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# **MD Anderson Practices In Onco-Cardiology**



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**Edward T. H. Yeh, M.D., F.A.C.C.**

Editor

# MD Anderson Practices In Onco-Cardiology

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ISBN: 978-1-944785-94-9

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The authors and publisher have made every effort to ensure that the patient care recommended herein, including choice of drugs and drug dosages, is in accord with the accepted standard and practice at the time of publication. However, since research and regulation constantly change clinical standards, the reader is urged to check the product information sheet included in the package of each drug, which includes recommended doses, warnings, and contraindications. This is particularly important with new or infrequently used drugs. Any treatment regime, particularly one involving medication, involves inherent risk that must be weighed on a case-by-case basis against the benefits anticipated. The reader is cautioned that the purpose of this book is to inform and enlighten; the information contained herein is not intended as, and should not be employed as, a substitute for individual diagnosis and treatment.

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## MAP Contents

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MAP 2	Monitoring and Management of Trastuzumab-Induced Cardiotoxicity with Echocardiography
MAP 3	Differential Diagnosis of Left Ventricular Dysfunction
MAP 4	Heart Success Program
MAP 5	Radiation Follow-Up
MAP 6	Monitoring Cardiac Devices During Radiation Therapy
MAP 7	High-Risk Chemotherapy
MAP 8	Vandetanib
MAP 9	Nilotinib
MAP 10	Vemurafenib
MAP 11	Arsenic Trioxide
MAP 12	Managing Pericardial Effusion
MAP 13	Acute Coronary Syndrome with Thrombocytopenia
MAP 14	Diagnosing a Cardiac Mass
MAP 15	Managing Benign Cardiac Tumors
MAP 16	Managing Malignant Cardiac Tumors

## Videos can be viewed at [www.cancerandtheheart.org](http://www.cancerandtheheart.org)

1	LV Function Assessment: Part 1
2	LV Function Assessment: Part 2
3	Monitoring and Management for Chemotherapy-Induced Cardiotoxicity with Echocardiography
4	New Onset Acute Left Ventricular Systolic Dysfunction (Sinus Rhythm)
5	Heart Success Program: A Patient-Centered Approach to Improve Outcomes
6	Radiation and Cardiovascular Disease
7	Management of Cardiac Devices During Radiation Therapy
8	QT Monitoring in Chemotherapy
9	Management of Pericardial Diseases in Cancer Patients
10	Cardiovascular Procedures in Patients with Cancer and Thrombocytopenia
11	Cardiac Mass Evaluation
12	Management of Cardiac Tumors

## MD Anderson Practices In Onco-Cardiology

### Introduction

The Department of Cardiology at The University of Texas MD Anderson Cancer Center was established on September, 1, 2000. In the past 15 years, we have evaluated and treated more than 20,000 cancer patients with cancer therapy-related cardiovascular complications. Three years ago, we initiated the MD Anderson Practice (MAP) project to distillate our practice patterns into algorithms to be shared with the onco-cardiology community. Because cancer is often an exclusion criterion for cardiology studies, purely evidence-based management of cancer therapy-related cardiovascular complications is not possible. With this vacuum of knowledge, various “guidelines” have proliferated that are either misleading or difficult to practice. In this manual, we present 16 MAPs that have been extensively reviewed by the cardiologists at MD Anderson. These MAPs should be considered our best practices rather than “guidelines.” These MAPs will be updated frequently to reflect advances in the field. This manual consists of MAPs, figures, and tables. We hope you will find these materials useful to your practice and provide us with feedback to improve these MAPs.

Edward T.H. Yeh, M.D., F.A.C.C.

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## Chapter 1

### Monitoring Cardiotoxicity with Left Ventricular Ejection Fraction

Saamir Hassan, Jose Banchs

Monitoring cancer therapy-related cardiotoxicity at MD Anderson Cancer Center (MDACC) is done by assessment of left ventricular ejection fraction (LVEF) by echocardiography. Our patients are also routinely assessed for global longitudinal strain (GLS) during cancer therapy. However, the procedure used to identify GLS is not practiced routinely in many laboratories. Thus, we do not recommend the routine use of GLS assessment unless the cardiologist is confident that his or her laboratory can generate accurate results. We also do not routinely use biomarkers, such as troponin or B-type natriuretic peptide, to follow patients undergoing cancer therapy.

Routine MD Anderson practice for LVEF assessment starts with a baseline echocardiogram to calculate two-dimensional (2D) LVEF. At MD Anderson, we perform 2D left ventricular assessment using a biplane method of discs, as per guidelines. If needed, 2D LVEF assessment is done with the aid of ultrasonic contrast which aids in endocardial border definition and subsequent volume calculations. 3D chamber quantification in patients receiving chemotherapy is also employed at

MD Anderson. 3D echocardiography has been shown to be the most reproducible technique for LVEF and LV volume measurements in patients undergoing cancer chemotherapy.

As noted in the algorithms for trastuzumab and anthracycline-based chemotherapy, if the baseline LVEF is greater than or equal to 50%, patients can proceed to chemotherapy. If the LVEF is reduced on subsequent echocardiograms, patients are started on cardioprotection with angiotensin converting enzyme inhibitors (ACEi) and/or beta blockers (BB). Typical starting dose for carvedilol is 3.125 mg twice daily with slow up-titration as tolerated to a maximum of 25 mg twice daily. The typical starting dose for lisinopril is 2.5 mg daily with slow up-titration as tolerated to a maximum dose of 20 mg daily.

The decision to continue with chemotherapy or stop depends on the absolute LVEF and the drop in LVEF associated with the patient’s chemotherapy regimen. After the initiation of cardioprotective therapy, we recommend an echocardiogram prior to the next scheduled chemotherapy dose to re-evaluate LVEF.

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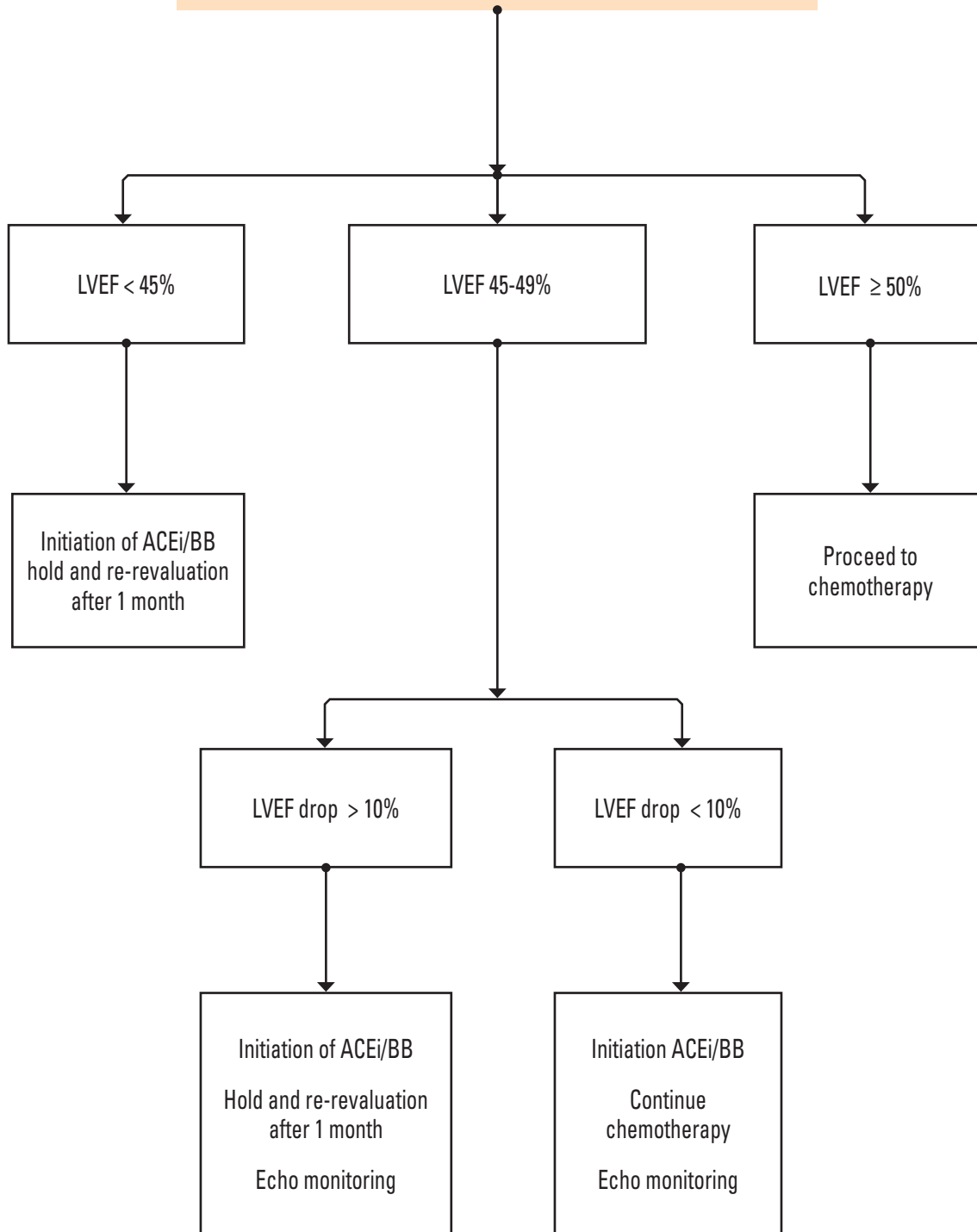
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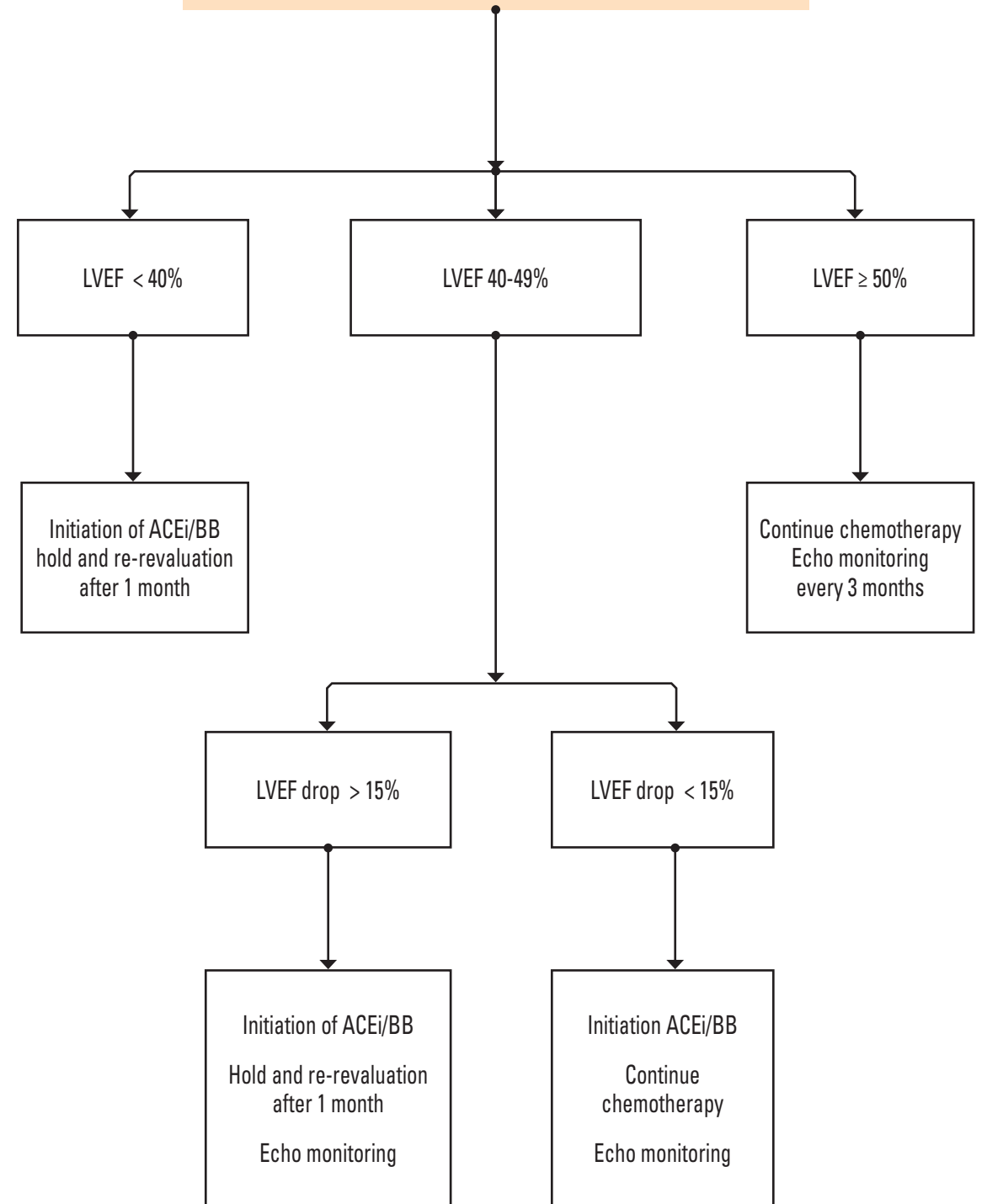
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**ANTHRACYCLINE**



