Cardiotoxicities of Contemporary Cancer Treatment

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September 2022

Pre-test Question #1

Which of the following is true about HER2 targeted therapy and LV dysfunction?

A. Once LVEF <50%, need to permanently discontinue treatment
B. LVEF recovers in about 60% of cases
C. It is safe to continue treatment despite drop in LVEF to 40% range if there is no clinical heart failure
D. HER2 treatment associated cardiotoxicity can present decades after exposure

Pre-test Question #2

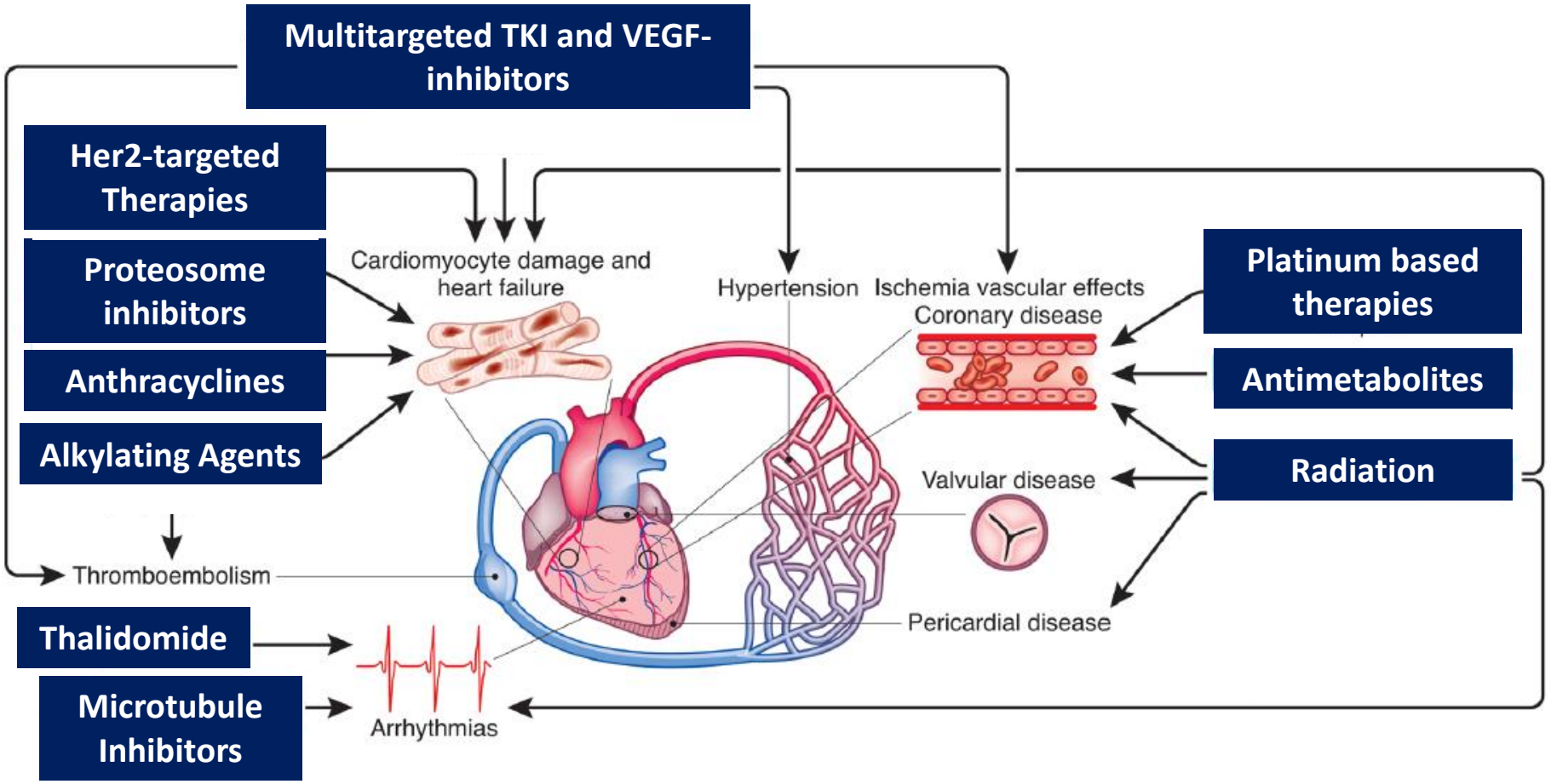
Which of the following is true about ponatinib?

A. Significant hypertension is uncommon
B. Ponatinib has a safer CV side effect profile compared to imatinib
C. Arterial vascular disease is a potential side effect
D. Ponatinib increases QTc significantly

Learning objectives

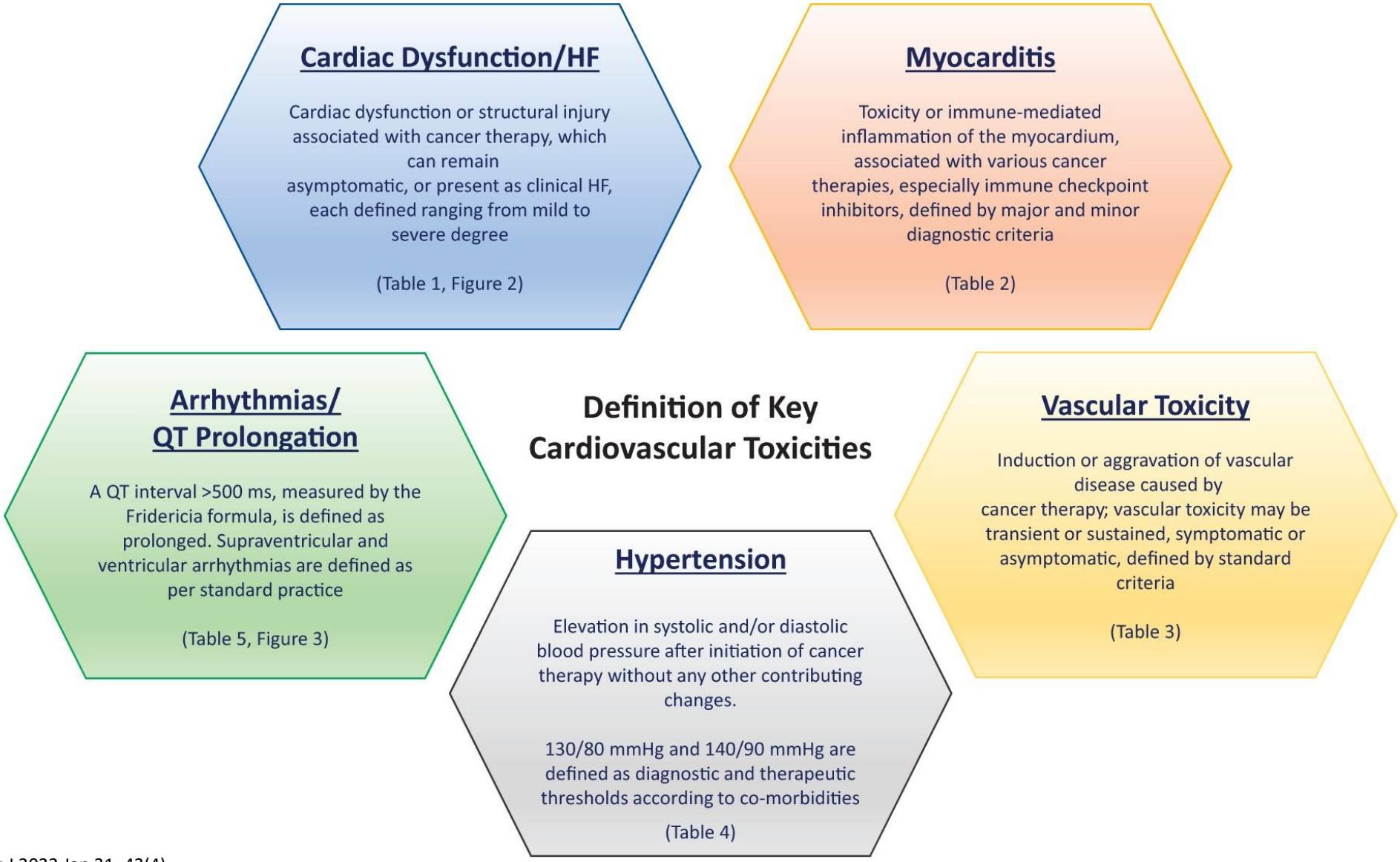
1. Discuss how to manage LV dysfunction from anthracyclines and HER2 targeted therapies
2. Recognize cardiovascular side effects of TKI's
3. Highlight future directions in cardio-oncology

Cardiac effects of chemotherapy: Beyond LV function

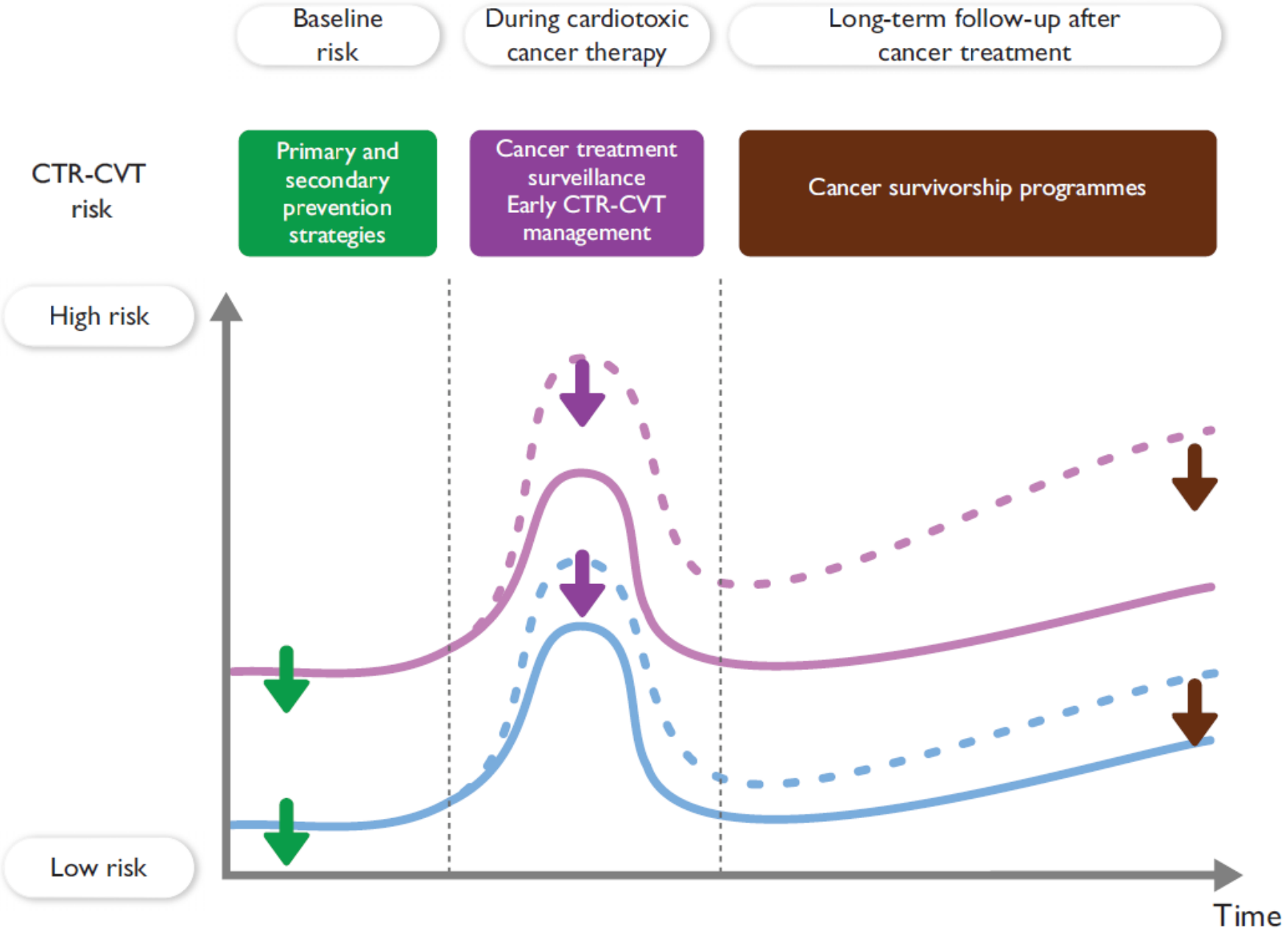


Modified from: Lenneman CG and Sawyer DB. Circ Res. 2016; 118: 1008-1020

ICOS 2022 definitions for cardiotoxicity



Herrmann J et al. Eur Heart J 2022 Jan 31; 43(4)



