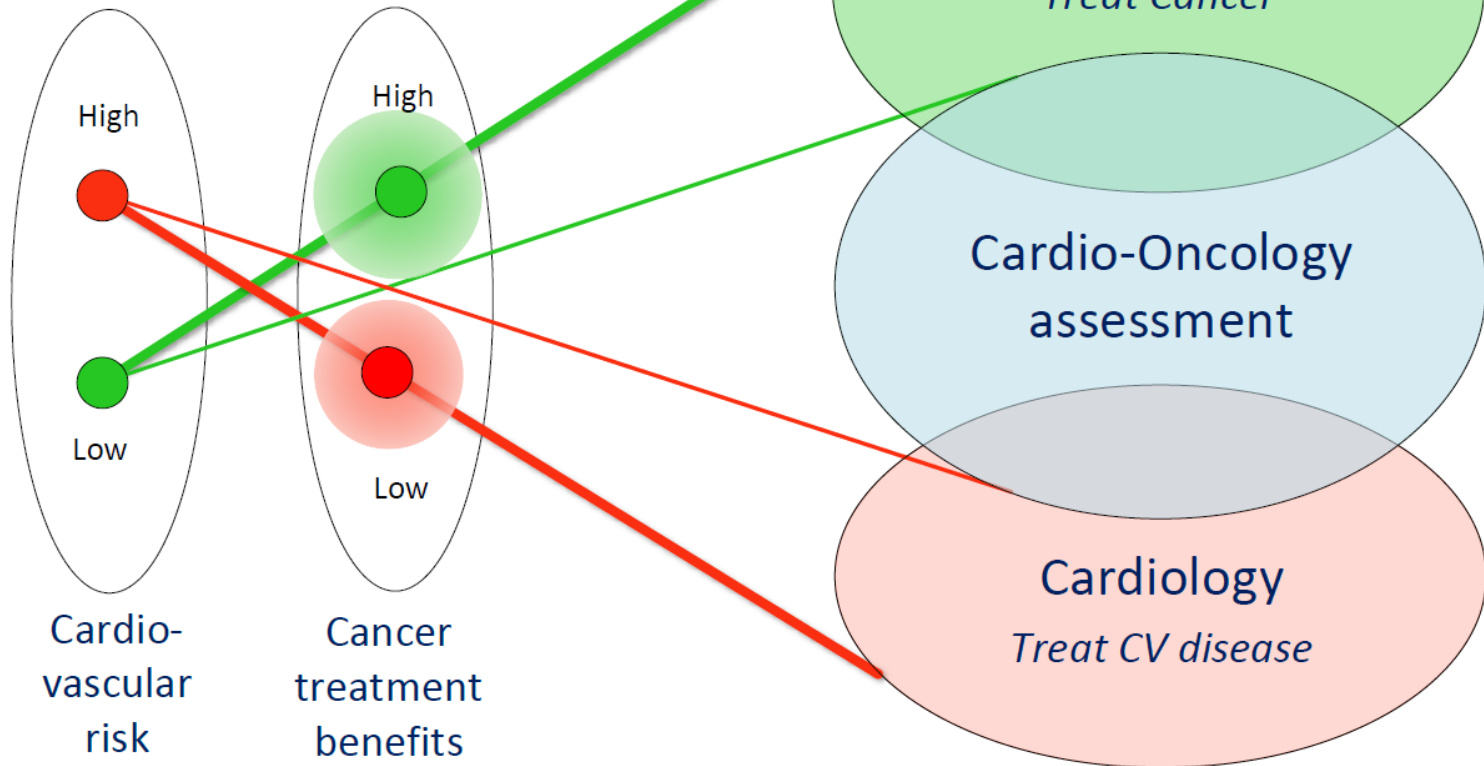
Rapid access to cardiologists with an understanding of systemic /targeted therapies.

Education of patients and health care providers
Resident/fellowship training
Preceptorship
Multidisciplinary rounds

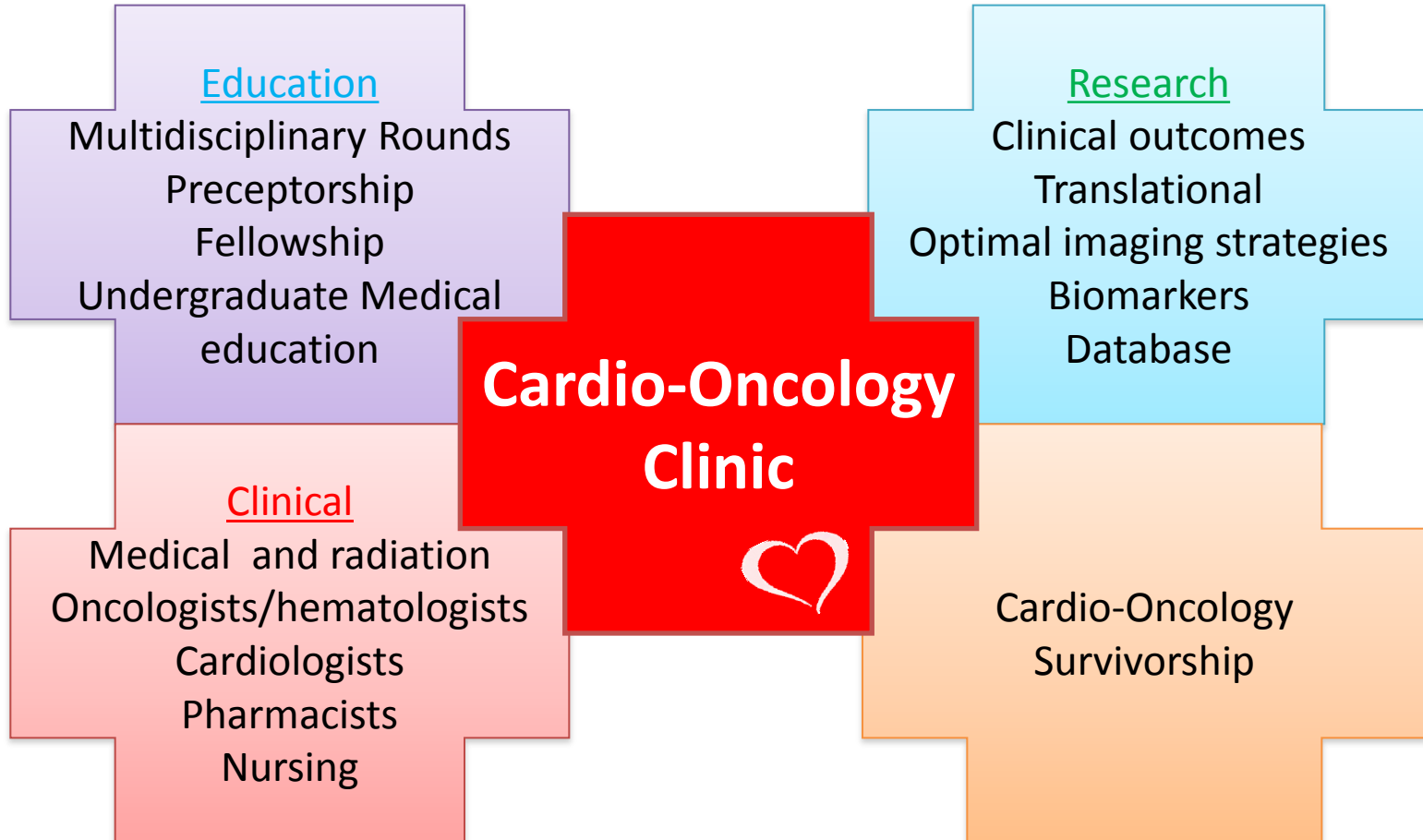
Development of a collaborative research environment: basic/translational research and clinical/health outcomes research.