**TRASTUZUMAB**



## Chapter 2

# Differential Diagnosis of Left Ventricular Dysfunction during Chemotherapy

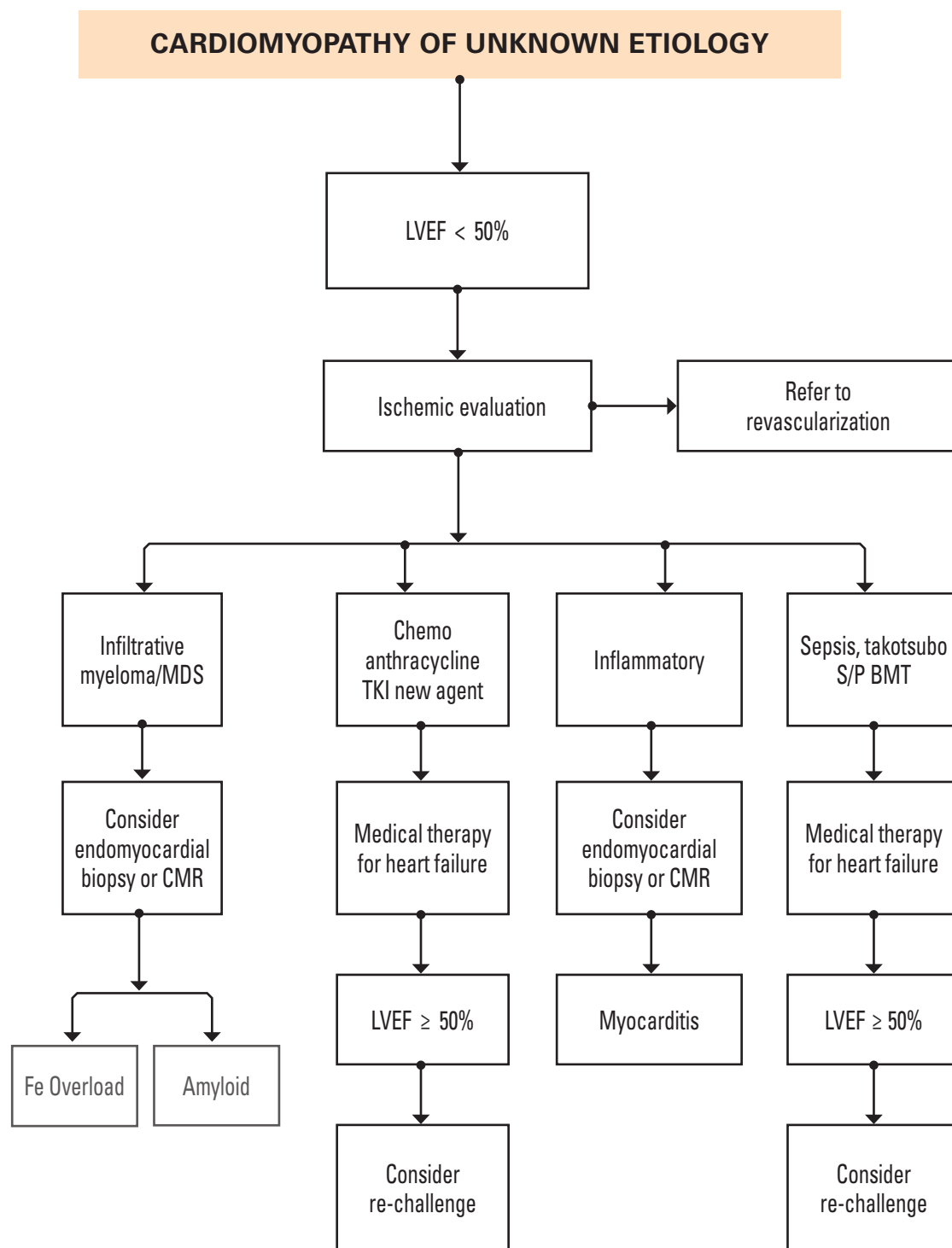
Jean-Bernard Durand

When a patient experiences a drop in LVEF during chemotherapy, we do not automatically assume it is due to chemotherapy-induced cardiotoxicity. Careful evaluation of the patient's risk factors and comorbid conditions is required. The differential diagnosis includes ischemia, sepsis, stress cardiomyopathy, acute myocarditis, cardiac amyloidosis, and transfusion-related cardiomyopathy. Useful blood tests include B-type natriuretic peptide, troponin, viral titers, thyroid-stimulating hormone,

and ferritin. Ischemic evaluation is considered in the initial work-up. Cardiac biopsy can be useful in selected patients when myocarditis, amyloidosis, or iron-overload cardiomyopathy are suspected. Cardiac magnetic resonance imaging (MRI) is also useful in diagnosing myocarditis, amyloidosis, and iron-overload cardiomyopathy. It should be emphasized that chemotherapy-induced left ventricular dysfunction is a diagnosis of exclusion.

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### Chapter 3

## Heart Success Program

Anecita Fadol

### General Principles

Chemotherapy-induced Cardiomyopathy/Heart Failure

- A decline of >10% in absolute LVEF from a normal baseline or an LVEF < 50%
- Exclude patients with ischemic heart disease or takotsubo cardiomyopathy

### Heart Success Program

A collaborative, interdisciplinary program for the management of patients with cancer and heart failure across the continuum of care

### Patient and Family Education Materials

View the 15 minute DVD - Heart Success for Cancer Patients

Patient education booklet - Heart Success: A Resource Guide for Individuals Living with Cancer and Heart Failure

Discharge instruction – SMART health

- **S**ymptoms
- **M**edications
- **A**ctivity
- **R**egular weight monitoring
- **T**oss the salt shaker

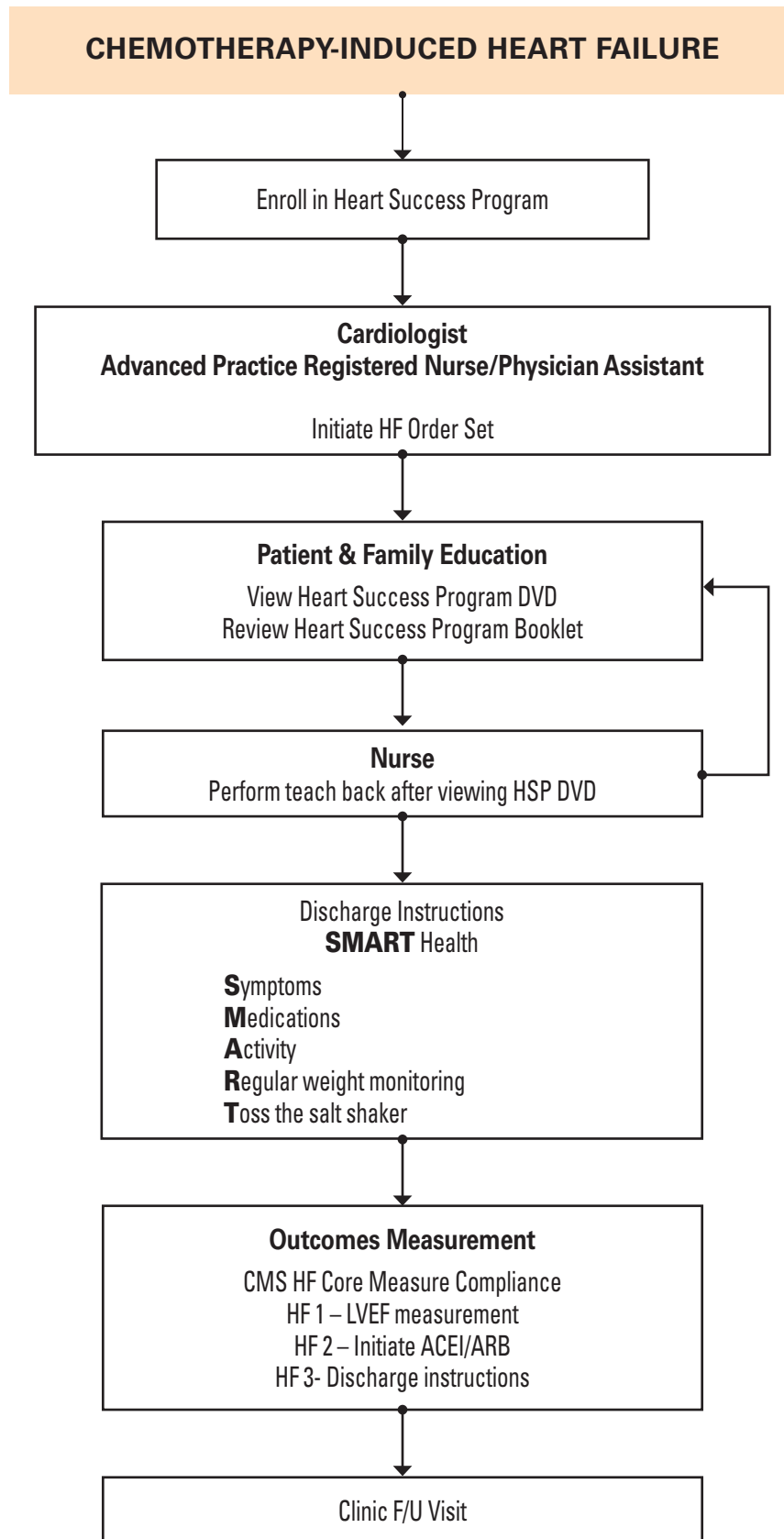
### Teach-Back

a method of communication used to confirm that healthcare information have been explained clearly in a manner understood by patients. This is done by asking a patient (or family member) to explain in their own words what they need to know or do, in a caring way.

### Outcomes Measurement

CMS HF core measures

- LV function measurement
- ACE I/ARB at discharge
- Discharge instructions



## Symptoms

Call your doctor if you have any of the following symptoms:

- Trouble breathing or shortness of breath
- Swelling in your abdomen, legs, or feet
- Racing heartbeat
- Increased weakness or tiredness
- Dizziness, lightheadedness, or restlessness
- Chest pain

## Medicines

- Take your medicines at the same time every day as prescribed.
- Do not skip doses, even if you are not feeling well.
- Do not stop taking your medicines without talking to your doctor or nurse.
- Bring your medicines when you come for your clinic visits.

## Activity

- Follow your doctor’s instructions about physical activity.
- Set up an exercise plan that includes activities that you enjoy.
- Stop and rest if you feel tired or short of breath.
- Be active every day. Try taking the stairs or walking for short periods.

## Regular Weight Monitoring

- Weigh yourself every morning at the same time, on the same scale, and with the same amount of clothing.
- Call your doctor or nurse if you gain more than two pounds in one day for two consecutive days or more than five pounds in one week.

## Toss the Salt Shaker

- Use salt sparingly, no more than 2 grams per day.
- Read food labels so you will know how much salt is in the food you eat.
- Eat plenty of fresh fruits and vegetables (unless you have restrictions).

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## Chapter 4

# Radiation and Cardiovascular Complications

Syed Wamique Yusuf

Before administering radiation therapy, we assess each patient's clinical risk factors for atherosclerotic heart disease. A 12-lead electrocardiogram (ECG) and an echocardiogram are recommended. The risk factors (e.g., hypertension and hyperlipidemia) are treated as per American College of Cardiology/American Heart Association guidelines.

After radiation therapy is completed, a clinical follow-up is done only if the patient develops any symptoms. During this early phase, the most common complication is acute pericarditis, which is treated according to European Society of Cardiology guidelines. Patients who develop even minimal pericardial effusion after radiation therapy receive a periodic echocardiogram to monitor for progression to chronic large pericardial effusion.

At the patient's annual visit, an ECG and echocardiogram are obtained only if clinically indicated. However, at the 5-year follow-up visit, an ECG and echocardiogram are recommended. At the 10-year follow-up visit, in addition to the ECG and echocardiogram, a stress test or computed tomography (CT) scan of the coronary arteries are recommended to screen for accelerated coronary artery disease. At each visit, a comprehensive cardiovascular examination is carried out, with particular attention to heart murmurs and carotid bruits. A CT scan (usually obtained by the radiation oncologist) is reviewed for an enlarging cardiac silhouette, which may suggest a pericardial effusion. An increase in calcium in the coronary arteries or large blood vessels may suggest accelerated atherosclerosis.