2022 ESC Guidelines on cardio-oncology

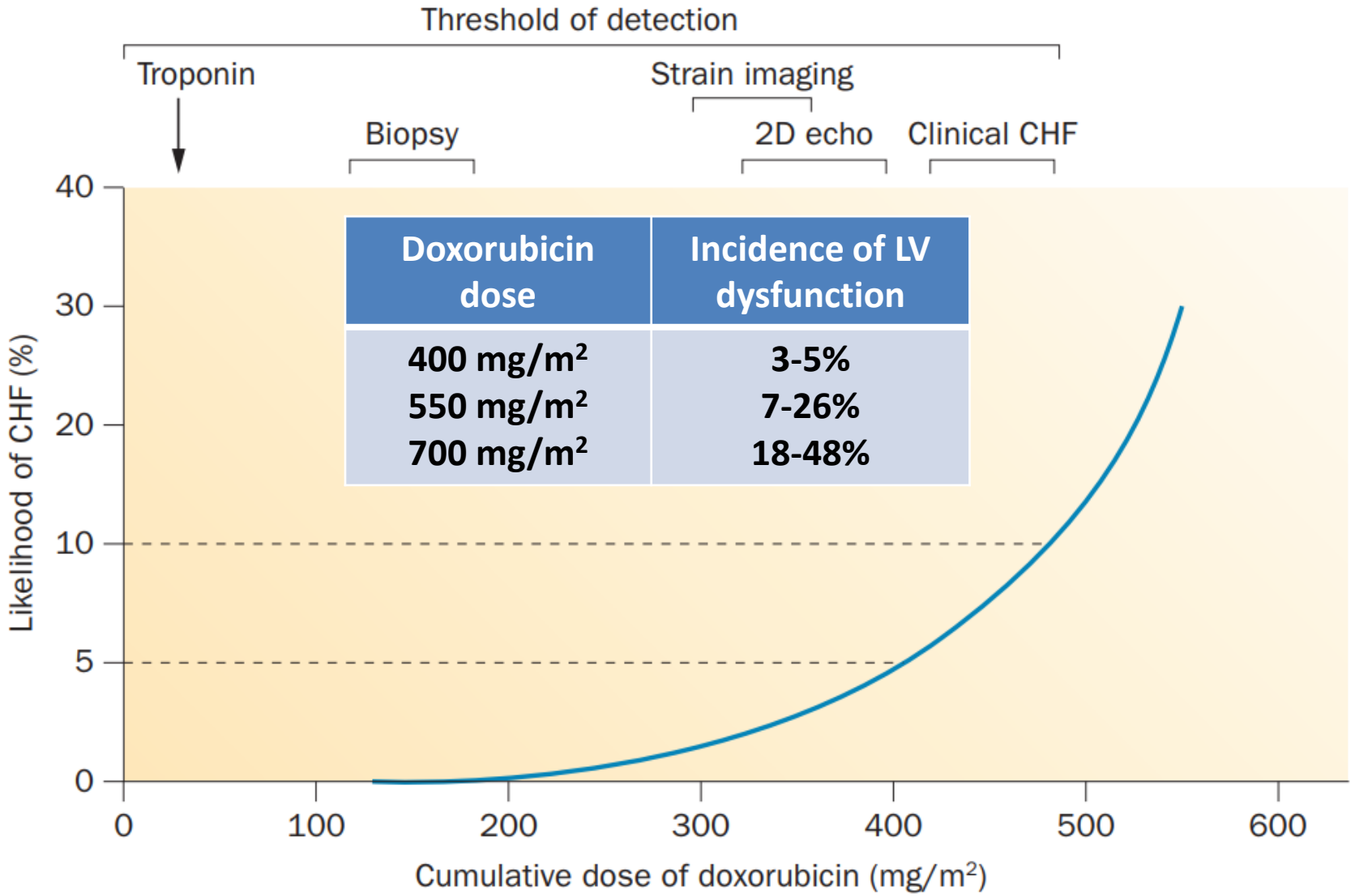
Case study: Breast cancer

- JC: 35 y/o woman, no PMH
- Dx: Infiltrating lobular carcinoma of L breast, ER-/PR-, HER2+, no mets

What is her risk of cardiotoxicity?

- Lumpectomy, Radiation therapy, ddAC-T (doxorubicin, cyclophosphamide and paclitaxel)
- HER2+ → Starts trastuzumab 1 mo later
- Breast cancer in remission

Anthracycline cardiotoxicity



Doxorubicin dose	Incidence of LV dysfunction
400 mg/m²	3-5%
550 mg/m²	7-26%
700 mg/m²	18-48%

Ewer MS. Nat Rev Cardiol. 12; 547-558 2015

Anthracyclines and timing

Acute: **Within 2 weeks** from treatment

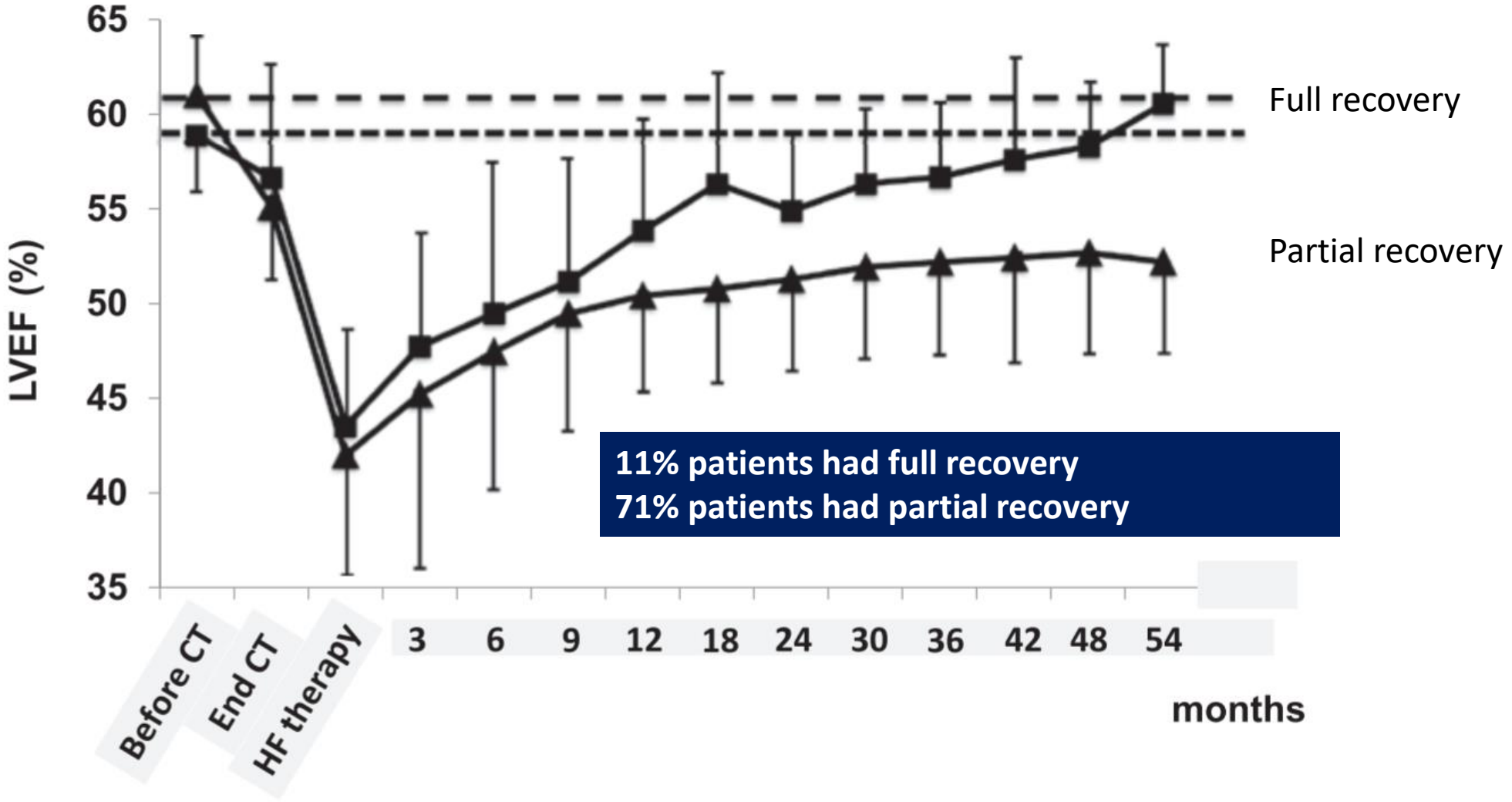
Early-onset: **Within 1 year**. **Most frequent** form of CTX

Late-onset: **Years to decades** later

Incidence of cardiotoxicity 9%
98% occurred within first year

Cardinale et al. Circulation. 2015;131:1981-1988

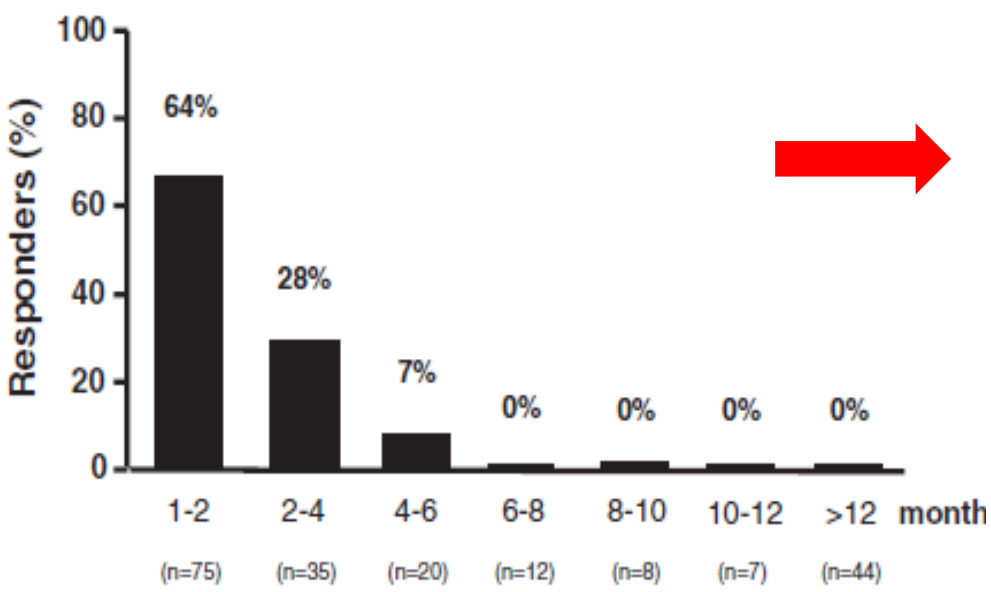
Anthracycline cardiotoxicity is reversible?

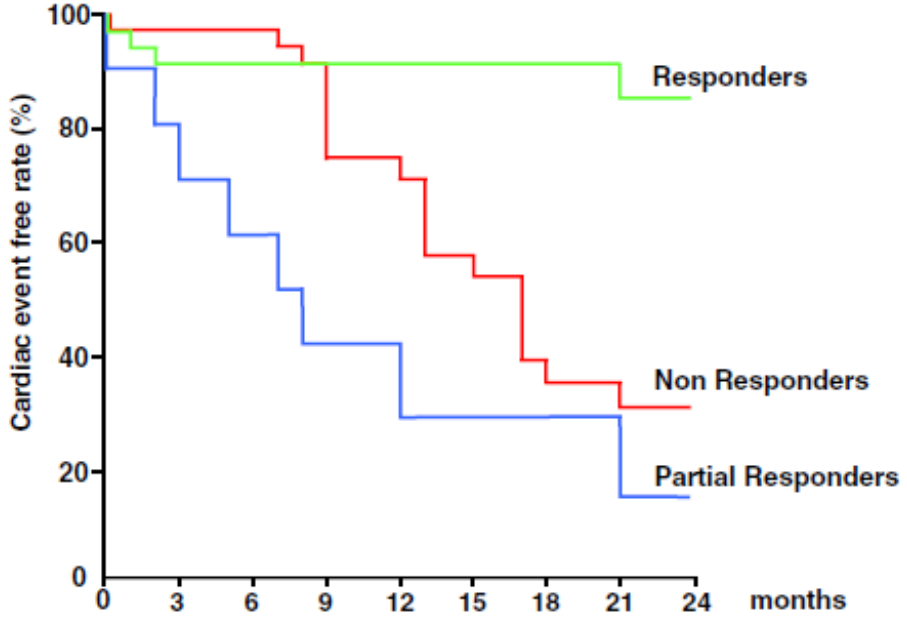


Cardinale et al. Circulation. 2015;131:1981-1988

Timing of intervention matters

201 patients with LVEF < 45% due to anthracyclines
Enalapril and carvedilol were added, followed LVEF q3 mo





Time between chemo and HF meds

Earlier is Better!