Cardio-oncology treatment decision process

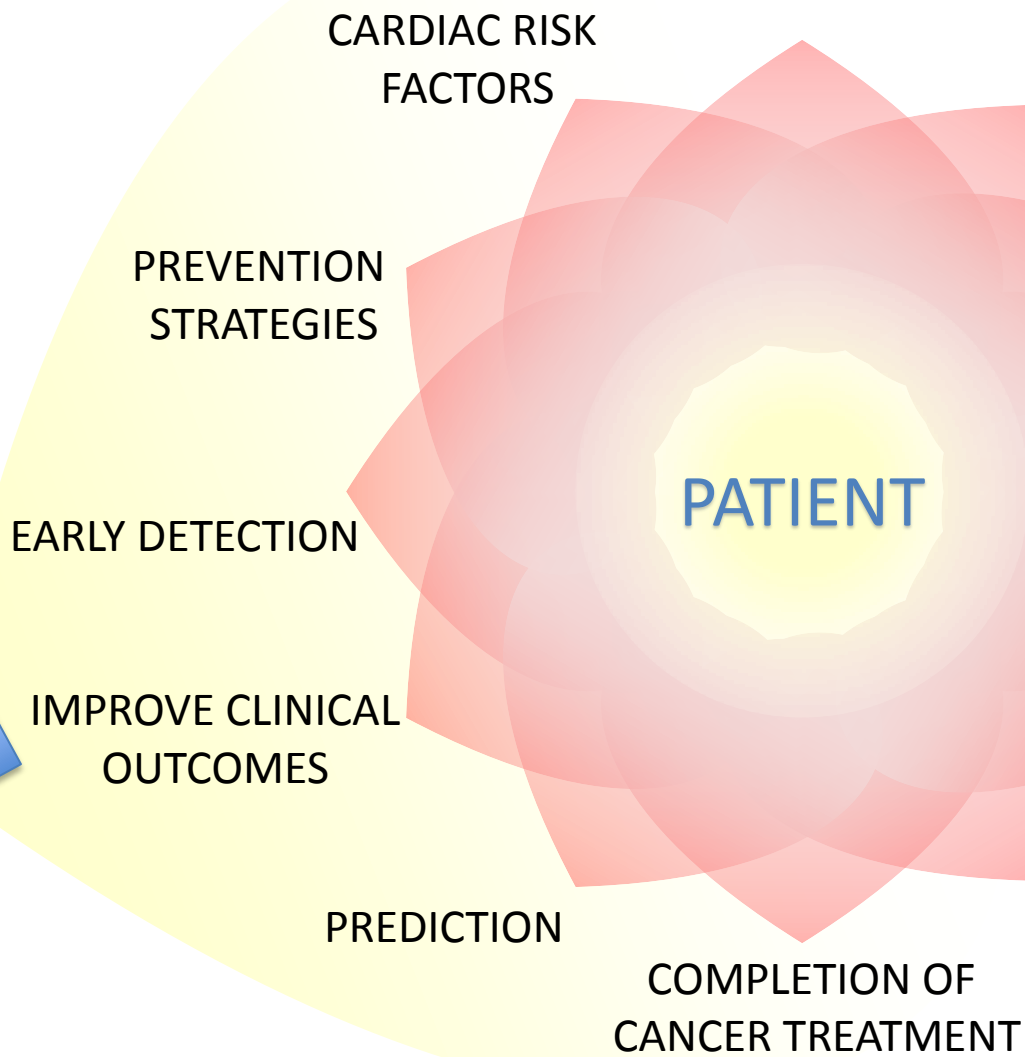


The Ottawa Cardio-Oncology Program



CARDIO-ONCOLOGY PROGRAM CLINICAL WORK

- SINCE 2008
- > 1,000 patients



**CARDIO-
ONCOLOGY
SURVIVORSHIP
CLINIC**