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## Chapter 5 Device Check during Radiation Therapy

Kaveh Karimzad

All patients are required to visit the cardiac device clinic for a device check before radiation therapy. Along with the radiation oncology team, we first determine whether the device is directly in the radiation field. If the device is directly in the radiation field, we consider device relocation. Factors favoring relocation of the device are pacemaker dependency and the device interfering with an effective radiation dose reaching the tumor. If the device is not directly in the radiation field, we use the pulse check method to monitor the effects of the radiation on the device.

For the pulse check method, we program the pacing rate at 75 beats per minute, which is slightly faster than the reset mode for all

device manufacturers. The radiation therapy team checks the heart rate after each radiation fraction. If the heart rate is less than 75 beats per minute, the device is checked immediately for damage or reset. If heart rate is greater than 75 beats per minute after each radiation session, the device is presumed to be functioning normally. When the pulse check method is not possible, we have to do more frequent device checks: after each session for patients who are pacemaker-dependent or have an implantable cardioverter defibrillator and weekly for those who are not pacemaker-dependent.

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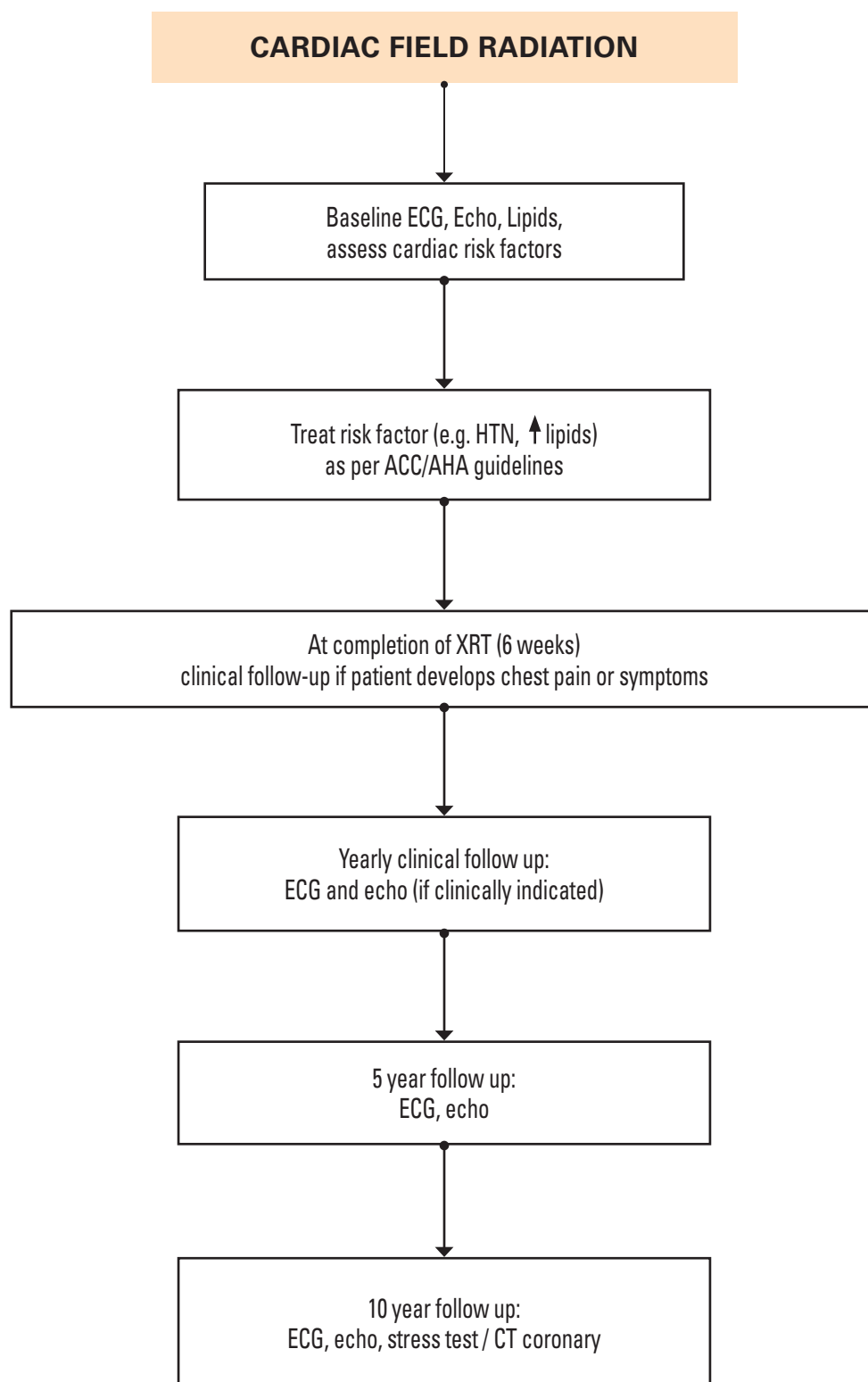
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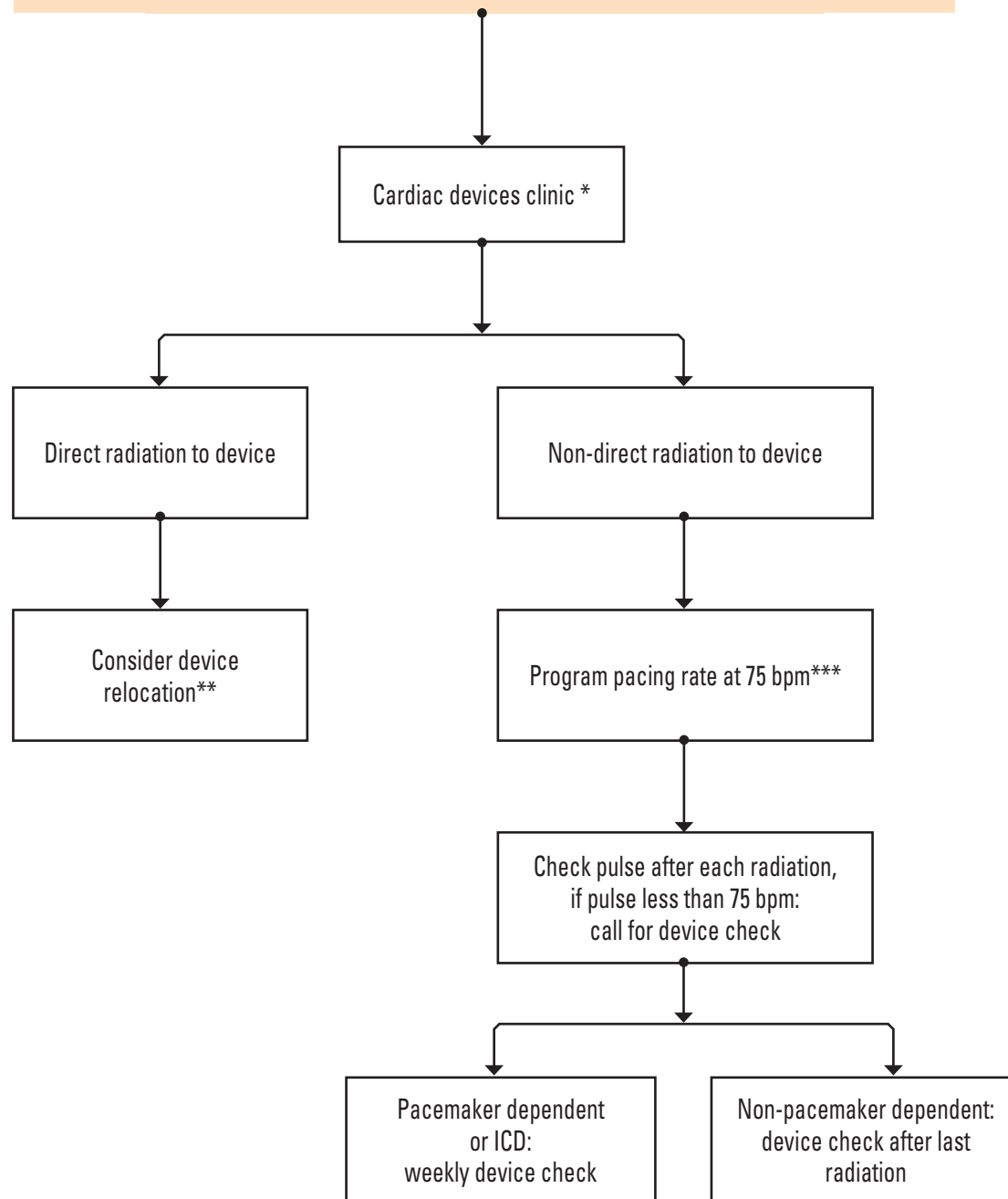
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## CARDIAC IMPLANTABLE ELECTRONIC DEVICE & RADIATION THERAPY



\* Enrollment in remote monitoring if available

\*\* Factors favoring relocation: pacemaker dependency and interference with effective radiation dose to tumor

\*\*\* If pacing at 75 bpm not possible:

Pacemaker dependent or ICD: device check after each radiation

Non-pacemaker dependent: weekly device check

## Chapter 6 QT Monitoring

Peter Kim

Prevention of QT interval prolongation requires at least three components in our practice. First, there should be a consistent methodology for QT interval measurement and heart rate correction. Second, risk factors leading to QT prolongation should be readily identified and eliminated. Third, when possible, a standardized practice for monitoring should be followed. At MD Anderson, QT monitoring can be done during chemotherapy in conjunction with practice guidelines published by the US Food and Drug Administration for selected high-risk chemotherapeutic agents. These five points are considered:

1. During chemotherapy, precautions must be met for safe administration and monitoring of patients to prevent QT prolongation and Torsade de Pointes.
2. Accurate and consistent QT measurement can be achieved through the use of the "tangent method" (see Figure 1).
3. Fridericia's formula is recommended for heart rate correction in QT measurement (Table 1).
4. Reversible risk factors should be identified and eliminated when possible (Table 2).
5. QT monitoring during chemotherapy should be encouraged for all high-risk chemotherapeutic agents, following US Food and Drug Administration guidelines for agents such as vandetanib, vemurafenib, nilotinib, and arsenic trioxide (MAP 8-11, Table 3).