Early = Response = Survival!

Cardinale D et al. JACC. 2010; 55:213-20

Trastuzumab Cardiotoxicity

Selected Trials	Time interval between anthracycline and trastuzumab	Incidence of CHF (%)	Incidence of LV dysfunction (%)	Reversibility
Slamon *et al.*‡	Concurrent	16	27	Yes
NCCTG N9831;arm B	105 days	2.8	7.8	Yes
NCCTG N9831;arm C	21 days	3.3	10.4	Yes
BCIRG-006; Anthracycline arm	21 days	2.0	18.6	Yes
BCIRG-006; Nonanthracycline arm	NA	0.4	9.4	Yes

Administration w/ anthracyclines increases risk

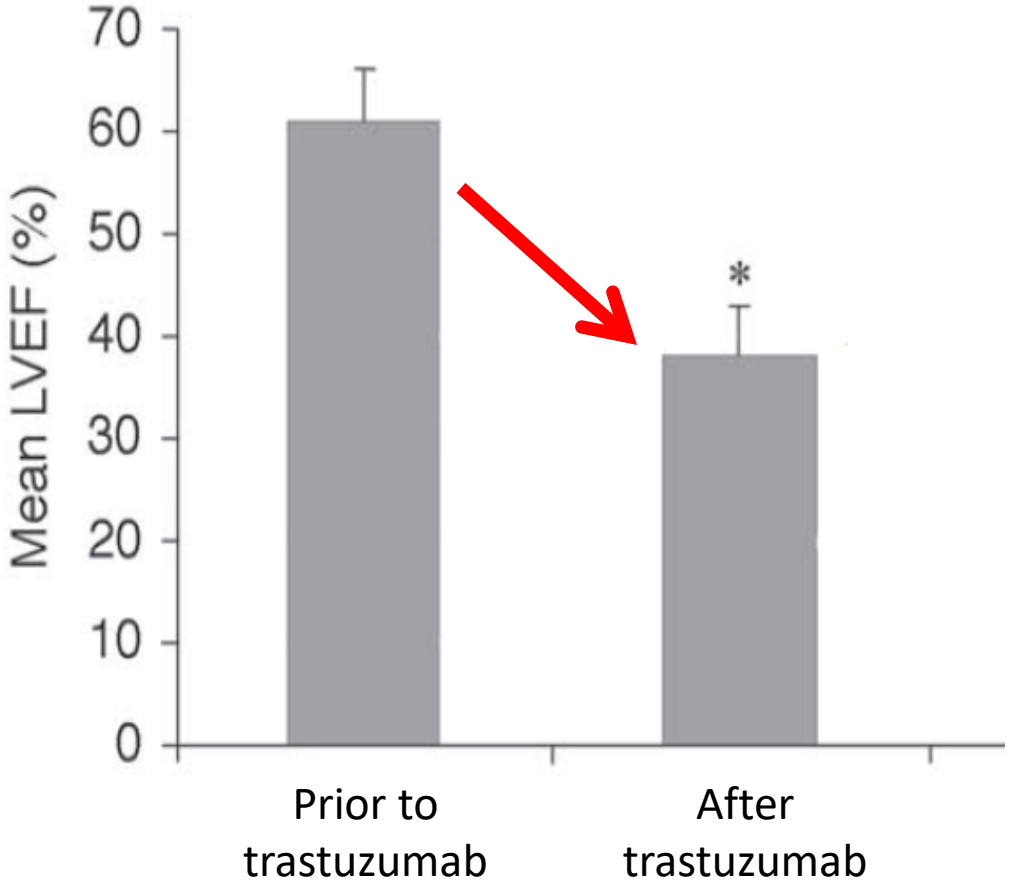
Increased delay between therapies decreases risk

Toxicity is usually reversible

Modified from: Ewer MS and Ewer SM. Nat Rev Cardiol. 2015. 12. 547-58

What about trastuzumab rechallenge?

38 patients with HER2/neu+ breast cancer
All received anthracyclines

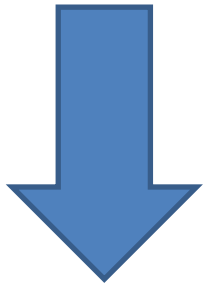


Ewer MS et al. JCO 2005. 23: 7820-26

Case study: Breast cancer

- **Echo shows LVEF of 40% (baseline 60%)**

  GLS is now -13% (baseline -19%)



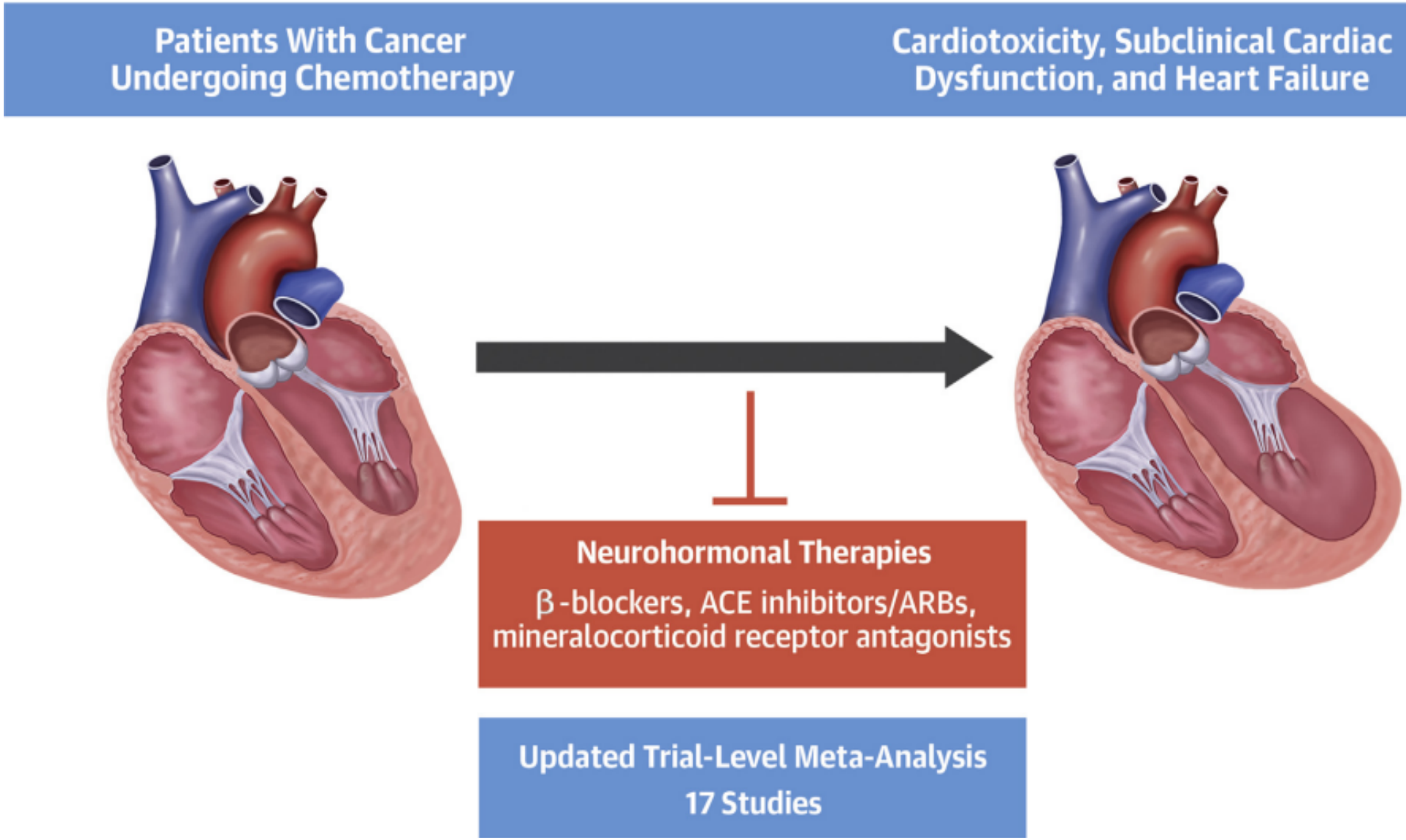
Could we have prevented this?

Summary of Select Cardioprotection Studies

Study	Year	Cohort and Exposure	Cardiac Intervention	Outcome Measures	Results
OVERCOME	2013	Hematologic malignancies (AML or auto-HSCT)	Enalapril and carvedilol vs. placebo	Change in LVEF on echo and cardiac MRI	Enalapril and coreg prevented drop in LVEF; also lower incidence of death or HF
PRADA	2016	Early stage breast cancer treated with anthracyclines +/- trastuzumab or RT	2x2 factorial treatment with candesartan or metoprolol succinate vs. placebo	5% drop in LVEF by cardiac MRI	Candesartan attenuated drop in LVEF (0.8% vs. 2.6%); no effect of metoprolol succ
MANTICORE	2017	HER2-positive early breast cancer +/- anthracyclines	Perindopril vs. bisoprolol vs. placebo	Change in LVEDVi (primary) and LVEF (secondary, LVEF ≥ 10% drop to less than 53%) by cardiac MRI	No difference in LVEDVi; bisoprolol (-1%) and perindopril (-3%) protected against change in LVEF vs. placebo (-5%)
CECCY	2018	HER2-neg breast cancer exposed to anthracylines	Carvedilol vs. placebo	≥ 10% drop in LVEF by echo	No difference in LVEF or BNP between groups; carvedilol protected against troponin elevation and diastolic dysfunction
USF (Guglin)	2018	Breast cancer exposed to trastuzumab +/- anthracyclines	Lisinopril vs. carvedilol vs. placebo	≥ 10% drop in LVEF by echo	No difference in trastuzumab alone; for those exposed to anthracyclines and trastuzumab, lisinopril and carvedilol were protective
ICOS-One	2018	Mixed cohort with exposure to anthracyclines	Enalapril starting with anthracyclines vs. only starting with Troponin elevation	Troponin elevation	No difference between strategy of primary prevention vs. Troponin-triggered strategy