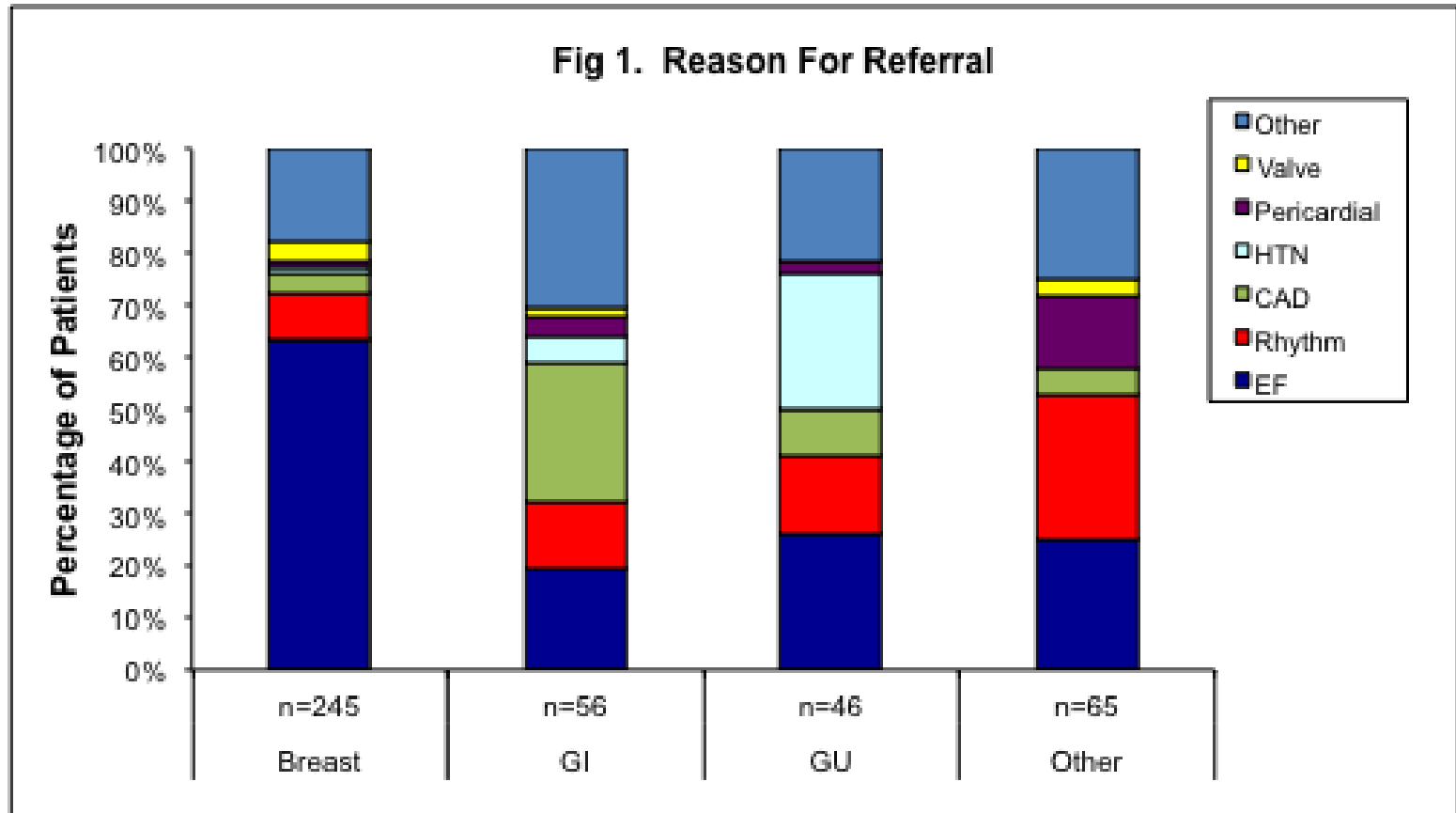


Canadian Cardiac
Oncology Network

cardiaconcolgy.ca

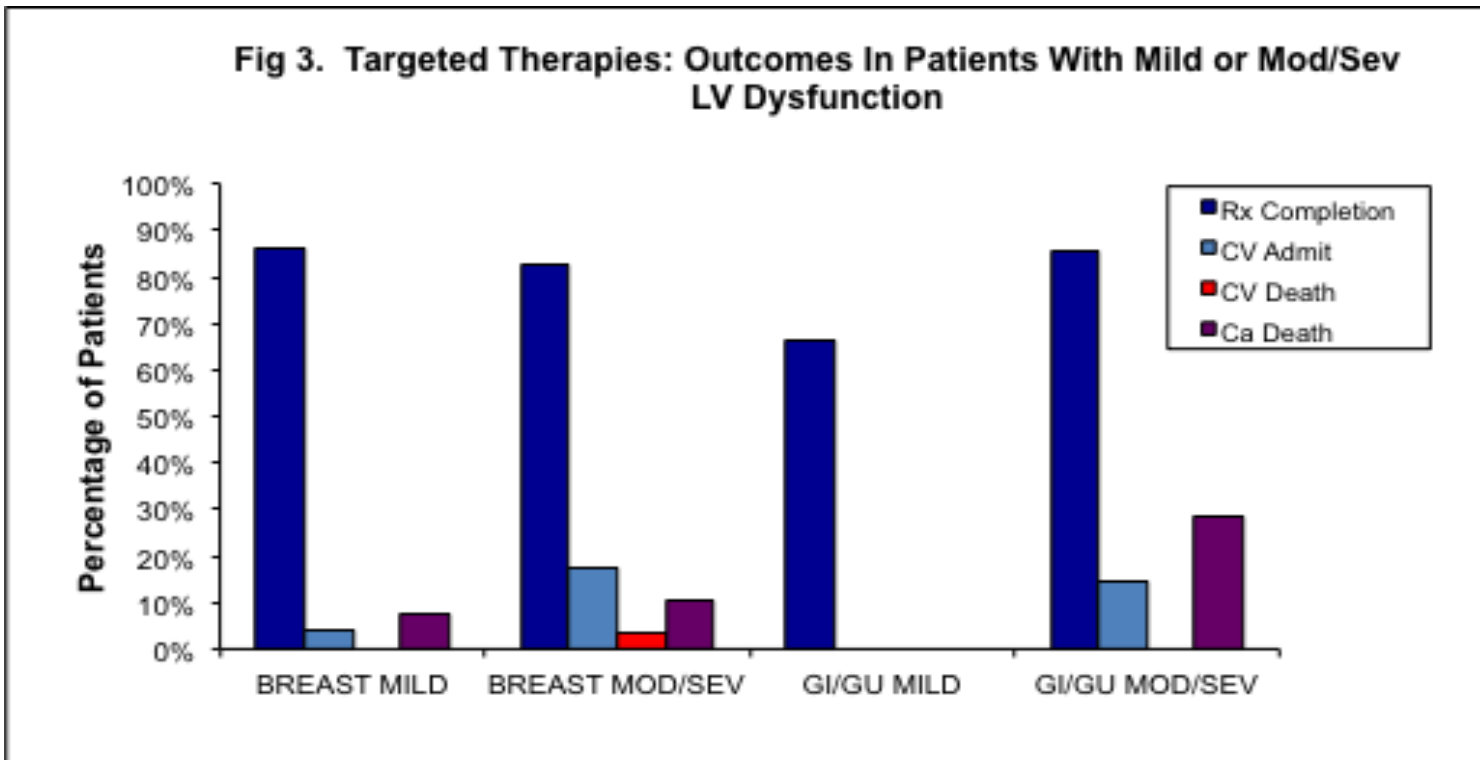
Initial Five Years Experience Of The Ottawa Hospital Cardio-Oncology Clinic: Patient Characteristics & Clinical Outcomes (n=412)