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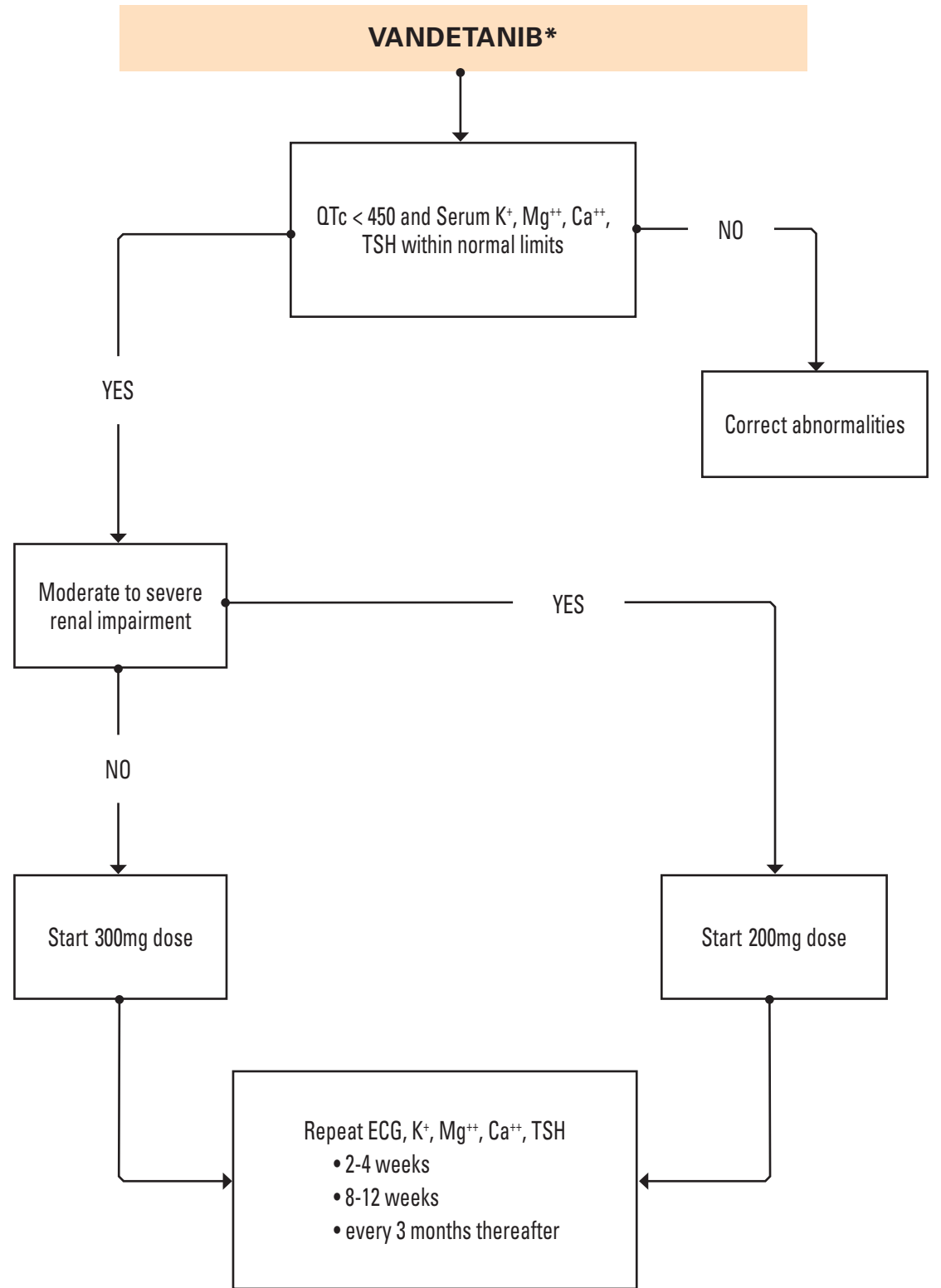
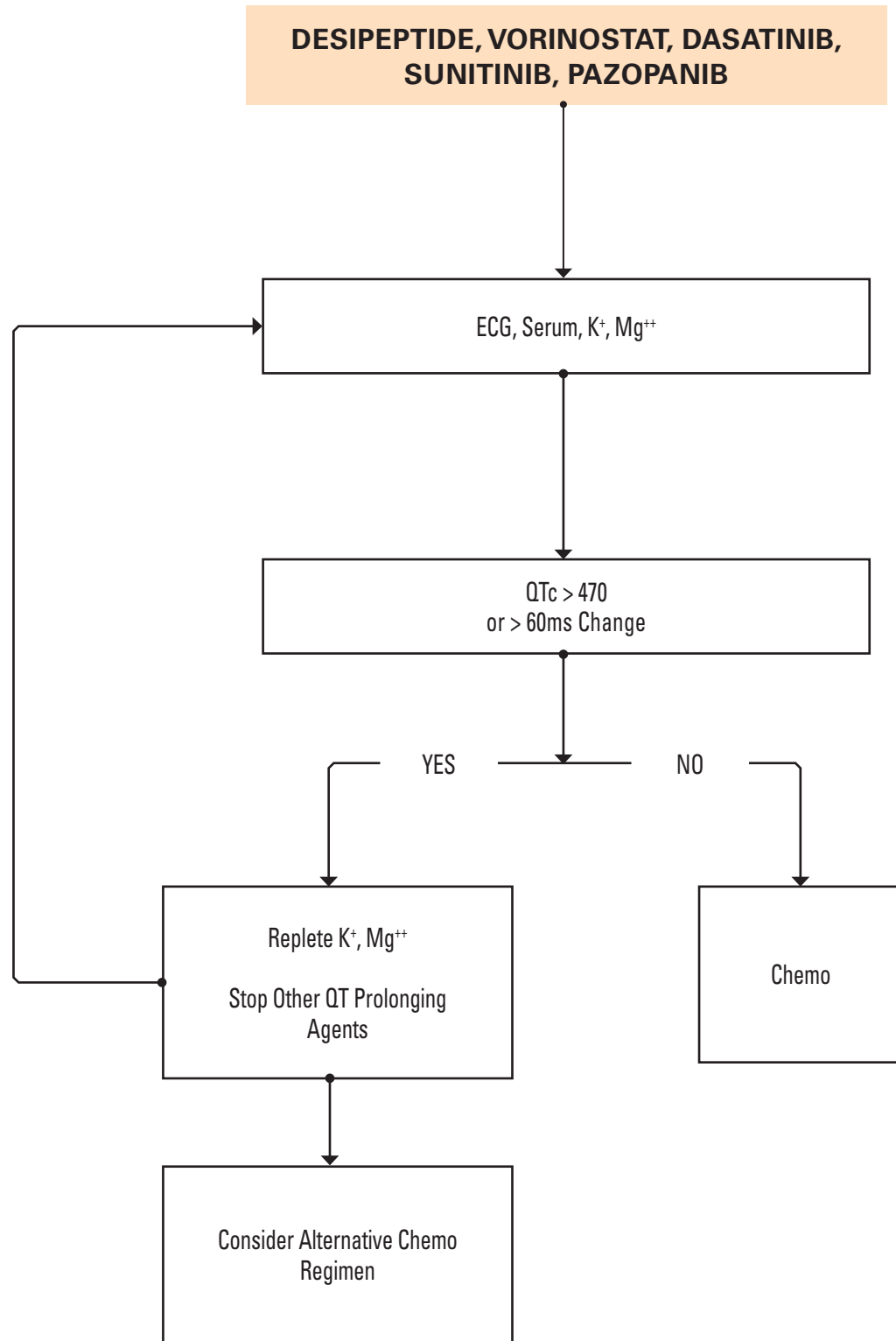
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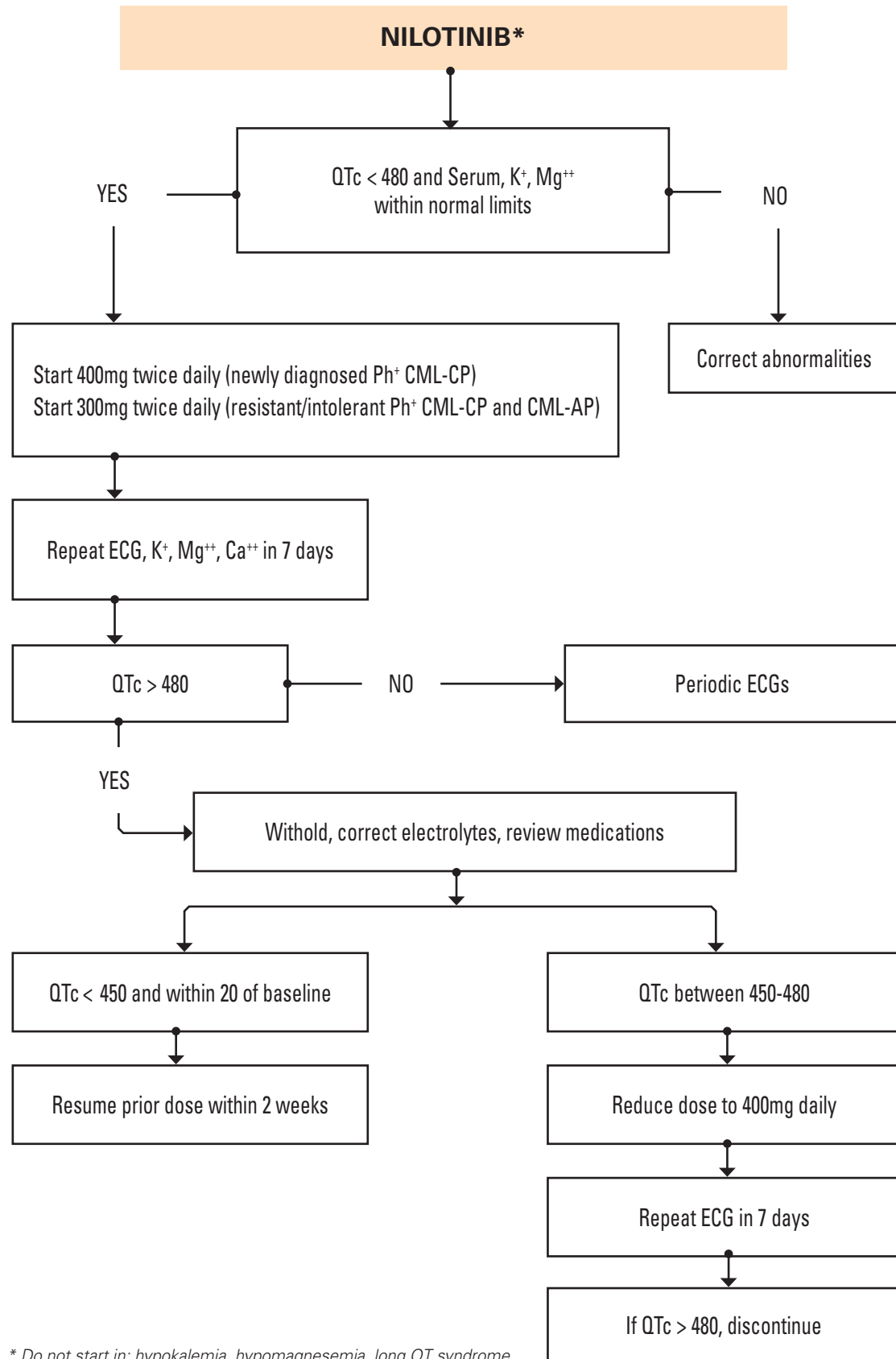
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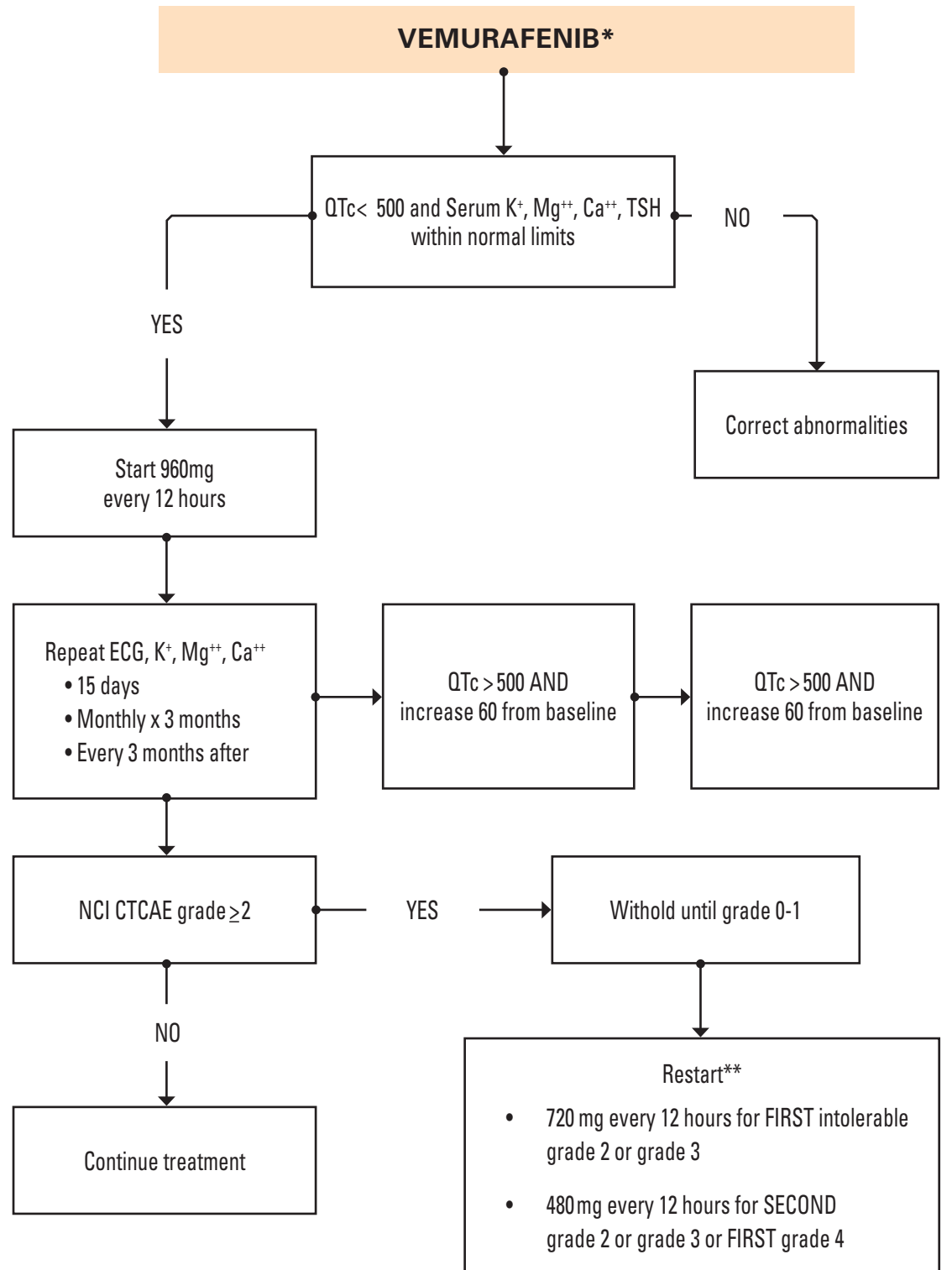
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\* Do not start in: congenital long QT syndrome, history of Torsades de pointes, bradyarrhythmias, uncompensated heart failure