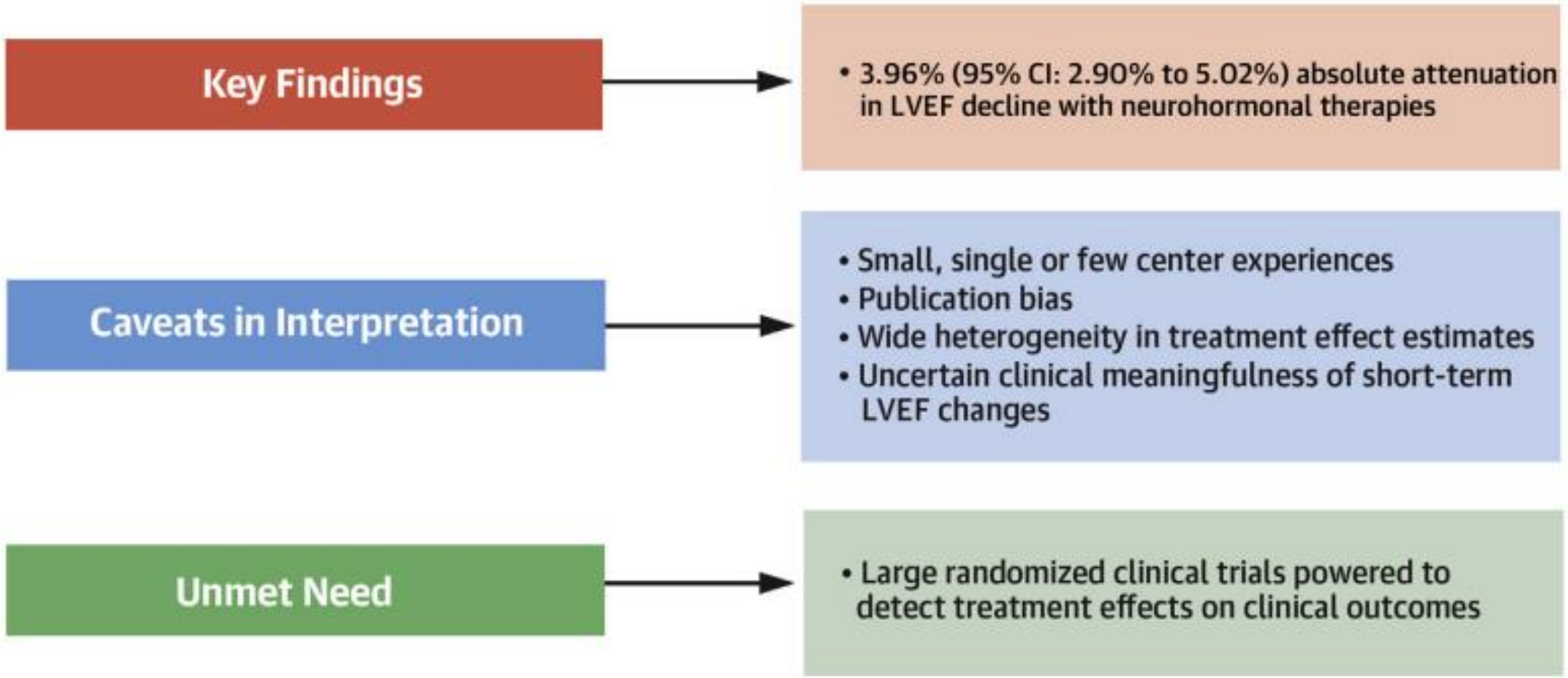
OVERCOME: Bosch X et al. JACC 2013; 61(23): 2355-62
PRADA: Gulati G et al. Eur Heart J 2016; 37(21): 1671-80
MANTICORE: Pituskin et al. JCO 2017; 35(8): 870-7
CECCY: Avila MS et al. JACC 2018; 71(20): 2281-90
USF: Guglin M. Presented at ACC 2018, NCT01009918
ICOS-One: Cardinale D et al. Eur J Cancer. 2018; 94: 126-37

Meta-analysis of NH blockade as cardioprotection



Vaduganathan M et al. JACCCO 1(1): Sept 2019

Meta-analysis of NH blockade as cardioprotection

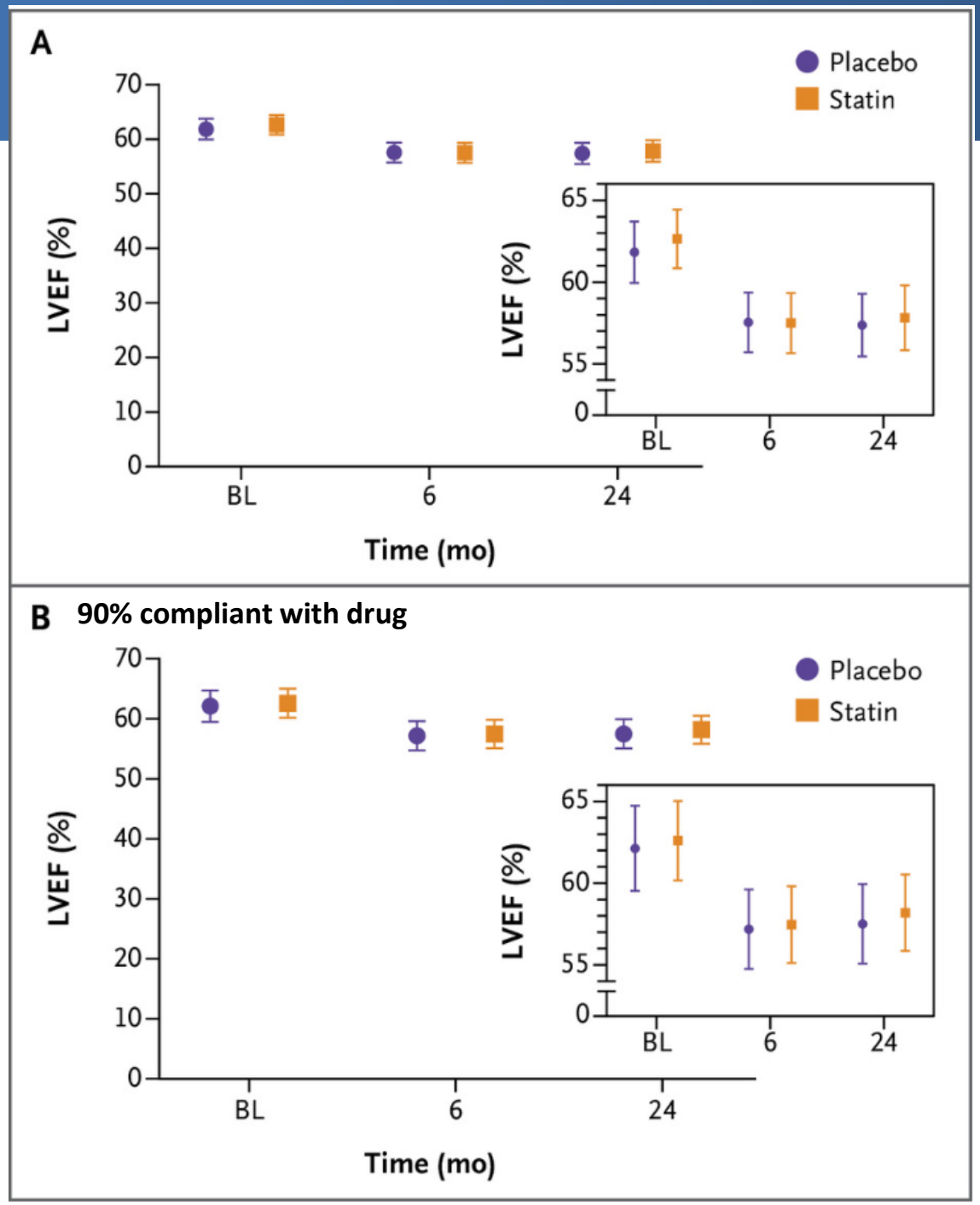


Vaduganathan M et al. JACCCO 1(1): Sept 2019

What about statins?

- Stage I-III breast CA or stage I-IV lymphoma
- Chemotherapy w/ anthracycline
- 279 randomized to atorvastatin 40 mg vs placebo

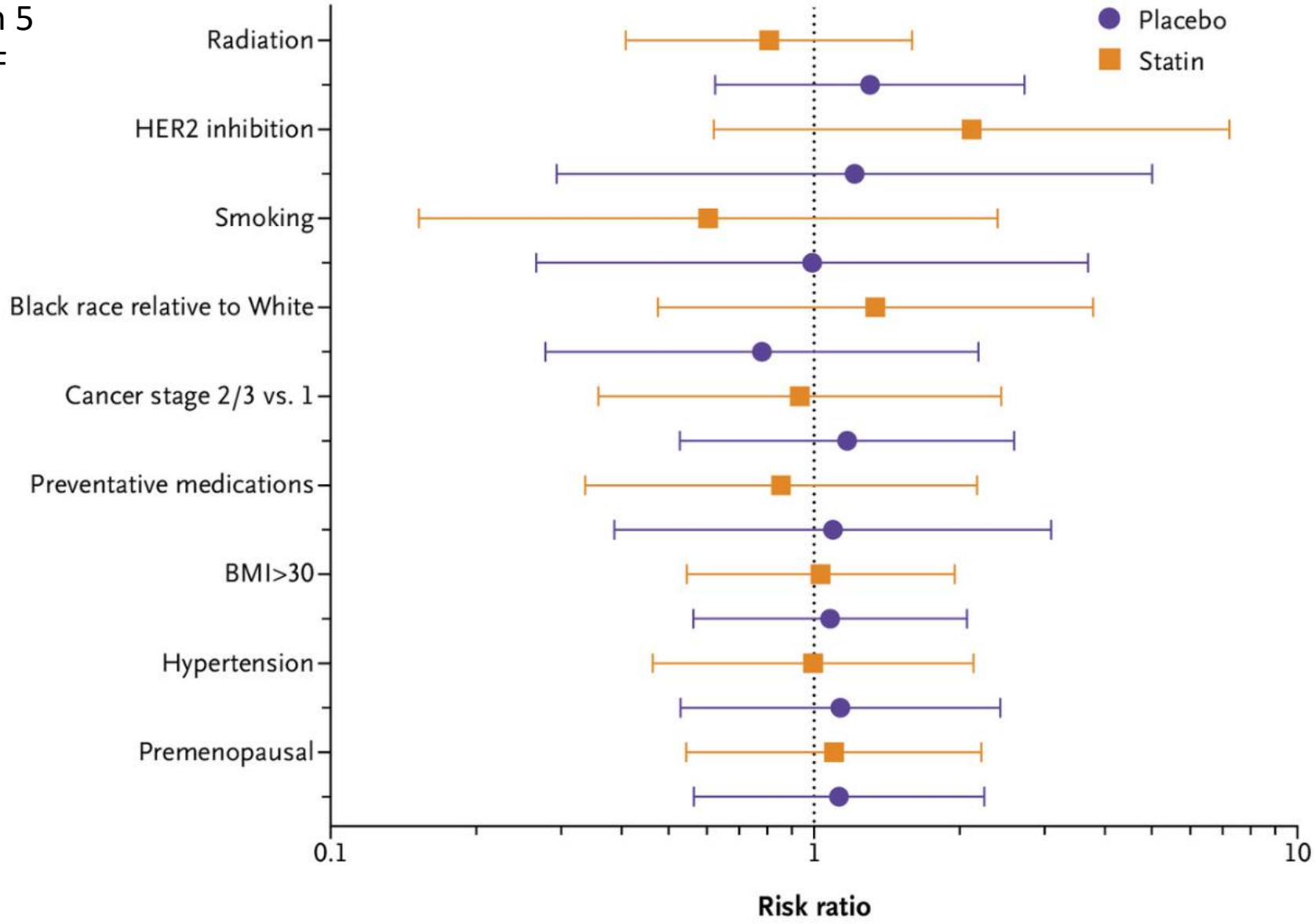
- Followed for 24 months
- Primary endpoint change in LVEF on CMR



Hundley WG et al. NEJM Evidence. Aug 2022.

Subgroup analyses

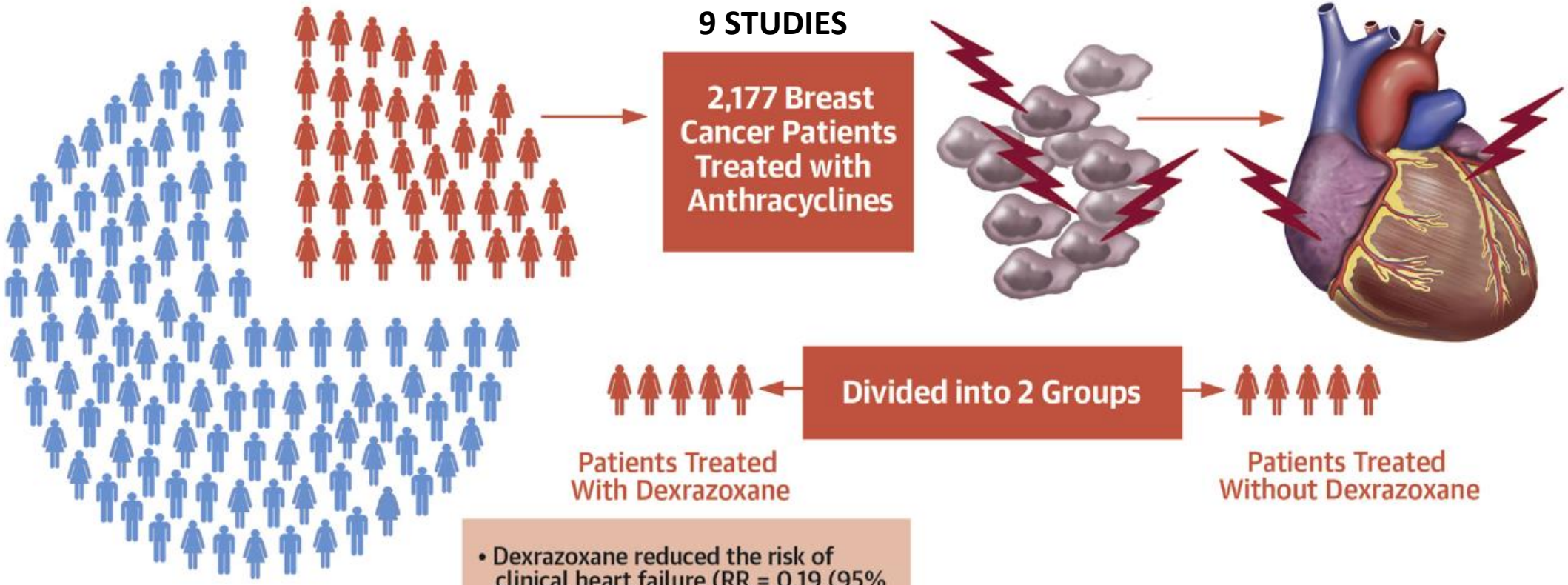
Risk ratios for greater than 5 percentage decline in LVEF over 24 months



Hundley WG et al. NEJM Evidence. Aug 2022.