Christopher Johnson, Michele Turek, Angeline Law, Ellamae Stadnick, Sean Hopkins,
Nadine Graham, Franco Dattilo, Jeff Sulpher, Susan Dent



Initial Five Years Experience Of The Ottawa Hospital Cardio-Oncology Clinic: Patient Characteristics & Clinical Outcomes (n=412)

Christopher Johnson, Michele Turek, Angeline Law, Ellamae Stadnick, Sean Hopkins,
Nadine Graham, Franco Dattilo, Jeff Sulpher, Susan Dent



Ottawa Cardio-Oncology Clinic

Journal of Oncology

Volume 2015 (2015), Article ID 671232, 5 pages

<http://dx.doi.org/10.1155/2015/671232>

Research Article

Clinical Experience of Patients Referred to a Multidisciplinary Cardiac Oncology Clinic: An Observational Study

Jeffrey Sulpher,¹ Shrey Mathur,¹ Nadine Graham,¹ Freya Crawley,¹ Michele Turek,² Christopher Johnson,² Ellamae Stadnick,² Angeline Law,² Jason Wentzell,³ and Susan Dent¹

Cardiotoxicity in breast cancer patients: A single center, retrospective review

[Maira Rushton](#), [Freya Crawley](#), [Jeffrey Sulpher](#), [Christopher Johnson](#), [Susan Dent](#)  

Progress in Pediatric Cardiology, 2015



Canadian Cardiac
Oncology Network

cardiaconcolgy.ca

ESTABLISHING A CARDIAC ONCOLOGY CLINIC - TIPS FOR ACHIEVING SUCCESS

- Logistics
 - Location of clinic, close interaction between oncologists and cardiologists
- Resources
 - Access to space, imaging, \$\$
- Expertise
 - Cardiologist with imaging experience and knowledge of cancer therapies
- Allied Health Support
- Collaboration
 - Support from other health care providers (nursing, pharmacy)
 - Consistent communication between health care providers



ESTABLISHING A CARDIAC ONCOLOGY CLINIC - BARRIERS AND OBSTACLES

- lack of Institutional support
- lack of academic and administrative mentorship – novelty of field, a shortage of evidence-based clinical standards
- lack of opportunities for education and training
- limited awareness among oncology and cardiology specialists about the need for cardio-oncology services

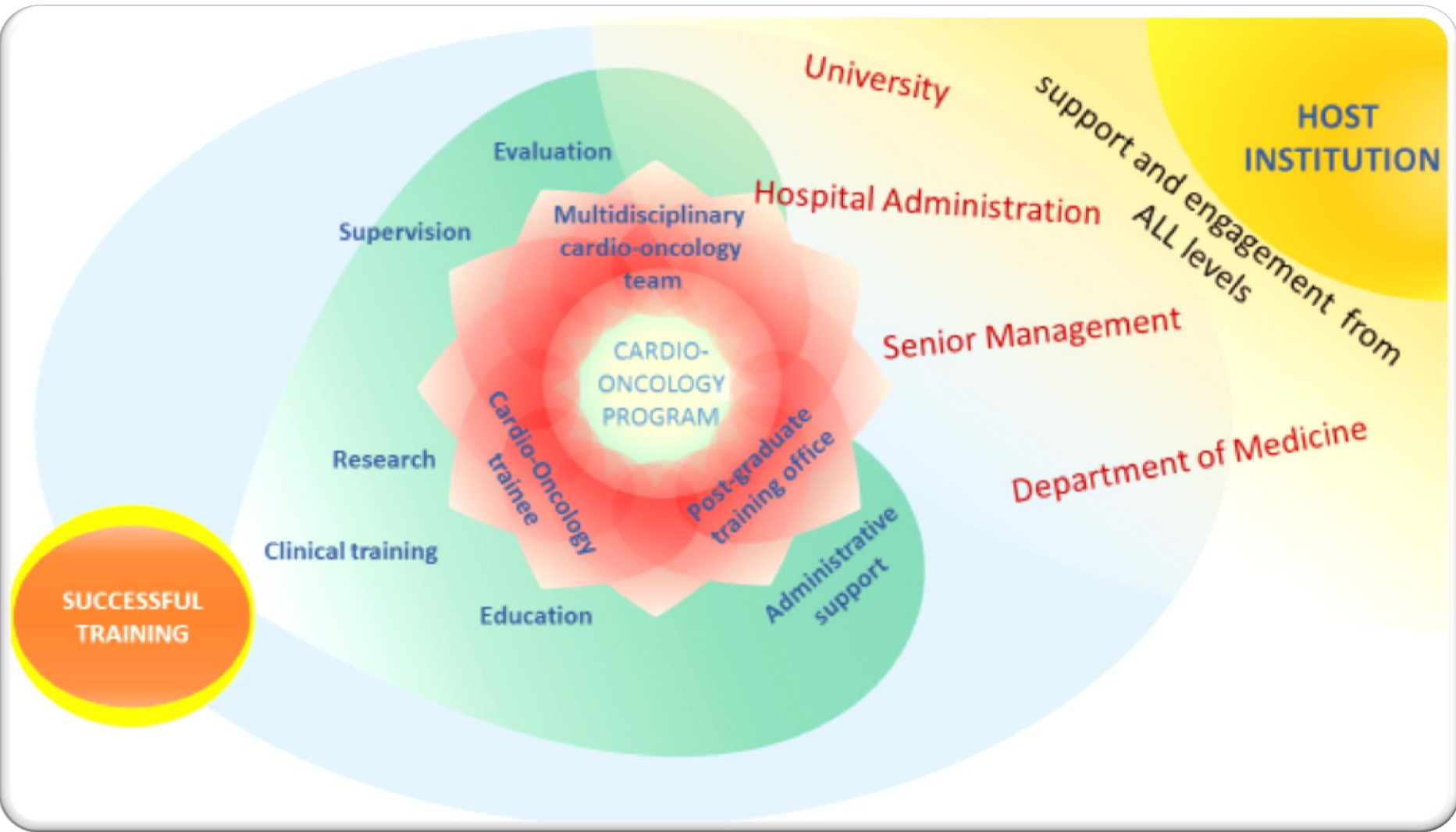
Okwuosa and Barac JACC, 2015



Canadian Cardiac
Oncology Network

cardiaconcolgy.ca

A Successful Cardio-Oncology Program



Education

- Multidisciplinary rounds (accredited)
- CME presentations (allied HCP's)
- Preceptorship program
- Training- Residency/Fellowships
- Cardio-Oncology Meetings (ICOS-NA, GCOS)
- Special education sessions – ASCO, SABCS
- Courses (ACC workshop)