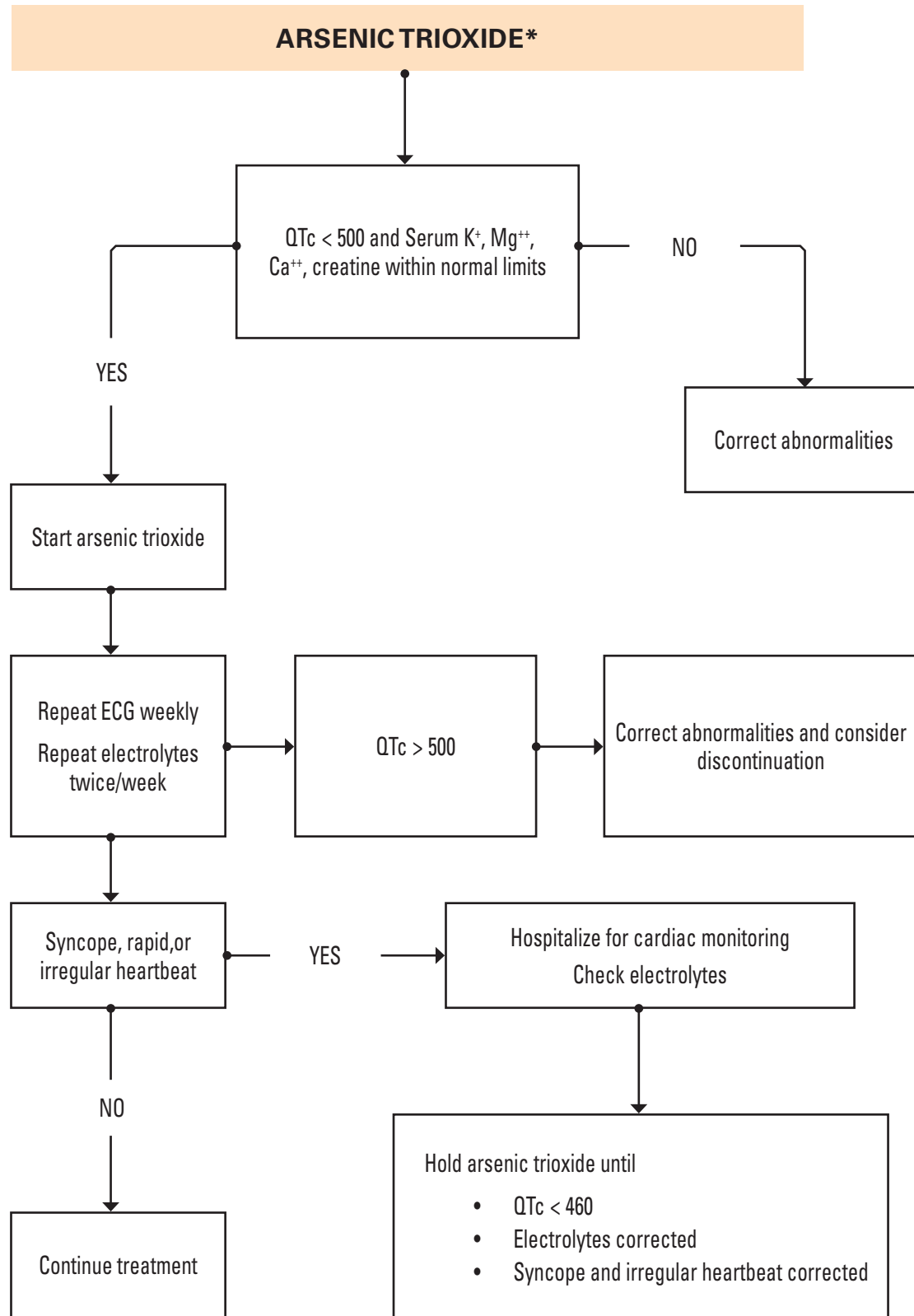


\* Do not start in: hypokalemia, hypomagnesemia, long QT syndrome



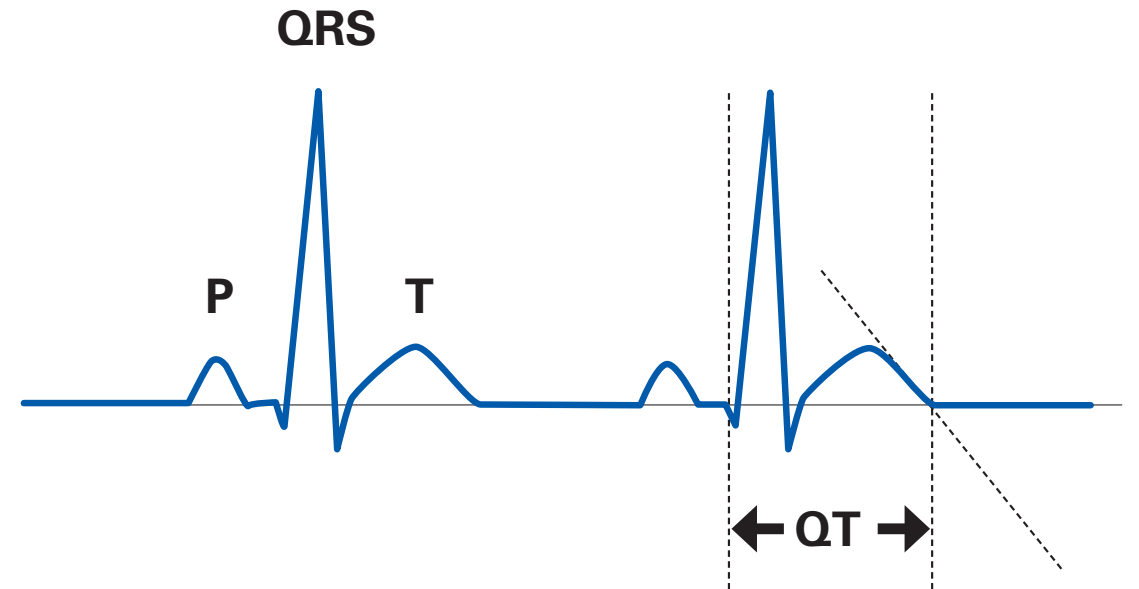
\*Do not start in: uncorrectable electrolyte abnormalities, QTc > 500, long QT syndrome, taking medications known to prolong QT

\*\*Do not restart below 480 mg every 12 hours



\* Use with caution in patients on medications that can cause QT prolongations or electrolyte abnormalities

**FIG 1. TANGENT METHOD OF QT MEASUREMENT**



**TABLE 1. HEART RATE CORRECTION FOR QT FORMULAS**

	Bazett	Fridericia	Framingham	Hodges
<b>Formula</b>	$QT_c = \frac{QT}{\sqrt[2]{RR}}$	$QT_c = \frac{QT}{\sqrt[3]{RR}}$	$QT_c = QT + 0.154(1000 - RR)$	$QT_c = QT + 105(1/RR - 1)$
<b>Type</b>	Nonlinear	Nonlinear	Linear	Linear
<b>Unique Limitation</b>	Overcorrects at high HR Undercorrects at low HR	Overcorrects at high HR	Overcorrects at high HR	Overcorrects at high HR

TABLE 2. MEDICATIONS KNOWN TO CAUSE QT PROLONGATION

Antiarrhythmic	Antibiotic	Antifungal	Antiviral
Amiodarone	Azithomycin	Fluconazole	Telaprevir
Disopyramide	Ciprofloxacin	Itraconazole	Atazanavir
Dofetilide	Clarithromycin	Ketoconazole	Foscarnet
Flecainide	Gemifloxacin	Voriconazole	Nelfinavir
Ibutilide	Levofloxacin		Rilpivirine
Quinidine	Moxifloxacin		Ritonavir
Sotalol	Norfloxacin		Saquinavir
Dronedarone	Ofloxacin		
	Trimethoprim-Sulfa		
	Erythromycin		
	Metronidazole		
Antiemetic	Antipsychotic	Immunosuppressant	Opiate
Droperidol	Haloperidol	Tacrolimus	Methadone
Promethazine	Clozapine		
Chlorpromazine	Quetiapine		
Ondansetron	Risperidone		

TABLE 3. EFFECTS OF CHEMOTHERAPY ON CARDIAC REPOLARIZATION

Chemotherapy	Effect on QTc	Torsades de Pointes	Sudden Cardiac Death
BRAF Inhibitor			
Vemurafenib	↑ 15 ms	N/A	N/A
HDAC Inhibitor			
Depsipeptide	↑ 14 ms	N/A	1.2%
Vorinostst	3.4 - 4%	1 CR	N/A
Tyrosine Kinase Inhibitors			
Dasatinib	↑ 7 - 13 ms	N/A	N/A
Lapatinib	16% with ↑ 60 ms or QTc > 480 ms	N/A	N/A
Nilotinib	0.4% with ↑ 60 ms	N/A	0.3%
Pazopanib	2%	< 1%	N/A
Sunitinib	↑ 9.6 ms	< 0.1%	N/A
Vandetanib	0.9% with ↑ 35 - 60 ms	2 CRs	0.3%
Miscellaneous			
Arsenic Trioxide	40% with > 500 ms	2.5%	N/A

## Chapter 7

### Pericardial Effusion

Elie Mouhayar

Pericardial effusion is reported in up to 34% of autopsies performed on cancer patients. However, two-thirds of these pericardial effusions are non-malignant. The mechanism of effusion in this setting is likely related to loss of adequate lymphatic drainage of the pericardial sac, which is secondary to lymphangitic spread of the malignancy or mediastinal irradiation. Clarifying the specific etiology of effusion helps determine not only the best treatment modality but also prognosis; malignant effusions are associated with a dismal 16% 1-year survival rate compared with 55% for nonmalignant effusions.

There is no evidence that medical therapy plays any role in the management of effusion, except in cases of concomitant inflammation (i.e., pericarditis). At MD Anderson, there are three main indications for pericardial fluid drainage:

1. Large effusion (>2 cm in diameter)
2. The need for etiologic diagnosis
3. The presence of clinical or echocardiographic evidence of tamponade physiology

Draining pericardial effusion can be achieved percutaneously or surgically by creating a pericardial window. At MD Anderson, the vast majority of patients undergo echocardiography- or fluoroscopy-guided pericardiocentesis. The decision regarding which procedure to use depends on many factors, including 1) effusion distribution and location, and 2) clinical presentation. Surgery is preferred in the setting of recurrent effusions, purulent effusions, or high-output drainage (>100 mL

per day > 5 days after pericardiocentesis). The percutaneous approach is preferred in most cases, especially if the patient is in shock or hypotensive and if coagulopathy is present.

With the intercostal or subxiphoid approach during pericardiocentesis, drainage can be easily achieved by selecting the shortest distance between the skin and pericardial fluid pockets. A short movie demonstrating our approach in performing pericardiocentesis is available at the following weblink: <http://www.youtube.com/watch?v=y0-K2RcThi0>.

Pericardial fluid is sent to the laboratory for specific testing, including chemistry, microbiology, cytology, flow cytometry, and, in certain circumstances, a check for tumor markers. When performed by experienced teams, pericardiocentesis is a safe procedure with a low complication rate (< 5%) and high success rate (98%), especially if the effusion is moderate to large. The pericardial draining catheter is typically left in place for five days because this approach has been shown to lower the effusion recurrence rate by two-thirds. For the occasional cases in which high output is present after 5-7 days, we sometimes request that a pericardial window be surgically created. Following initial pericardiocentesis, almost one in five patients develop recurrent effusions. We typically address recurrence by repeating pericardiocentesis and occasionally by referring patients for surgical pericardial window creation.