Meta-analysis of dexrazoxane in BC

CENTRAL ILLUSTRATION Dexrazoxane in Breast Cancer Patients Under Anthracycline-Based Chemotherapy



Macedo AV et al. JACC: Cardio-oncology 2019 1(1)

Case study: JC

- Trastuzumab held; Started carvedilol and lisinopril
- 1 month later: LVEF 60% (GLS -18%)
- Completed Trastuzumab, LVEF stable

Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-019-05191-2

CLINICAL TRIAL

Check for updates

Prospective evaluation of the cardiac safety of HER2-targeted therapies in patients with HER2-positive breast cancer and compromised heart function: the SAFE-HEaRt study

F. Lynce[1] · A. Barac[1,2] · X. Geng[3] · C. Dang[4,5] · A. F. Yu[4,5] · K. L. Smith[6,7] · C. Gallagher[8] · P. R. Pohlmann[1] · R. Nunes[6,7] · P. Herbolsheimer[9] · R. Warren[1] · M. B. Srichai[2,10] · M. Hofmeyer[2] · A. Cunningham[11] · P. Timothee[11] · F. M. Asch[2,11] · A. Shajahan-Haq[1] · M. T. Tan[3] · C. Isaacs[1] · S. M. Swain[1]

ORIGINAL RESEARCH

Safety of Continuing Trastuzumab Despite Mild Cardiotoxicity

A Phase I Trial

EBAC

ABIM CME MOC ACCREDITED

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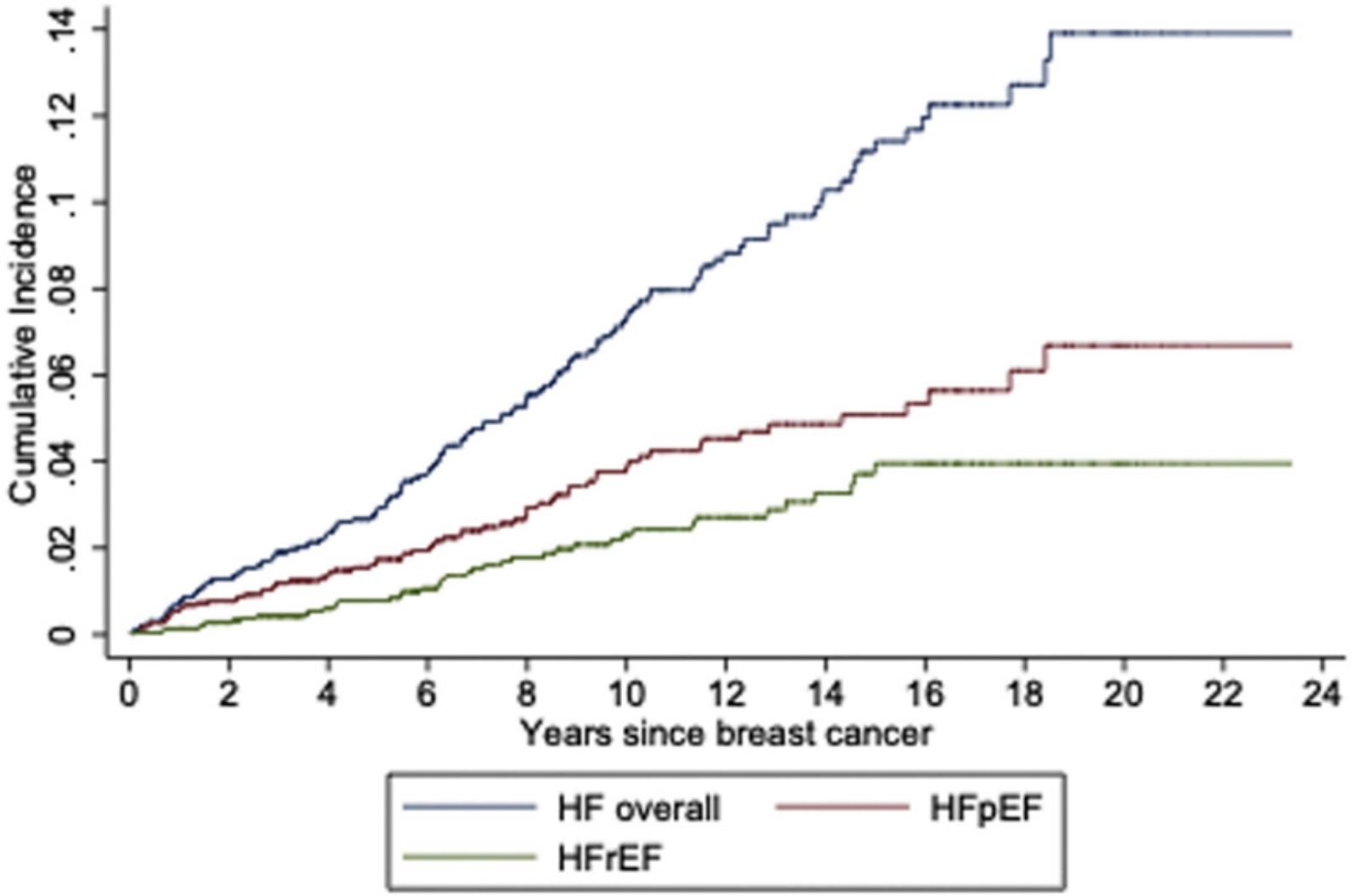
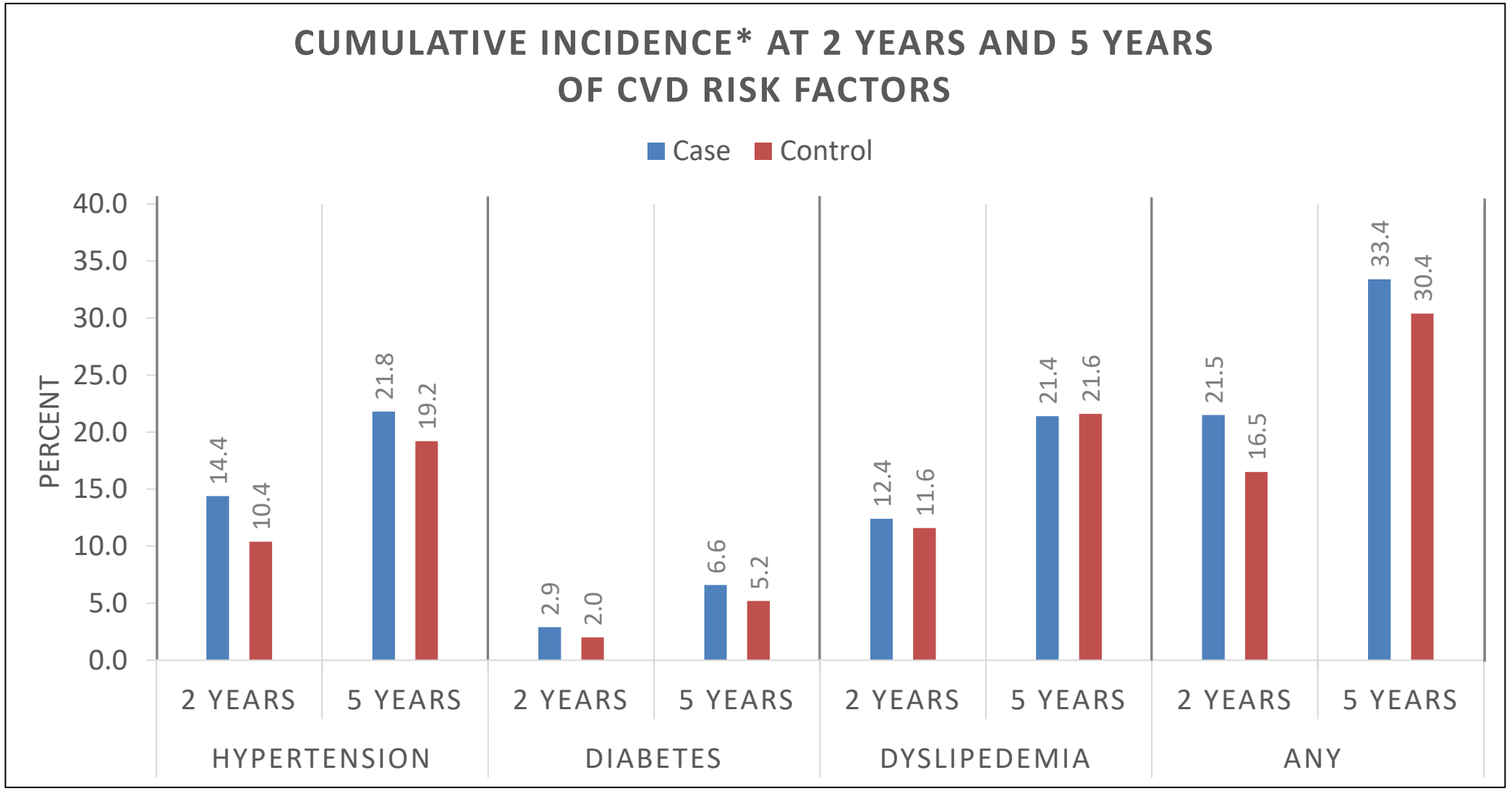
What about long term risk?

FIGURE 2 HF Hospitalizations After Breast Cancer



Reding KW, Cheng RK, et al. JACC: Cardio-oncology 2022 Mar. 4(1)

Kaiser Pathways – Incident CVRF



Kwan ML, Cheng RK… Greenlee H. J Clin Oncol 2022 May 20; 40(15)

Summary: anthracyclines +/- HER2

- **Anthracycline cardiotoxicity**
  - -Dose dependent (risk at 200 mg/m2; stop at 550 mg/m2)
  - -Occurs mostly within 1 year, partially reversible
- **HER2 targeted therapy cardiotoxicity**
  - -Not dose related
  - -Always reversible; Rechallenge is well-tolerated
- **Beta blockers and ACEi may be cardioprotective for primary prevention – but unclear <u>which</u> patients**
- **Think about long-term risk and surveillance for CV disease but also cardiometabolic disease (HTN, T2DM)**

Post-test Question #1

Which of the following is true about HER2 targeted therapy and LV dysfunction?