February 17, 2017 >

Advancing Cardiovascular Care of the
Oncology Patient | Live Meeting

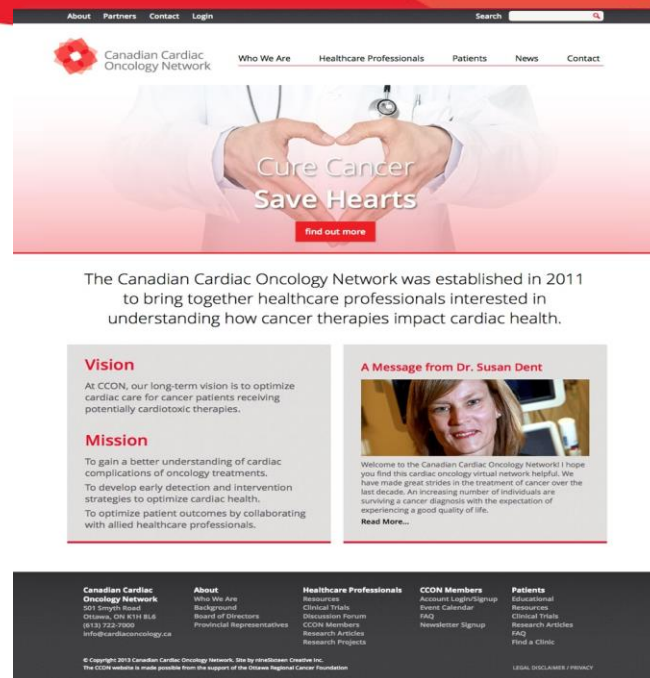
cardiaconcolgy.ca








Canadian Cardiac
Oncology Network

Education

- National Organization (Canadian Cardiac Oncology Network) in 2011
- Website -2013 (www.cardiaconcology.ca)
- ICOS (www.icosna.org)
- ACC – Cardio-Oncology Section (www.acc.org)
- ECOG-ACRIN cardiotoxicity working group



Guidelines/Position Statements

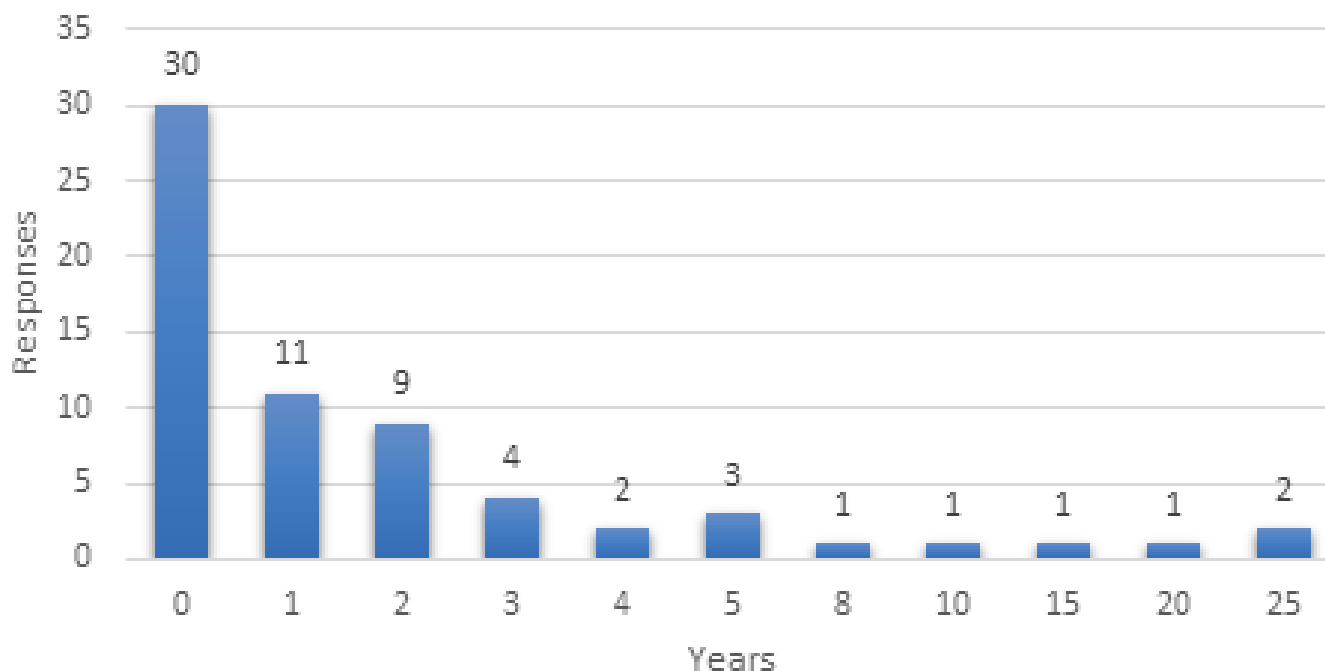
- CCS guideline* 
- ASCO survivorship guideline*** 
- ESC position statement update** 
- ESMO guideline update 
- ICOS position statement 