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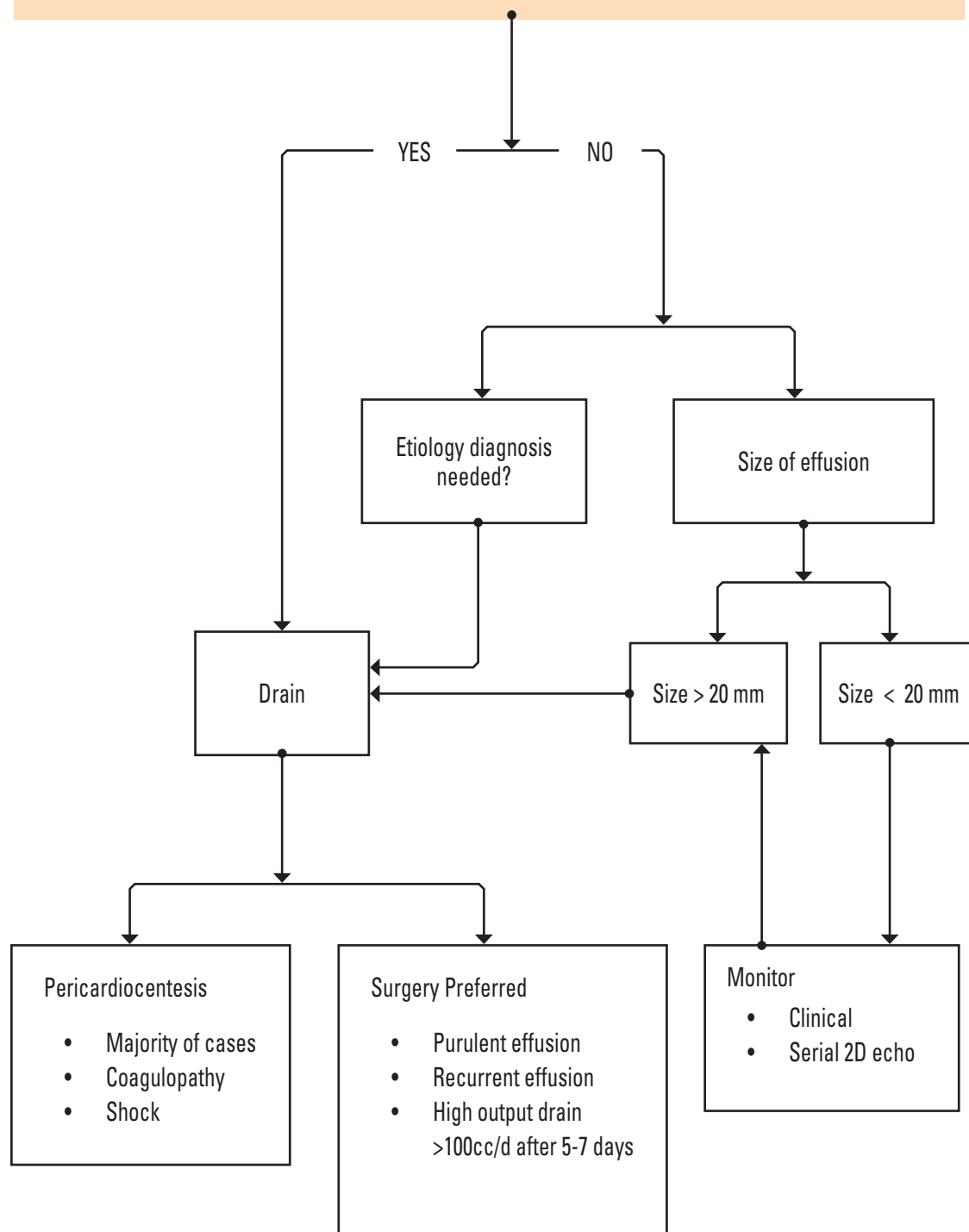
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**CLINICAL/ECHOCARDIOGRAPHIC EVIDENCE OF TAMPONADE**



**Chapter 8**

**Managing Acute Coronary Syndrome with Thrombocytopenia**

Cezar Iliescu

Acute coronary syndromes are often observed in thrombocytopenic cancer patients. Aspirin improves 7-day survival, and dual antiplatelet therapy (DAPT) with aspirin and clopidogrel appear to be safe in thrombocytopenic cancer patients without active major bleeding or sepsis. In our practice, cancer patients with thrombocytopenia should not be denied life-saving interventional cardiology procedures. Several important principles are noted:

1. Access is key, and procedures should always be done using a micropuncture technique/kit.
2. Radial access is preferred. If the Allen test is abnormal and femoral access is needed, start with a 4F sheath and catheters, and then up-size if intervention is indicated.
3. Decreased doses of heparin (30 - 50 units / kg) may be required for patients with platelet counts / $\mu\text{L}$  < 50,000/ $\mu\text{L}$ .
4. Response to anticoagulation /anti-platelet therapy in patients with platelet counts > 50,000 /  $\mu\text{L}$  appears similar to the response in patients with normal platelet counts.
5. Dual anti-platelet therapy with aspirin and clopidogrel should be used for patients with platelet counts >30,000/ $\mu\text{L}$  and aspirin only for those with platelet counts >10,000/ $\mu\text{L}$ . Below these values, an interdisciplinary evaluation is required: the cardiology and oncology teams have to balance the risk of thrombosis with that of bleeding and decide on the therapeutic plan. (The lowest platelet count for which we have performed an intervention was 4,000/ $\mu\text{L}$ .)
6. A fractional flow reserve (FFR) guided percutaneous coronary intervention (PCI) is the preferred approach FFR < 0.75-0.8.
7. Postdilatation and intravascular ultrasound or optical coherence tomography are recommended after stent deployment to ensure adequate apposition and expansion and lack of edge dissection, as the risk of early discontinuation of DAPT is high.
8. Closure devices for the artery entry site (Angioseal) and noninvasive methods (e.g., Neptune pad, Quick Clot, or Syvek) should be used to achieve hemostasis for those with platelet counts <50,000. Increased time (~30 minutes) should be allowed for groin pressure to achieve hemostasis when a femoral artery was the access site.
9. Bleeding from the procedure is more likely due to a procedural/access problem rather than thrombocytopenia.

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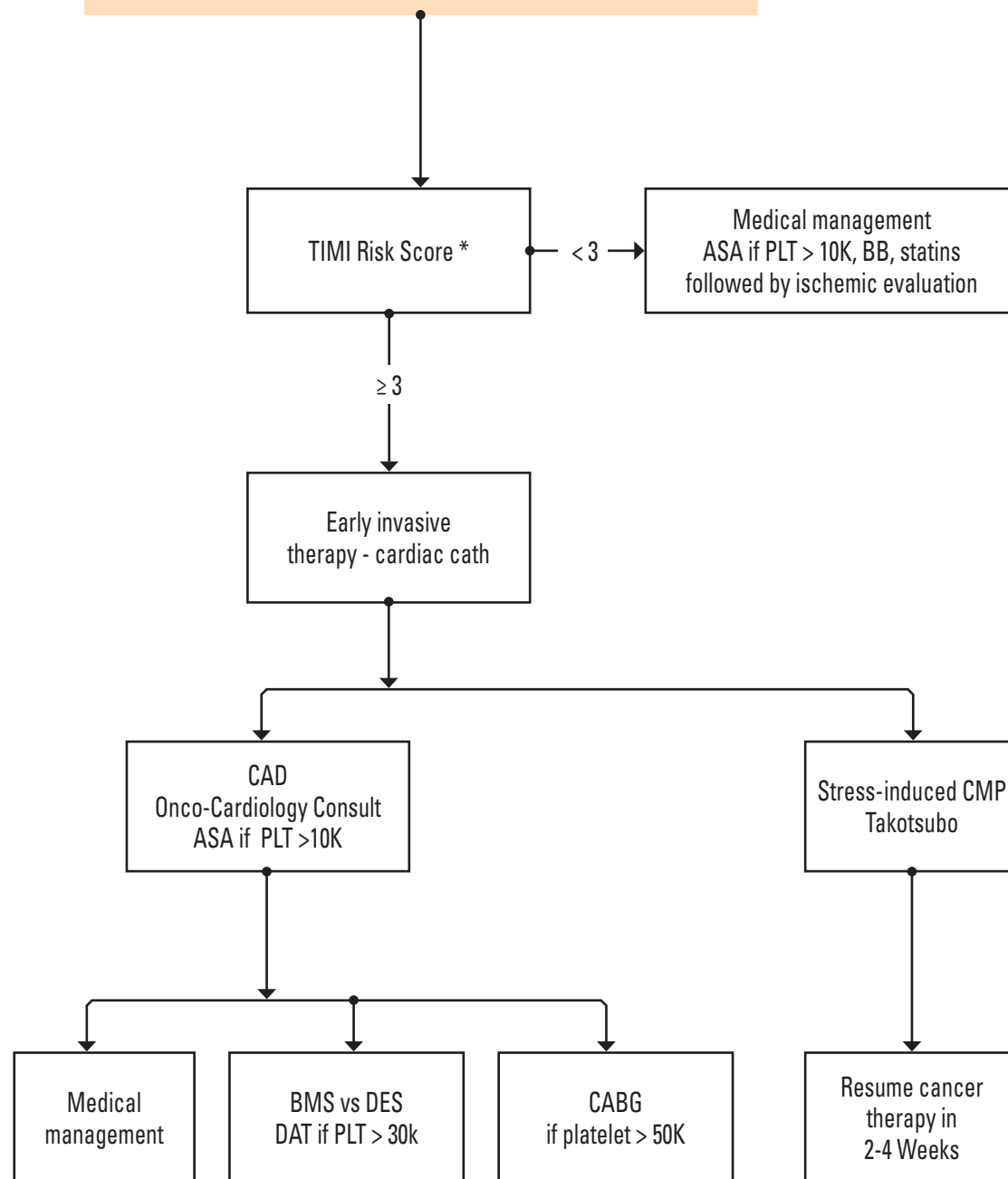
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**ACUTE CORONARY SYNDROME  
PLATELET < 100,000**



**TIMI Risk Score \***

= TIMI Risk score for UA/NSTEMI or STEMI + additional points for:

- h/o radiation to the chest (1 point)
- Ongoing prothrombotic chemo or Phase I drug (1 point)

**Chapter 9  
Evaluation of a Cardiac Mass**

Juan Lopez-Mattei

Evaluation of a cardiac mass starts with echocardiography. If the mass has thrombus characteristics, the patient is treated with anticoagulants and returns for follow-up imaging in 2 months. After 2 months of anticoagulation therapy, if the mass size has not changed, cardiac MRI is performed to help differentiate between a thrombus and a tumor.

If the mass has tumor characteristics, a cardiac MRI is performed for confirmation and further evaluation. In addition, whole body positron

emission tomography (PET)/CT is performed to determine whether the mass is a primary cardiac tumor (PET lights up only in the heart) or metastasis from another primary tumor (extracardiac signals). If cardiac MRI and PET/CT findings are suggestive of a primary cardiac tumor, then open biopsy or percutaneous biopsy are considered. If the cardiac mass is metastatic from a known primary tumor, then the primary malignancy is treated and followed up with serial imaging.