A. Once LVEF <50%, need to permanently discontinue treatment
B. LVEF recovers in about 60% of cases
C. It is safe to continue treatment despite drop in LVEF to 40% range if there is no clinical heart failure
D. HER2 treatment associated cardiotoxicity can present decades after exposure

Case 2: CML and BCR-ABL TKI

- **Diagnosed at age 71 with CML without significant PMH**

  -Treated w/ imatinib → stopped due to ocular symptoms

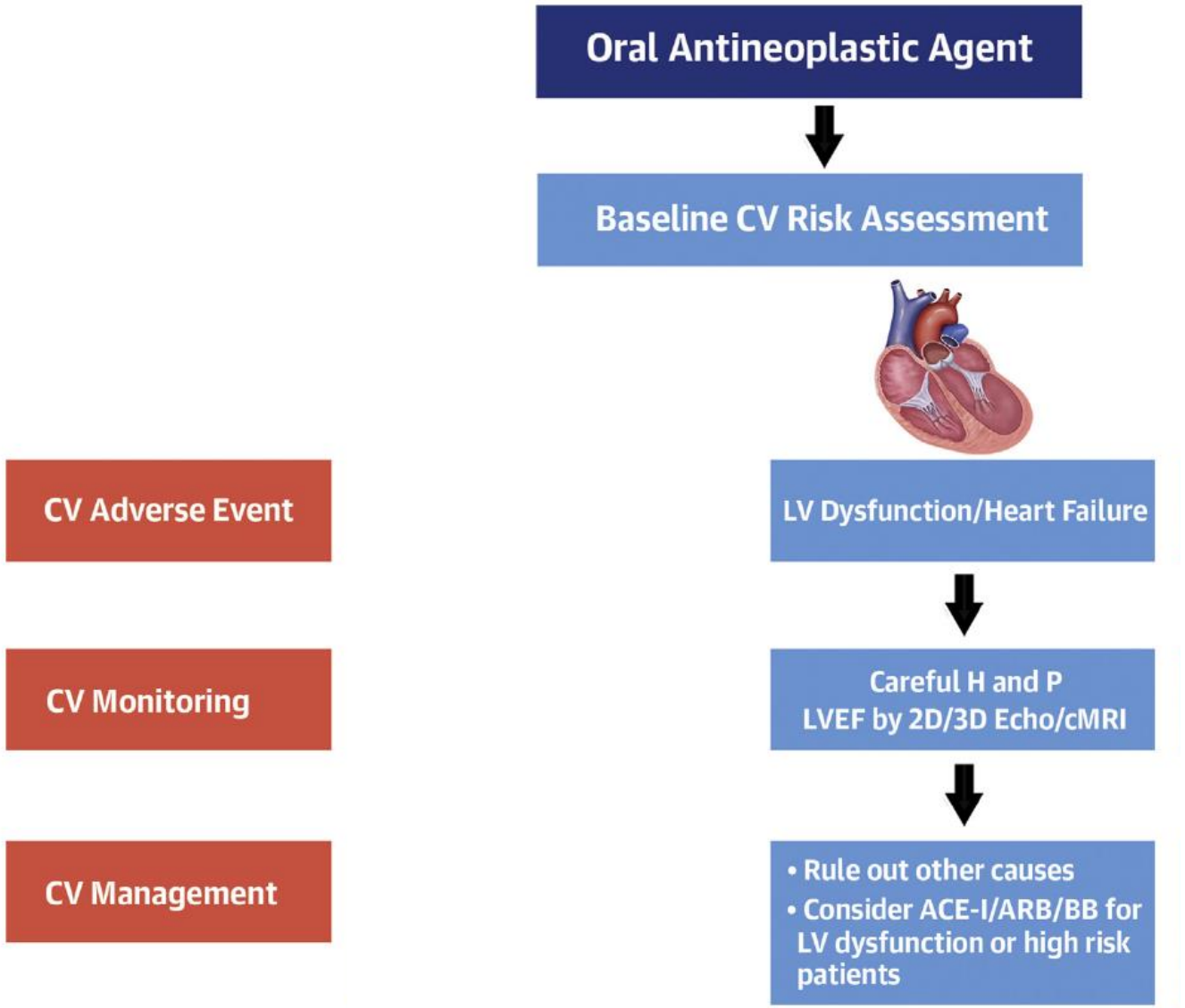
  -Treated w/ dasatinib → pleural effusions

  -Switched to nilotinib → good response but LE claudication with stenosis of bilateral SFA and L PTA

  - Switched to bosutinib

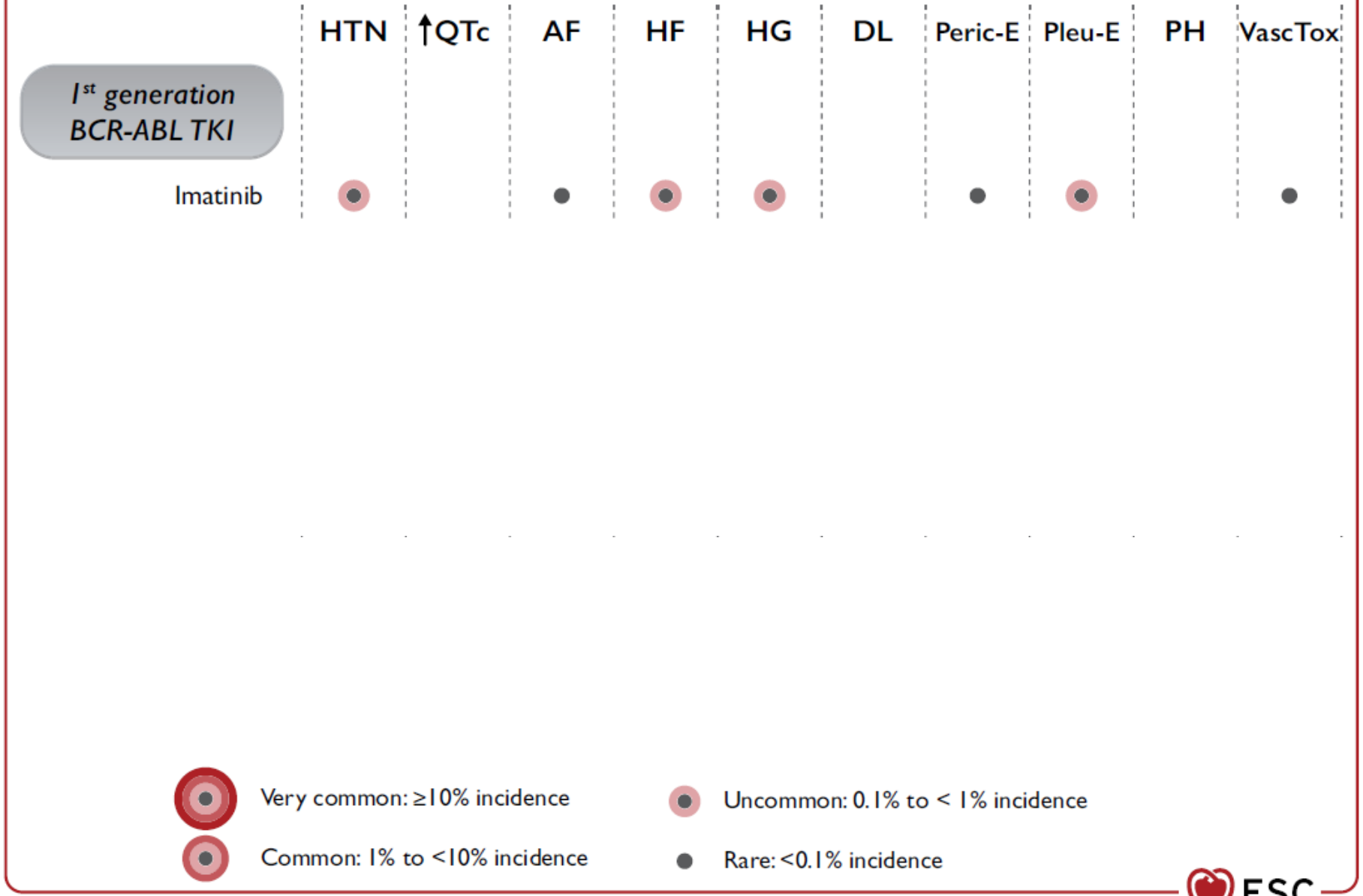
  - Ongoing hypertension, progressive aortic stenosis

Considerations of oral targeted therapies

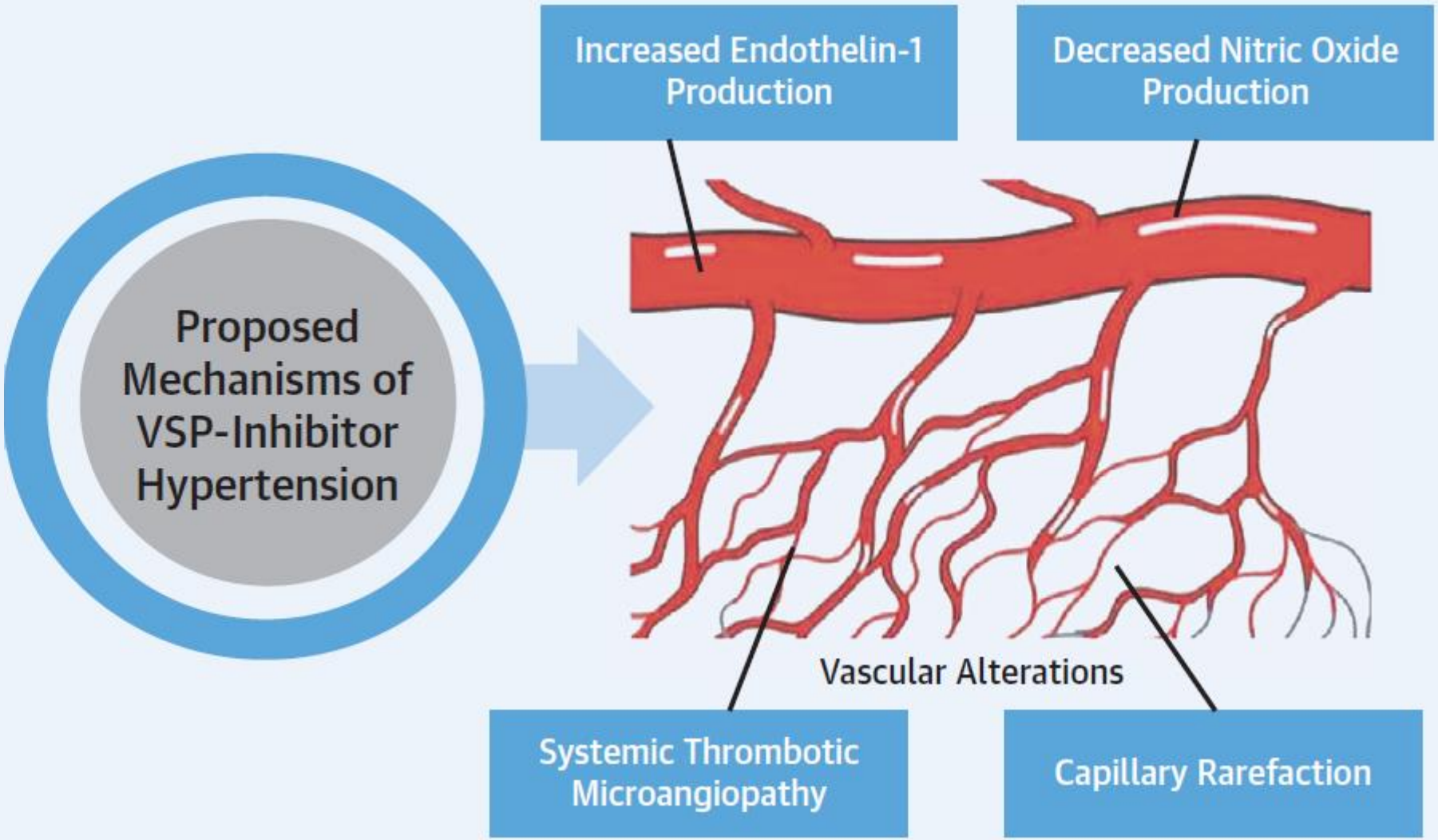


Rao, V.U. et al. J Am Coll Cardiol. 2021;77(21):2693-716.