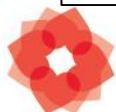
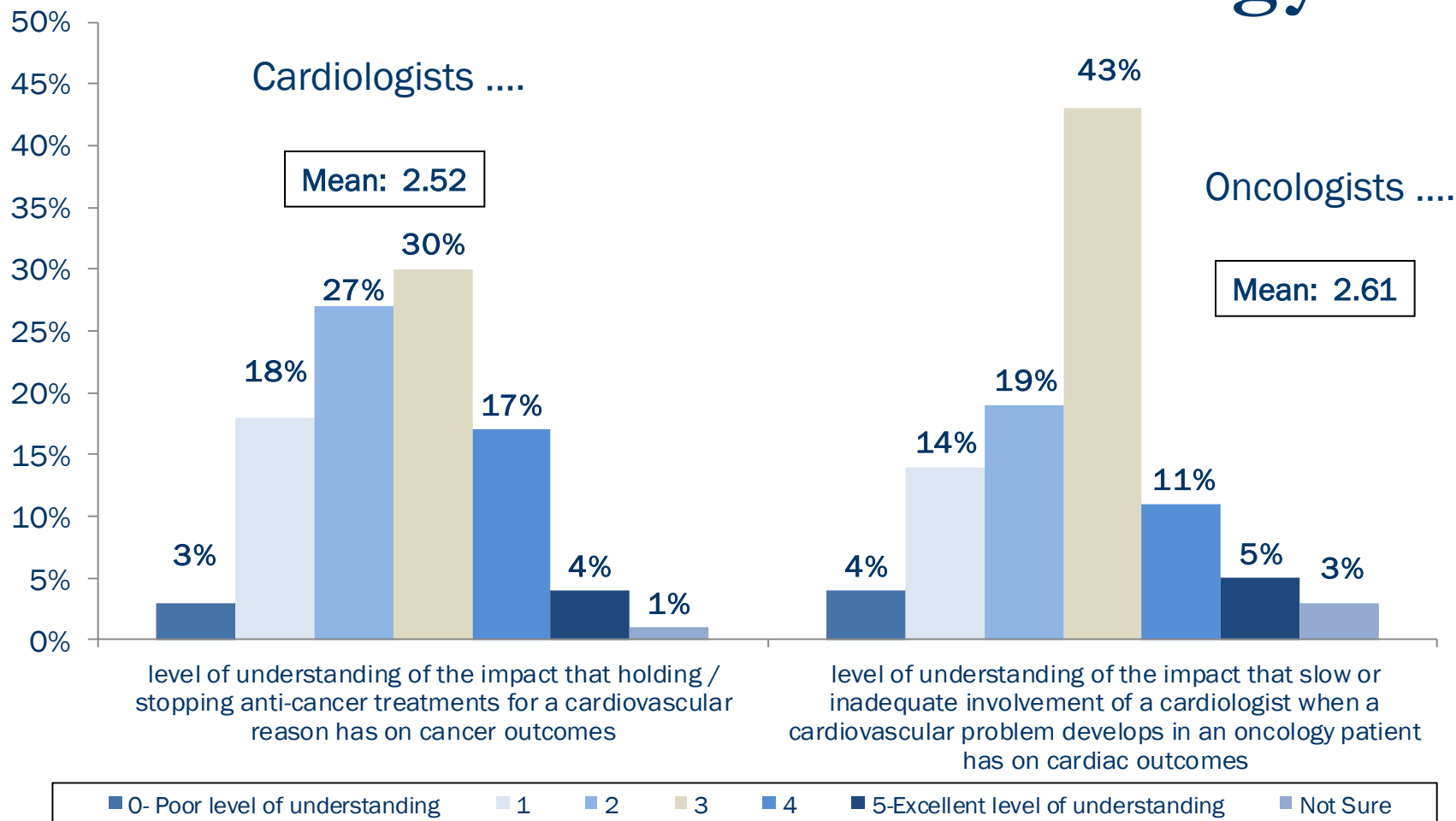
*Can J Cardiology April 2016, ** Eur Heart Journal, Sept 2016 ***Journal of Clinical Oncology, Dec 2016 cardiaconcolgy.ca

Education in Cardio-Oncology

Years of Experience in Cardio-Oncology



Education in Cardio-oncology



Canadian Cardiac
Oncology Network

Barac et al JACC 2015

cardiaconcolgy.ca

Q. Do you think cardiologists/oncologists in general have a good level of understanding of ..

Research in Cardio-Oncology

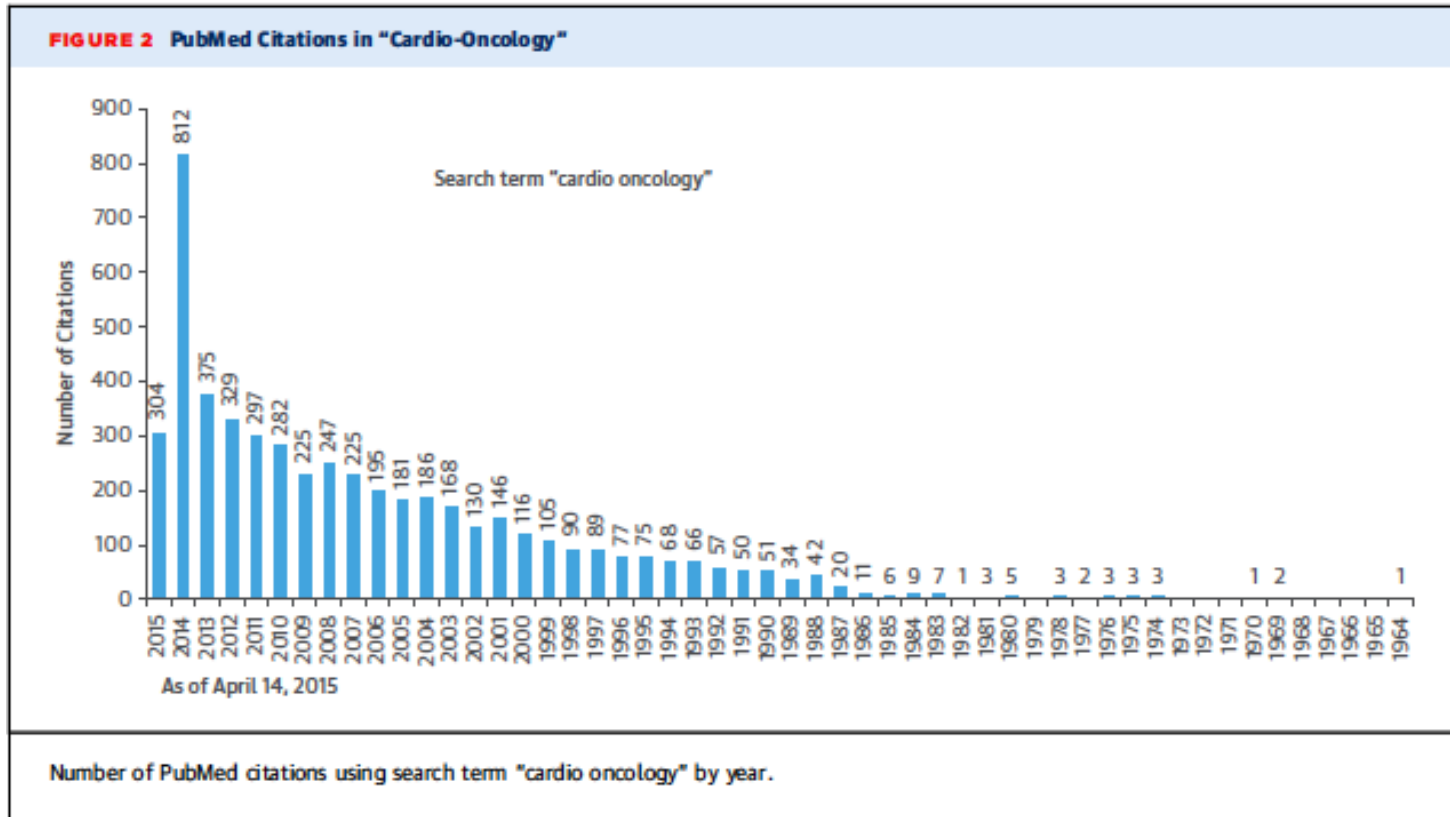
Where are we going?