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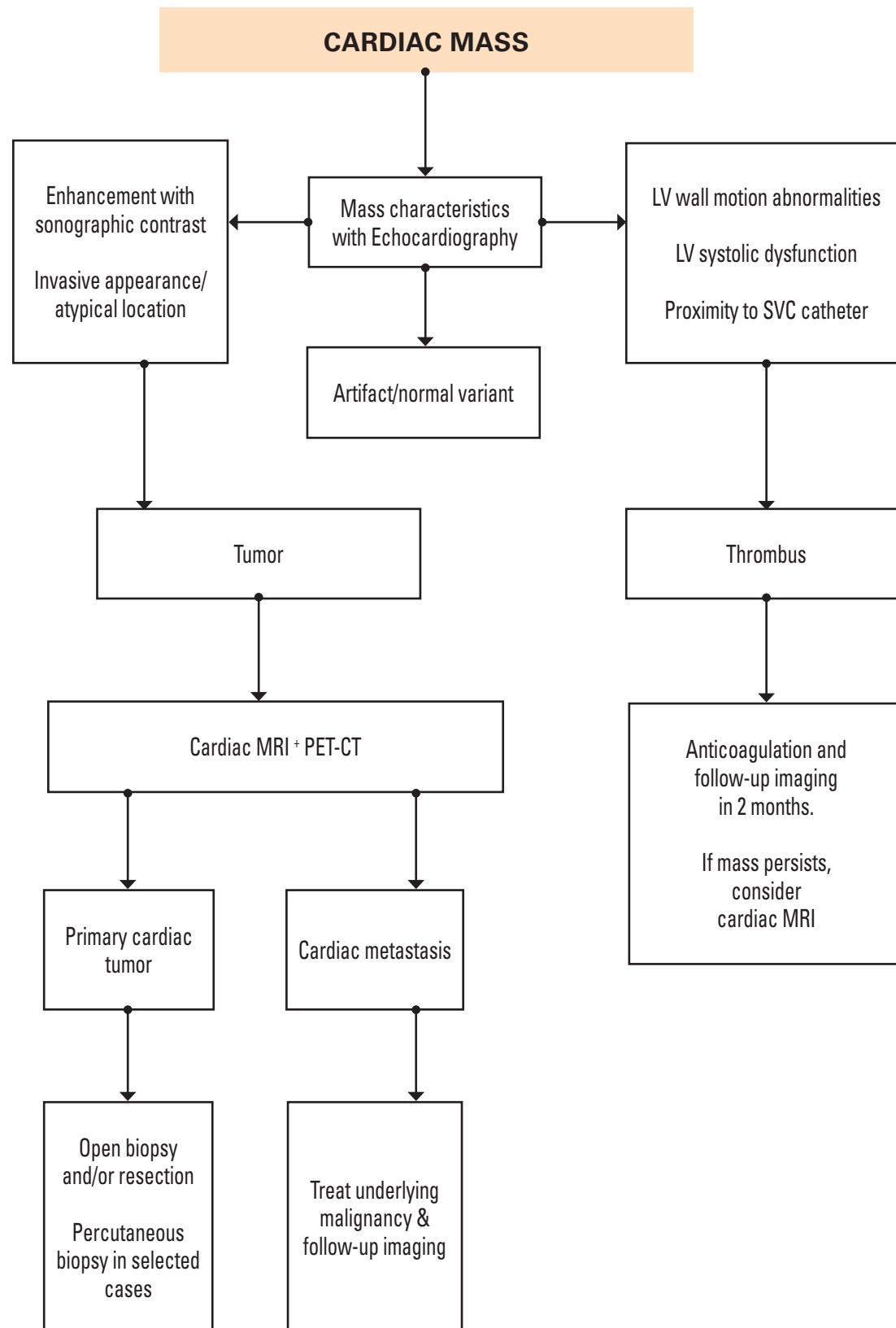
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## Chapter 10 Managing Benign Cardiac Tumors

Kara A. Thompson

Primary cardiac tumors are rare, and most (75%) are benign. These tumors are potentially curable with surgical resection. Important management points in our practice are as follows.

1. Myxomas are the most common primary benign cardiac tumors. Owing to risk of outflow obstruction or embolization, surgical excision is recommended and is the only effective treatment.
2. Papillary fibroelastomas are the second most common benign cardiac tumors. These tumors are most often located on the aortic valve, and the clinical concern is embolization. Surgical resection should be considered if the patient has had an embolic event or if the fibroelastoma is left-sided or highly mobile.
3. Lipomas rarely cause symptoms and can be managed with observation. It is important to identify these tumors correctly to avoid unnecessary cardiac surgery.
4. Rhabdomyomas are the most common benign cardiac tumors in children. These tumors are often associated with tuberous sclerosis, and, if asymptomatic, these tumors can be followed clinically because 70% regress spontaneously.
5. Other rare benign cardiac tumors are managed on an individual case basis. Surgical resection can be considered.

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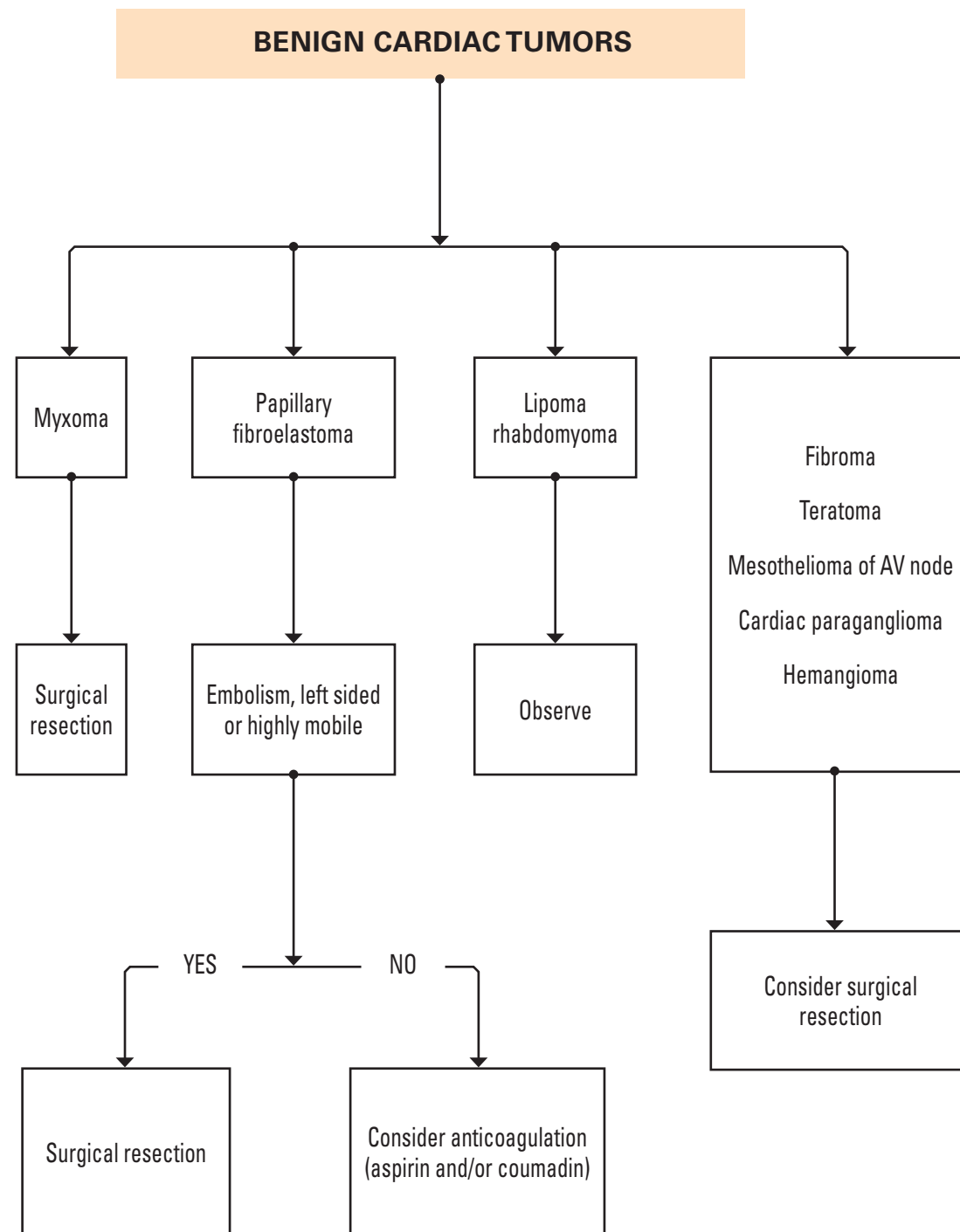
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## Chapter 11 Managing Malignant Cardiac Tumors

Kara A. Thompson

Of primary cardiac tumors, 25% are malignant. Metastatic tumors to the heart are far more common. Primary malignant cardiac tumors are generally associated with a dismal prognosis. Complete resection has been shown to provide some survival benefit for patients with sarcomas. Treatment of metastatic tumors is generally focused on treatment of the underlying malignancy. Surgical resection is reserved for select cases.

Sarcomas account for 75% of primary malignant tumors. Treatment is based on anatomic location rather than histologic type. Classification is categorized as right heart, left heart, or pulmonary artery sarcoma. Right heart sarcomas are treated with neoadjuvant chemotherapy for tumor reduction prior to surgical resection. Left heart sarcomas usually require urgent resection owing to obstructive

symptoms, precluding neoadjuvant chemotherapy. Complete resection can be challenging. The technique of autotransplantation was developed to achieve negative surgical margins with resection of these tumors. Pulmonary artery sarcomas also often require urgent resection because of symptoms. These tumors do not penetrate the wall of the pulmonary artery, generally allowing for mobilization. After surgical resection of sarcomas, adjuvant chemotherapy is recommended.

For renal cell cancers and other cancers that metastasize to the heart via the inferior vena cava, surgical resection does offer a survival benefit. Primary cardiac lymphoma is rare but important to identify because treatment is not surgical. Cardiac lymphomas are managed as a systemic disease and treated with chemotherapy.

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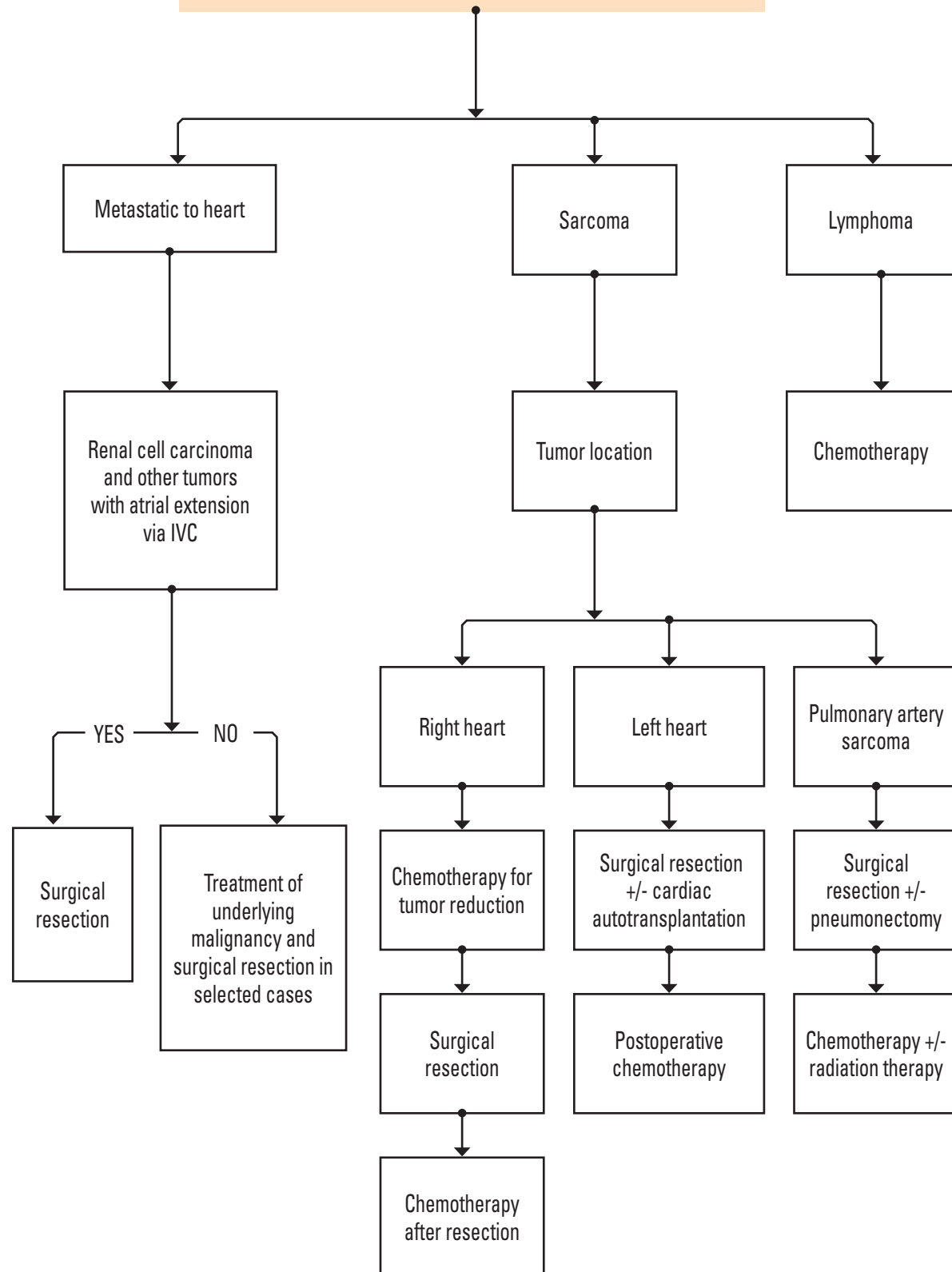
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**MALIGNANT CARDIAC TUMORS**



**Chapter 12**

**Drug Lists**

Courtney L. Meuth and Tara K. Lech

The following tables include cancer therapies in which the reported incidence of cardiac toxicity was  $\geq 3\%$ . However, agents were also included if the reported incidence was  $< 3\%$  but the manufacturer provided a black box warning and/or a specific monitoring algorithm for that toxicity. Anticancer therapies were excluded if the incidence of a particular cardiotoxicity was considered rare, or when there were only case reports available.