BCR-ABL TKI-related cardiovascular toxicities

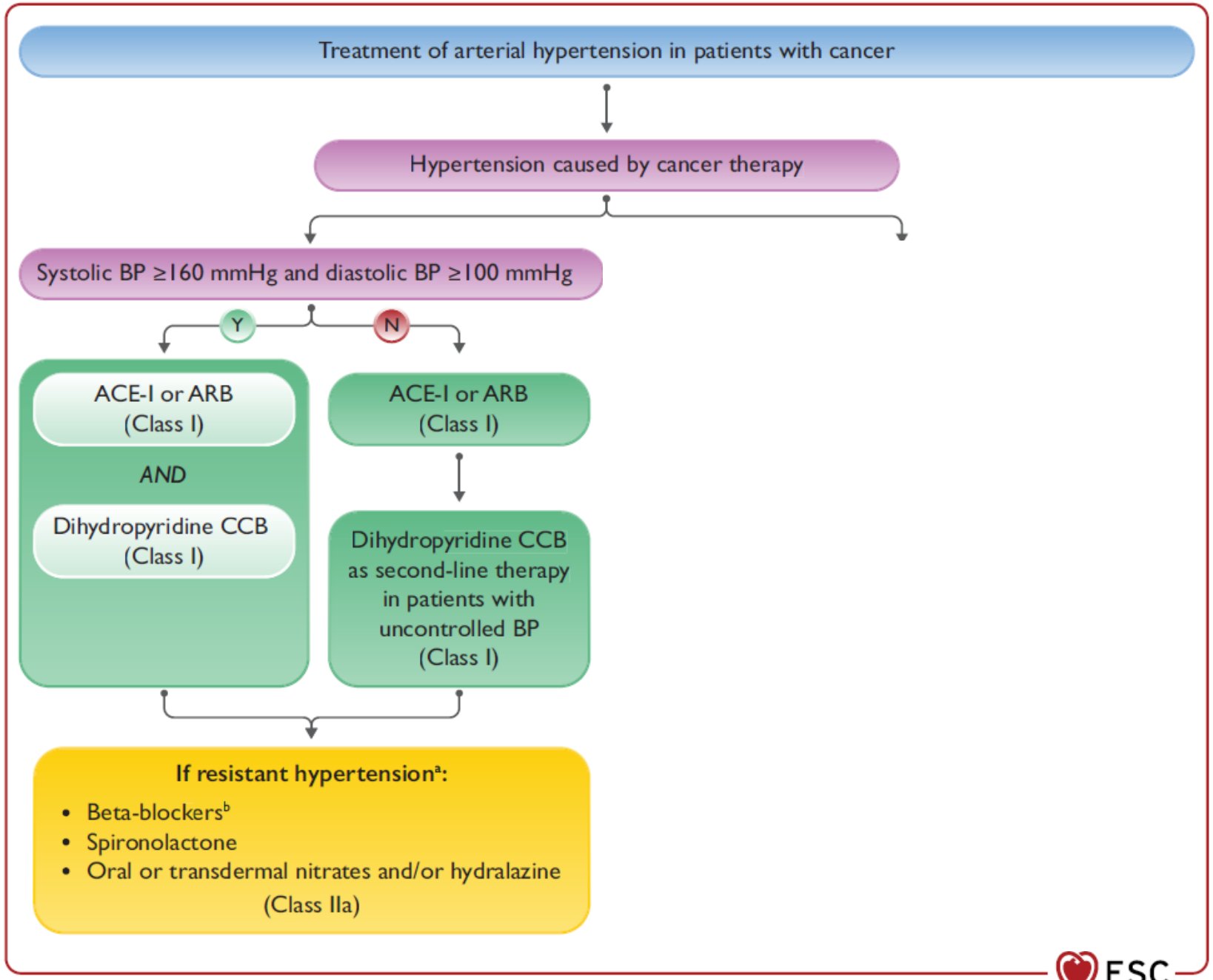


Hypertension from VSP inhibitors



Rao VU et al. JACC 2021; 77(21)

*Consider β-blockers
if indication
e.g. HF or CAD



Recommended threshold for asymptomatic hypertension treatment in different clinical scenarios

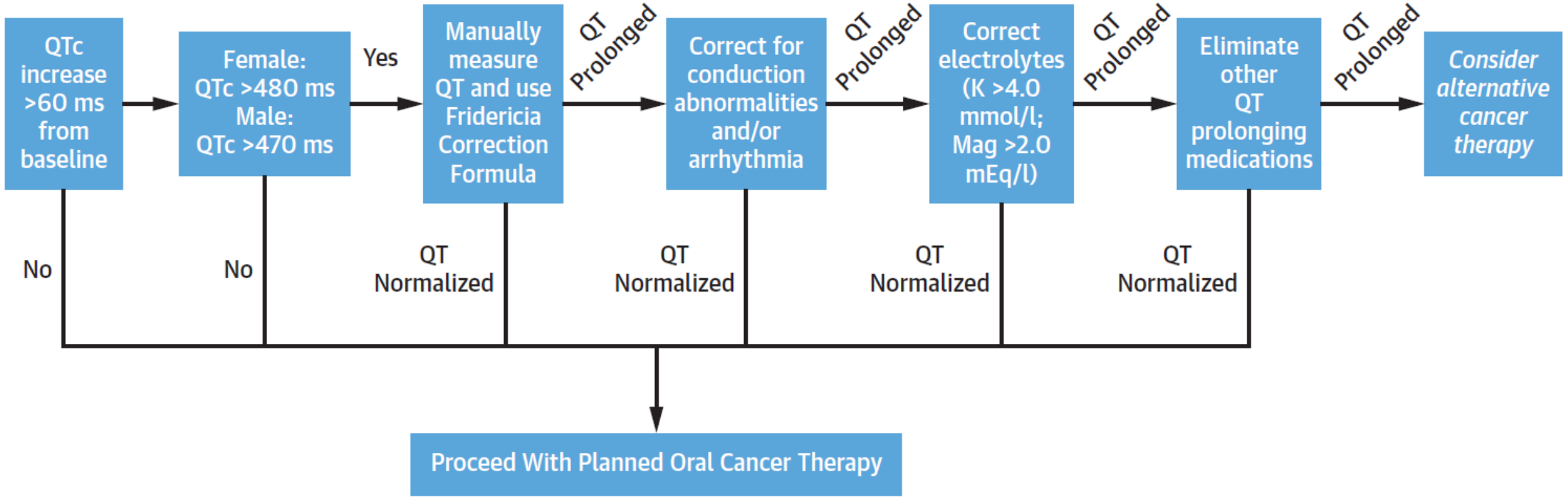
Class I
Class IIa
Class IIb

Home BP mmHg	CS	Curable cancer during treatment	Metastatic cancer Prognosis >3 years	Metastatic cancer Prognosis 1–3 years	Metastatic cancer Prognosis <1 year
160+	Treat	Treat	Treat	Treat	Treat
140–159	Treat	Treat	Treat	Consider treatment	May treat
135–139	Treat	May treat	Consider treatment	May treat	None
130–134	May treat	None	None	None	None
<130	None	None	None	None	None

2022 ESC Guidelines on cardio-oncology

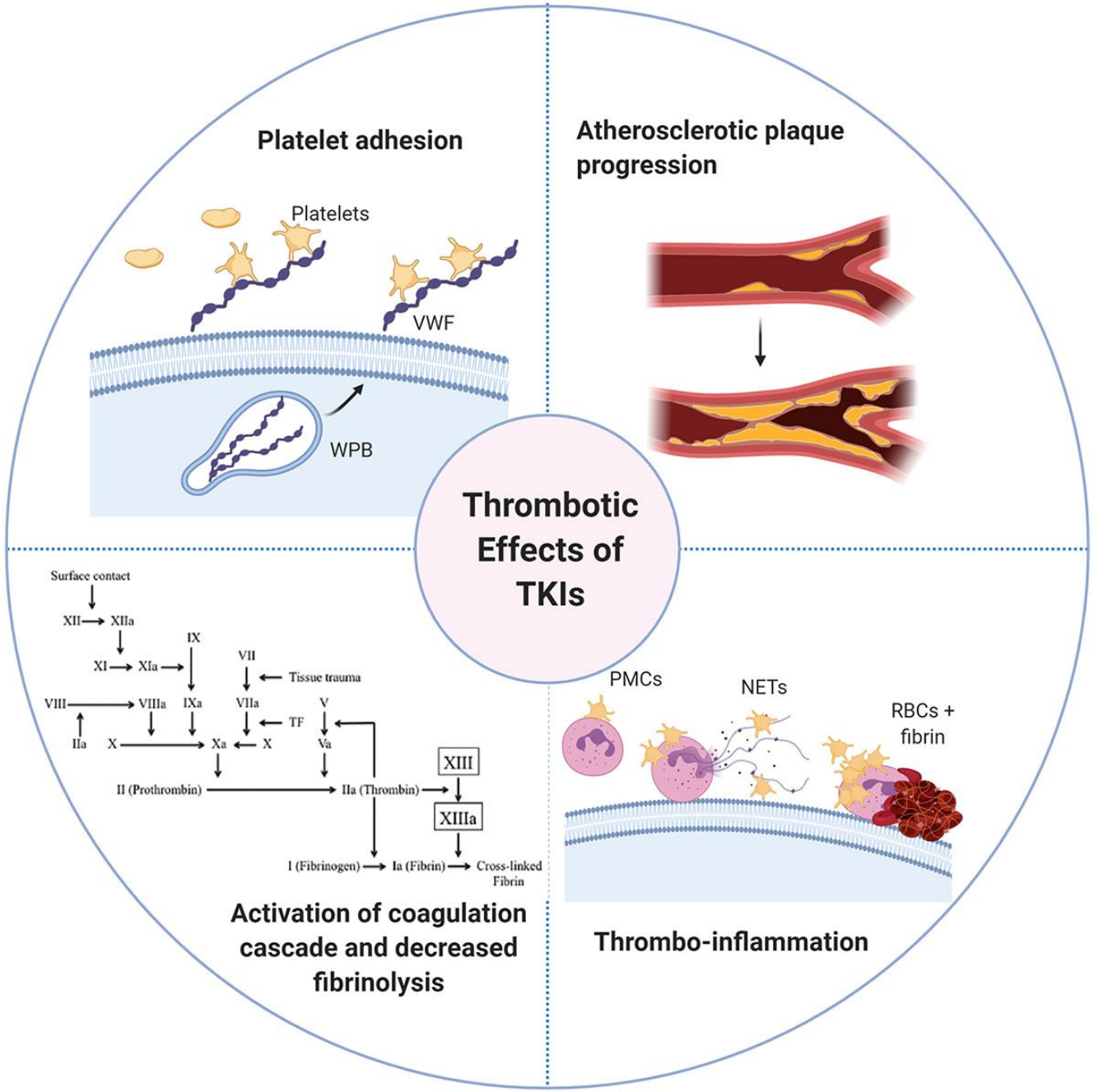
QTc prolongation on TKI therapy

FIGURE 2 Algorithm for QT-Interval Monitoring in Patients Receiving Oral Antineoplastic Agents



If baseline QT interval is prolonged, manual measurement and Fridericia correction should be completed. If QT increases by more than 60 ms from baseline to a level beyond 480 ms for females and 470 ms for males, QT should be corrected for conduction abnormalities/arrhythmias, electrolytes addressed, and concomitant QT-prolonging medications changed before proceeding with oral chemotherapy.

Rao VU et al. JACC 2021; 77(21)