Canadian Cardiac
Oncology Network

cardiaconcolgy.ca

Publications in Cardio-Oncology



Publications

Eur Heart J. 2016 Jun 1;37(21):1671-80. doi: 10.1093/eurheartj/ehw022. Epub 2016 Feb 21.

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.

Gulati G¹, Heck SL¹, Ree AH², Hoffmann P³, Schulz-Menger J⁴, Fagerland MW⁵, Gravdehaug B⁶, von Knobelsdorff-Brenkenhoff F⁷, Bratland A⁸, Storås TH⁹, Hagve TA¹⁰, Røsjø H¹, Steine K¹, Geisler J², Omland T¹¹.

JOURNAL OF CLINICAL ONCOLOGY

..... Official Journal of the American Society of Clinical Oncology

Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101–Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity

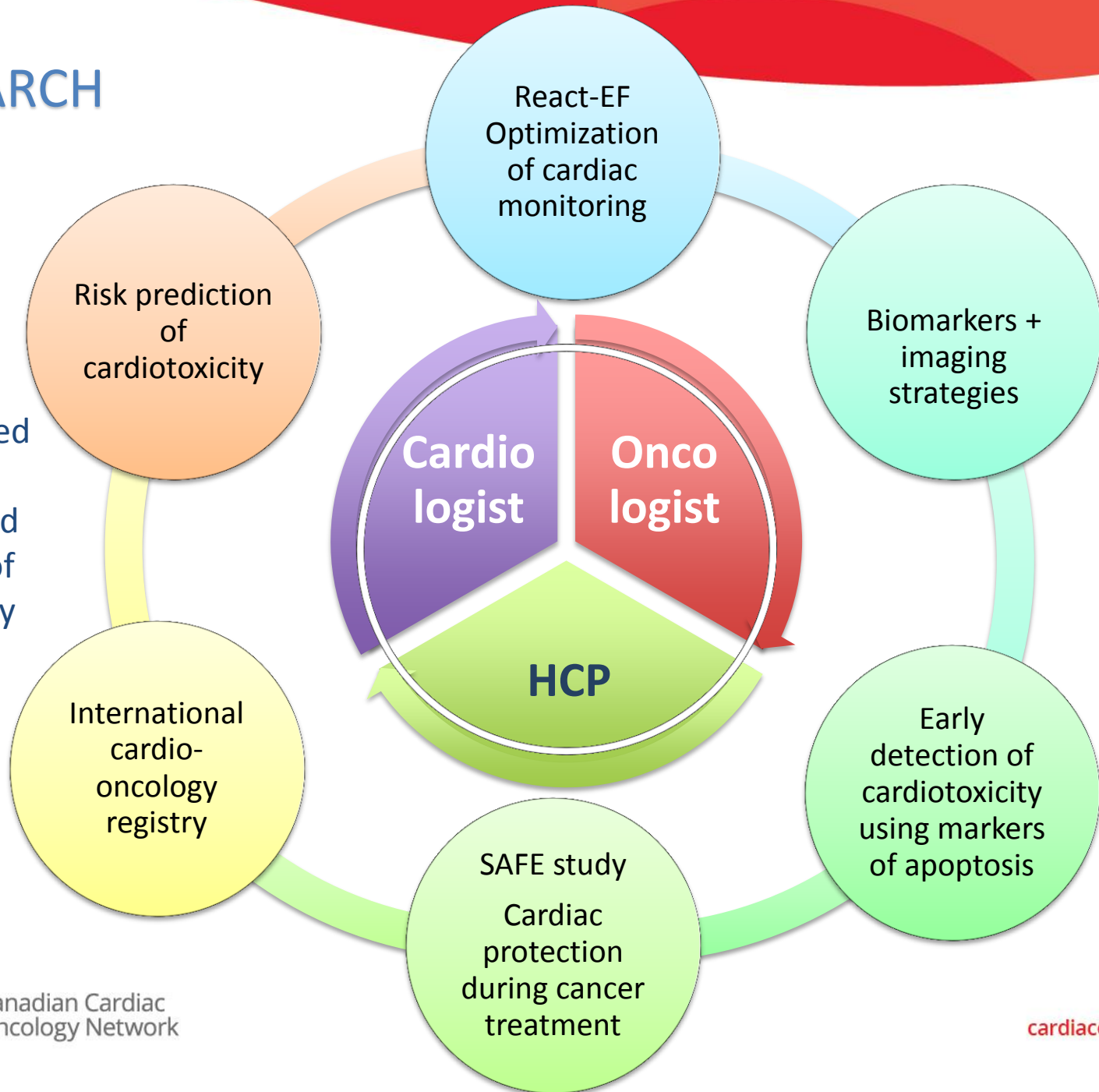
Edith Pituskin, John R. Mackey, Sheri Koshman, Davinder Jassal, Marshall Pitz, Mark J. Haykowsky, Joseph J. Pagano, Kelvin Chow, ...