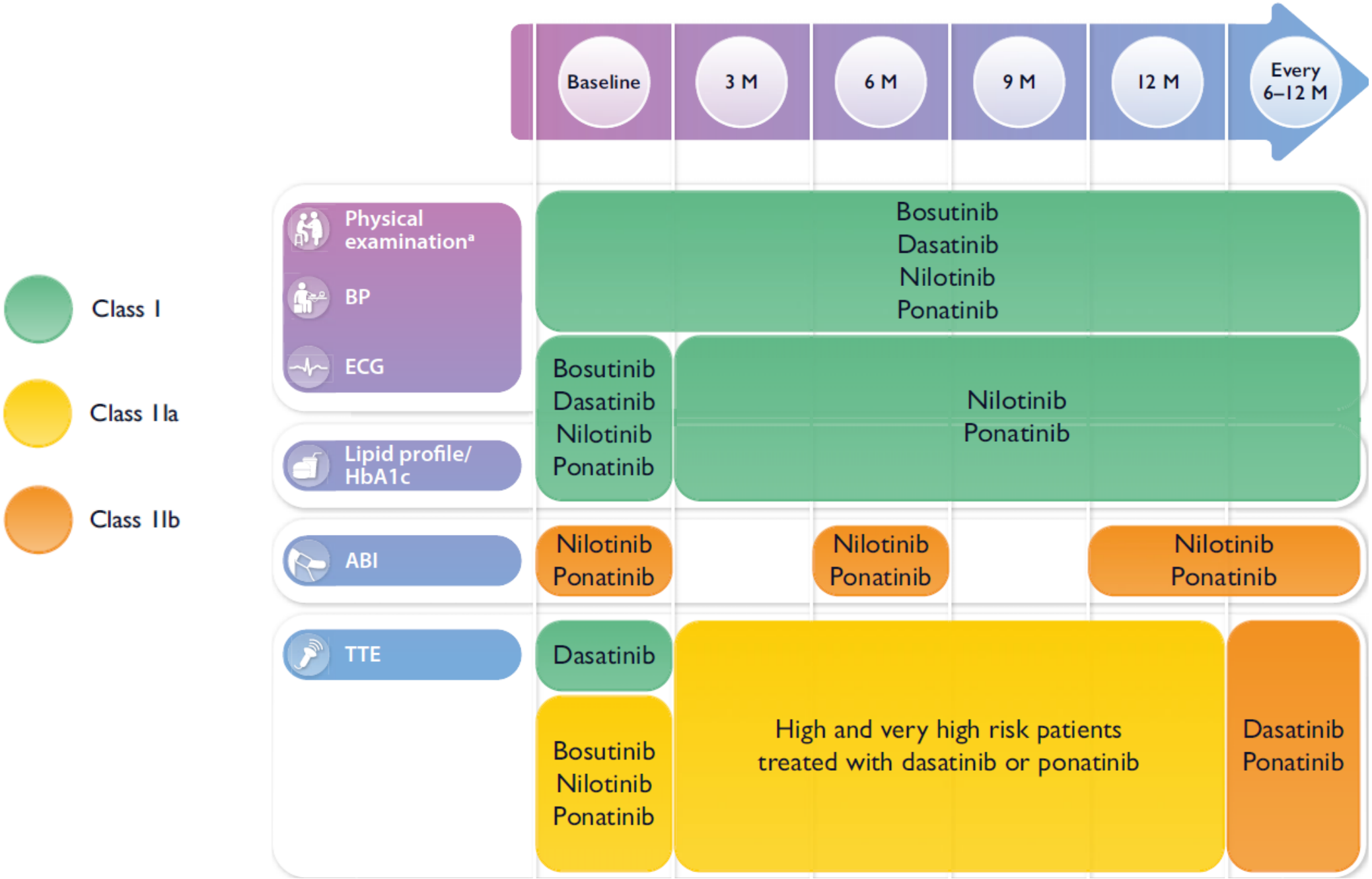


Nilotinib has been associated with AS

Wu MD et al. ATVB 2021; 41

Case 2: CML follow-up

- Peripheral arterial disease → angioplasty and stent, statin
- Progressive AS → TAVR
- HFpEF → diuretics
- Hypertension → ACEi, beta blocker
- Continue bosutinib, avoid nilotinib and ponatinib



2022 ESC Guidelines on cardio-oncology

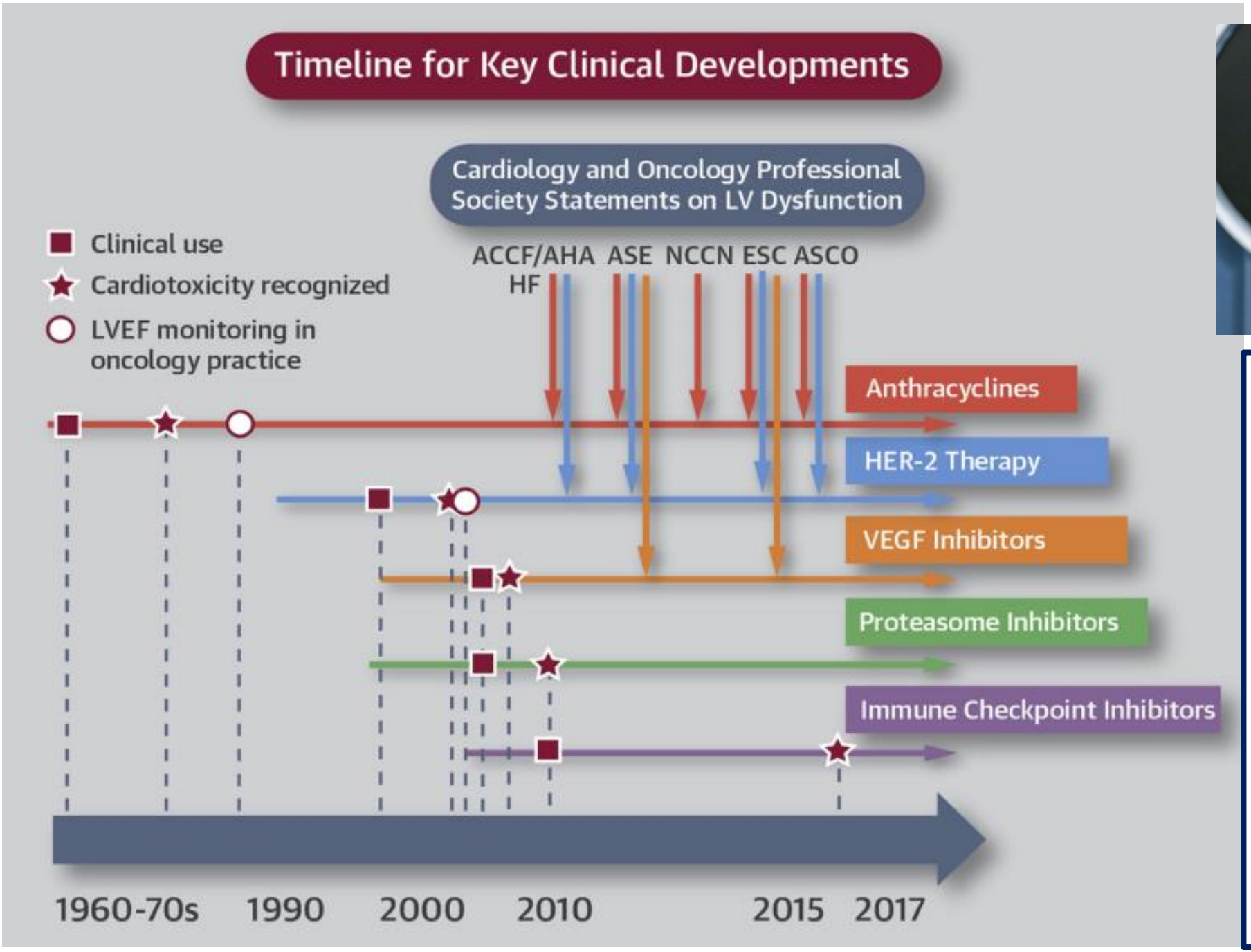
Summary: CV concerns with TKI for CML

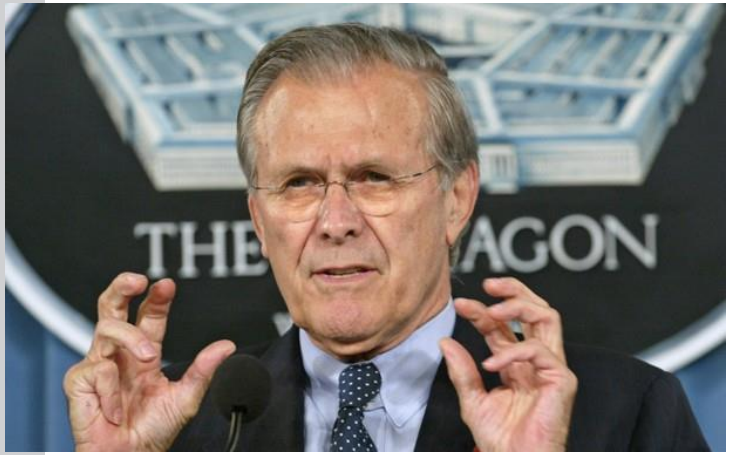
- Many TKI are multitargeted with on- and off-target risk for cardiotoxicity
- Wide spectrum of CV risk that varies by TKI; Even within a class, differences by specific drug
- Treat HTN with ACEi and CCB
- Be vigilant of other cardiovascular effects such as QT prolongation, HF, AF, vascular effects

Post-test Question #2

Which of the following is true about ponatinib?

A. Significant hypertension is uncommon
B. Ponatinib has a safer CV side effect profile compared to imatinib
C. Arterial vascular disease is a potential side effect
D. Ponatinib increases QTc significantly



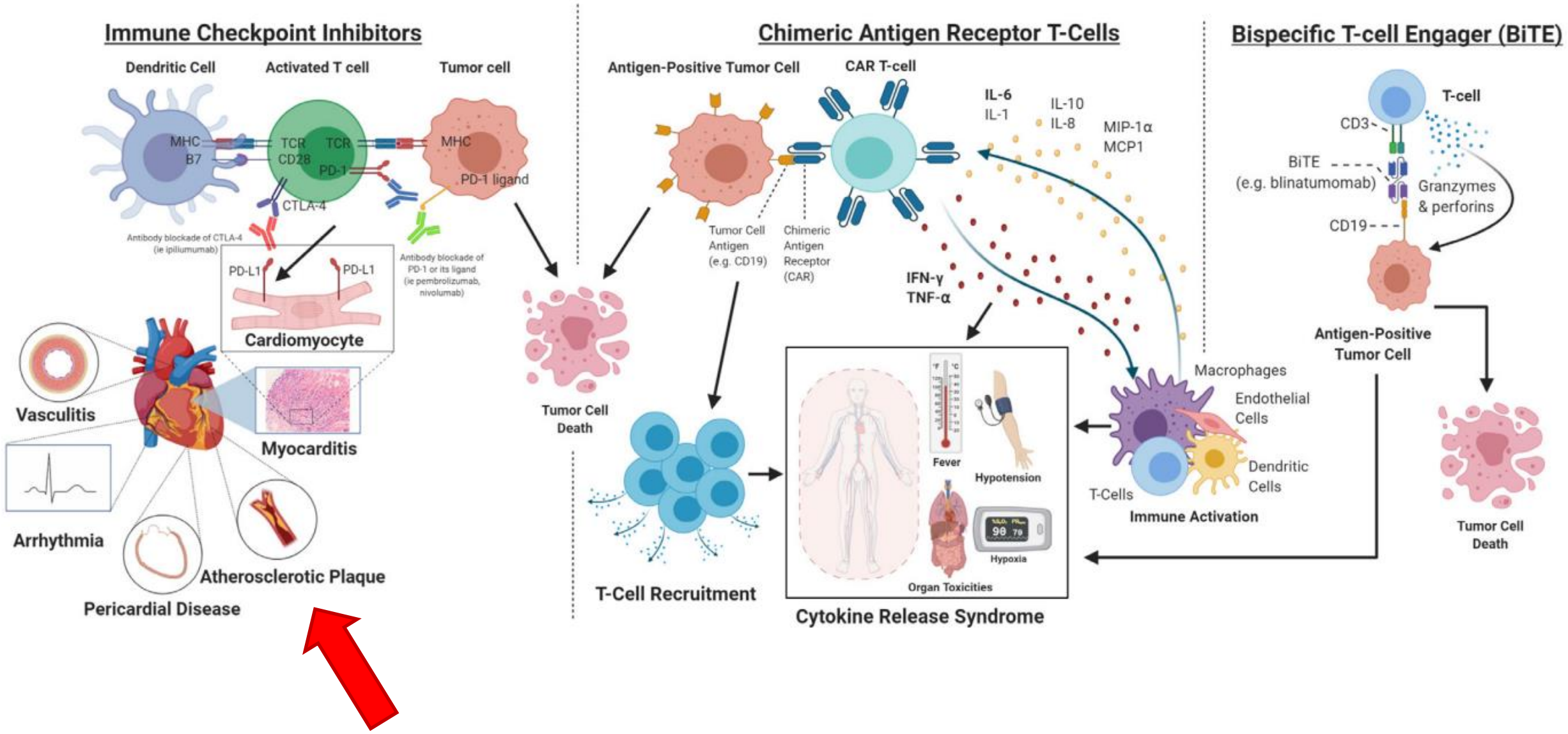


“There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don’t know.”

- Donald Rumsfeld

Kenigsberg B et al. JACC HF 2018; 6:87-95

Immunotherapy and cardiovascular risk



Stein-Merlob et al. Heart 2020. 107(21)

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2022) **00**, 1–133
https://doi.org/10.1093/ehjci/jeac106

ESC GUIDELINES

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS)

Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC)

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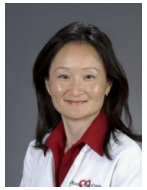

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Opportunities to learn more cardio-oncology

- **UW/SCCA/Fred Hutch/Seattle Children's Cardio-oncology Symposium, led by Dr. Eric Chow – Seattle, May 2023**

- **American College of Cardiology Cardio-oncology Meeting – Washington D.C. + virtual option, April 2023**

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