Canadian Cardiac
Oncology Network

cardiaconcolgy.ca

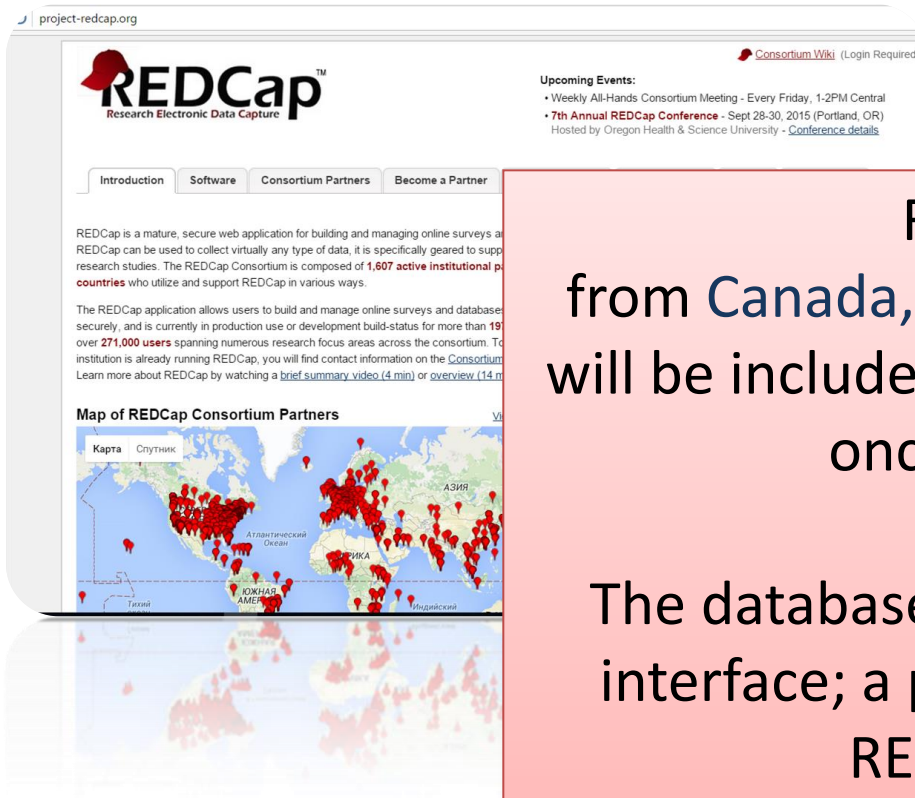
RESEARCH



198 registered
CT on
diagnosis and
treatment of
cardiotoxicity
clinical
trials.gov



INTERNATIONAL CARDIO-ONCOLOGY REGISTRY



project-redcap.org

REDCap™
Research Electronic Data Capture

Consortium Wiki (Login Required)

Upcoming Events:

- Weekly All-Hands Consortium Meeting - Every Friday, 1-2PM Central
- 7th Annual REDCap Conference - Sept 28-30, 2015 (Portland, OR)
Hosted by Oregon Health & Science University - [Conference details](#)

Introduction Software Consortium Partners Become a Partner

REDCap is a mature, secure web application for building and managing online surveys and databases. REDCap can be used to collect virtually any type of data, it is specifically geared to support research studies. The REDCap Consortium is composed of **1,607 active institutional partners** in **100 countries** who utilize and support REDCap in various ways.

The REDCap application allows users to build and manage online surveys and databases securely, and is currently in production use or development build-status for more than **19** over **271,000 users** spanning numerous research focus areas across the consortium. To learn more about REDCap, you will find contact information on the [Consortium](#) page. Learn more about REDCap by watching a [brief summary video \(4 min\)](#) or [overview \(14 min\)](#).

Map of REDCap Consortium Partners

Карта Спутник

Азия

Атлантический Океан

ЮЖНАЯ АМЕРИКА

Индийский

Five centers
from Canada, United States, and Spain
will be included in the inaugural cardio-
oncology registry.

The database will have a web-based
interface; a possible platform is the
REDCap-project.

REDCap is a secure web application for building and managing online databases. It is specifically geared to support data capture for research studies.

What are the Challenges ?

- Early identification of cardiac risk
 - e.g cardiac imaging, biomarker
- Strategies to prevent cardiotoxicity
 - Primary and secondary prevention
- Optimal cardiovascular drugs to manage cardiotoxicity
- Surveillance and monitoring
 - Imaging, frequency and duration



Opportunities

“Cardio-oncology partnerships are needed to decrease the burden of cardiotoxicity with our ‘newer’ therapies”

Dr. Christine Brezden-Masley , 2011





cardiaconology.ca

CNN Health News



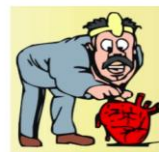
Take Home Messages

- Cancer and heart disease are significant causes of morbidity and mortality in North America
- Improvement in cancer therapies has resulted in long term survivors who may be at risk of cardiotoxicity.
- Individuals with heart disease may develop cancer and require potentially cardiotoxic cancer therapy.



Take Home Messages

- Close collaboration among health care providers is needed in order to provide the best cancer care while optimizing cardiac health
- Research is urgently needed to determine the best prevention, early detection and treatment strategies for patients who experience cardiotoxicity from their cancer treatment



Save the Date



Global Cardio-Oncology Summit 2017

September 20-21, 2017
London, UK

Additional details to follow.



British Cardio-Oncology Society
BC-OS.org



Canadian Cardiac
Oncology Network

INTERNATIONAL
CardiOncology
SOCIETY



British Cardiovascular Society

**WE ARE
MACMILLAN.
CANCER SUPPORT**

Royal Brompton & Harefield **NHS**

NHS Foundation Trust

Topics include:

- How to deliver a Cardio-Oncology service
- Training in Cardio-Oncology
- eHealth and Cardio-Oncology
- How do I measure the quality of my service?
- Role of primary care in cancer survivors
- Immunotherapy and emerging cardiotoxicity
- Personalised medicine & genetics
- EP session –who should have ablation, ICDs, CRT?
- Anticoagulation and antithrombotic (AF, ACS)

Thank-you