**Frequency of Use:** This was quantified using inpatient and outpatient doses dispensed at MD Anderson Cancer Center during the time period of January 1, 2014 through December 31, 2014. + =  $< 1,000$  doses dispensed

++ = 1,000-5,000 doses dispensed

+++ = 5,000-10,000 doses dispensed

++++ =  $> 10,000$  doses dispensed

## Cancer therapy associated with Heart failure/Left Ventricular Dysfunction

Chemotherapy agents	Incidence (%)	Frequency of Use
<b>Anthracyclines</b>		
Doxorubicin (Adriamycin <sup>®</sup> ) <sup>1</sup>	3-26* <sup>#</sup>	++++
Epirubicin (Ellence <sup>®</sup> ) <sup>1</sup>	0.9-3.3 <sup>#</sup>	+
Idarubicin (Idamycin PFS <sup>®</sup> ) <sup>1</sup>	5-18 <sup>#</sup>	++
<b>Alkylating agents</b>		
Cyclophosphamide (Cytoxan <sup>®</sup> ) <sup>1</sup> (high dose)	7-28 <sup>++</sup>	++++
Ifosfamide (Ifex <sup>®</sup> ) <sup>1</sup>	17 <sup>+</sup>	
<b>Antimetabolites</b>		
Decitabine (Dacogen <sup>®</sup> ) <sup>2</sup>	5	++
<b>Antimicrotubule agents</b>		
Docetaxel (Taxotere <sup>®</sup> ) <sup>1</sup>	2.3-8	++
<b>Monoclonal Antibody-based tyrosine kinase inhibitors</b>		
Adotrastuzumab emtansine (Kadcyla <sup>®</sup> ) <sup>2</sup>	1.8 <sup>b</sup>	+
Bevacizumab (Avastin <sup>®</sup> ) <sup>2</sup>	1-10.9	+++
Pertuzumab (Perjeta <sup>®</sup> ) <sup>2</sup>	0.9-16 <sup>b</sup>	+
Trastuzumab (Herceptin <sup>®</sup> ) <sup>1</sup>	2-28 <sup>b</sup>	+++
<b>Proteasome Inhibitors</b>		
Bortezomib (Velcade <sup>®</sup> ) <sup>1</sup>	2-5 <sup>#</sup>	++
Carfilzomib (Kyprolis <sup>®</sup> ) <sup>2</sup>	7 <sup>#</sup>	++
<b>Small molecule tyrosine kinase inhibitors</b>		
Dabrafenib (Tafinlar <sup>®</sup> ) <sup>2</sup>	8-9 <sup>#</sup>	++++
Dasatinib (Sprycel <sup>®</sup> ) <sup>1</sup>	2-4 <sup>#</sup>	++++
Lapatinib (Tykerb <sup>®</sup> ) <sup>1,2</sup>	0.9-4.9 <sup>#</sup>	++++
Pazopanib (Votrient <sup>®</sup> ) <sup>2</sup>	0.6-11 <sup>#</sup>	++++
Ponatinib (Iclusig <sup>®</sup> ) <sup>2</sup>	3-15 <sup>b</sup>	+
Sorafenib (Nexavar <sup>®</sup> ) <sup>1,2</sup>	1.9-11	++++
Sunitinib (Sutent <sup>®</sup> ) <sup>2</sup>	1-27 <sup>#</sup>	++++
Trametinib (Mekinist <sup>®</sup> ) <sup>2</sup>	7-11 <sup>#</sup>	++++
<b>Miscellaneous</b>		
Tretinoin (Vesanoid <sup>®</sup> ) <sup>2</sup>	6	++++

\*at cumulative dose of 550mg/m<sup>2</sup>

<sup>†</sup>Occurs at high doses (cyclophosphamide doses >150 mg/kg and 1.5 g/m<sup>2</sup>/day and ifosfamide doses ≥ 12.5 g/m<sup>2</sup>)

<sup>#</sup>Listed as a warning/precaution in package insert

<sup>b</sup>Black box warning in package insert

## Cancer therapy Associated with Hypertension

Chemotherapy agents	Incidence (%)	Frequency of Use
<b>Antimetabolites</b>		
Decitabine (Dacogen <sup>®</sup> ) <sup>2</sup>	6	++
<b>Monoclonal Antibodies</b>		
Alemtuzumab (Campath <sup>®</sup> ) <sup>2</sup>	14	+
Ibritumomab (Zevalin <sup>®</sup> ) <sup>2</sup>	7	NA
Ofatumumab (Arzerra <sup>®</sup> ) <sup>2</sup>	5-8	+
Rituximab (Rituxan <sup>®</sup> ) <sup>2</sup>	6-12	+++
<b>Monoclonal Antibody-based tyrosine kinase inhibitors</b>		
Adotrastuzumab emtansine (Kadcyla <sup>®</sup> ) <sup>2</sup>	5.1	+
Bevacizumab (Avastin <sup>®</sup> ) <sup>1</sup>	23-34 <sup>#</sup>	+++
<b>mTOR Inhibitors</b>		
Everolimus (Afinitor <sup>®</sup> ) <sup>2</sup>	4-13	++++
Temsirolimus (Torisel <sup>®</sup> ) <sup>2</sup>	7	++
<b>Proteasome Inhibitors</b>		
Bortezomib (Velcade <sup>®</sup> ) <sup>1</sup>	6	++
Carfilzomib (Kyprolis <sup>®</sup> ) <sup>2</sup>	14.3	++
<b>Small molecule tyrosine kinase inhibitors</b>		
Axitinib (Inlyta <sup>®</sup> ) <sup>2</sup>	40 <sup>#</sup>	++++
Cabozantinib (Cometriq <sup>®</sup> ) <sup>2</sup>	33-61 <sup>#</sup>	NA
Ibrutinib (Imbruvica <sup>®</sup> ) <sup>2</sup>	17	++++
Nilotinib (Tasigna <sup>®</sup> ) <sup>1</sup>	10-11	++++
Pazopanib (Votrient <sup>®</sup> ) <sup>2</sup>	42 <sup>#</sup>	++++
Ponatinib (Iclusig <sup>®</sup> ) <sup>2</sup>	68 <sup>#</sup>	+
Ramucirumab (Cyramza <sup>®</sup> ) <sup>2</sup>	16 <sup>#</sup>	+
Regorafenib (Stivarga <sup>®</sup> ) <sup>2</sup>	30-59 <sup>#</sup>	++++
Sorafenib (Nexavar <sup>®</sup> ) <sup>2</sup>	9.4-41 <sup>#</sup>	++++
Sunitinib (Sutent <sup>®</sup> )	15-34 <sup>#</sup>	++++
Trametinib (Mekinist <sup>®</sup> ) <sup>2</sup>	15	++++
Vandetanib (Caprelsa <sup>®</sup> ) <sup>2</sup>	33 <sup>#</sup>	NA
Ziv-aflibercept (Zaltrap <sup>®</sup> ) <sup>2</sup>	41 <sup>#</sup>	+

<sup>#</sup>Listed as a warning/precaution in package insert

NA= no usage for the time period specified

## Cancer therapy Associated with Myocardial Infarction/Ischemia

Chemotherapy agents	Incidence (%)	Frequency of Use
<b>Angiogenesis Inhibitors</b>		
Lenalidomide (Revlimid®) <sup>1</sup>	0.-1.9 <sup>b</sup>	+++
<b>Antimetabolites</b>		
Capecitabine (Xeloda®) <sup>1</sup>	3-9 <sup>#</sup>	++++
Fluorouracil (Adrucil®) <sup>1</sup>	1-68 <sup>*</sup>	++++
<b>Antimicrotubule agents</b>		
Paclitaxel (Taxol®) <sup>1</sup>	< 1-5	++++
<b>Monoclonal Antibody-based tyrosine kinase inhibitor</b>		
Bevacizumab (Avastin®) <sup>1,2</sup>	0.6-8.5 <sup>#</sup>	+++
<b>Small molecule tyrosine kinase inhibitors</b>		
Nilotinib (Tasigna®) <sup>2</sup>	5-9.4 <sup>#</sup>	++++
Ponatinib (Iclusig®) <sup>2</sup>	12 <sup>b</sup>	+

*\*The incidence of ischemia varies widely in the literature for 5-fluorouracil due to the differences in study design, definition of ischemia, and numbers of patients.*

*<sup>#</sup>Listed as a warning/precaution in package insert*

*<sup>b</sup>Black box warning in package insert*

*<sup>^</sup>Combined incidence of myocardial ischemia and ventricular dysfunction reported with lxabepilone + capecitabine*

## Cancer therapy Associated with Venous Thromboembolism

Chemotherapy agents	Incidence (%)	Frequency of Use
<b>Alkylating agent</b>		
Cisplatin (Platinol-AQ®) <sup>1</sup>	8.5	+++
<b>Angiogenesis Inhibitors</b>		
Lenalidomide (Revlimid®) <sup>1</sup>	3-75 <sup>*b</sup>	+++
Thalidomide (Thalomid®) <sup>1</sup>	1-58 <sup>* b</sup>	++
Pomalidomide (Pomalyst®) <sup>2</sup>	3 <sup>b</sup>	+
<b>Histone deacetylase inhibitor</b>		
Vorinostat (Zolinza®) <sup>1</sup>	4.7-8 <sup>#</sup>	++++
<b>Monoclonal Antibody-based tyrosine kinase inhibitor</b>		
Bevacizumab (Avastin®) <sup>2</sup>	6-15.1 <sup>#+</sup>	+++
<b>mTOR inhibitors</b>		
Everolimus (Afinitor®) <sup>2</sup>	1-4	++++
<b>Small molecule tyrosine kinase inhibitors</b>		
Axitinib (Inlyta®) <sup>2</sup>	3 <sup>#</sup>	++++
Cabozantinib (Cometriq®) <sup>2</sup>	6 <sup>#</sup>	NA
Dabrafenib (Tafinlar®) <sup>2</sup>	7	++++
Erlotinib (Tarceva®) <sup>1</sup>	3.9-11	++++
Nilotinib (Tasigna®) <sup>3</sup>	1-10	++++
Pazopanib (Votrient®) <sup>2</sup>	1-5 <sup>#</sup>	++++
Ponatinib (Iclusig®) <sup>2</sup>	5 <sup>b</sup>	+
Sunitinib (Sutent®) <sup>2</sup>	3	++++
Trametinib (Mekinist®) <sup>2</sup>	7 <sup>#^</sup>	++++
Ziv-aflibercept (Zaltrap®) <sup>2</sup>	9	+

*\*The incidence of venous thromboembolism varies widely in the literature for angiogenesis inhibitors depending on the patients' disease status, concomitant use of high or low dose dexamethasone, erythropoietin, or other chemotherapeutic agents, and whether or not thromboprophylaxis was employed during the study period.*

*<sup>#</sup>Listed as a warning/precaution in package insert*

*<sup>^</sup>When used in combination with dabrafenib*

*<sup>+</sup>When used in combination with chemotherapy*

*<sup>b</sup>Black box warning in package insert*

*NA= no usage for the time period specified*

## Cancer therapy Associated with Bradycardia\*

Chemotherapy agents	Incidence (%)	Frequency of Use
<b>Angiogenesis Inhibitor</b>		
Thalidomide (Thalomid®) <sup>1</sup>	0.12-55* <sup>#</sup>	+
<b>Antimicrotubule agents</b>		
Paclitaxel (Taxol®) <sup>1</sup>	< 0.1-31 *	++++
<b>Small molecule tyrosine kinase inhibitors</b>		
Ceritinib (Zykadia®) <sup>2</sup>	3 <sup>#</sup>	
Crizotinib (Xalkori®) <sup>2</sup>	11 <sup>#</sup>	++
Pazopanib (Votrient®) <sup>2</sup>	2-19	++++
Trametanib (Mekinist®) <sup>3</sup>	Up to 10	++++

\*The incidence of bradycardia varies widely in the literature for these agents due to the differences in study design, definition of bradycardia, and numbers of patients.

<sup>#</sup>Listed as a warning/precaution in package insert

## Cancer Therapy Associated with QT Prolongation\*

Chemotherapy agents	Incidence (%)	Frequency of Use
<b>Histone deacetylase inhibitors</b>		
Belinostat (Beleodaq®) <sup>2</sup>	4-11	+
Vorinostat (Zolinza®) <sup>1</sup>	3.5-6	++++
<b>Miscellaneous</b>		
Arsenic trioxide (Trisenox®) <sup>1</sup>	26-93**	++
<b>Small molecule tyrosine kinase inhibitors</b>		
Ceritinib (Zykadia®) <sup>2</sup>	4 <sup>#</sup>	NA
Dabrafenib (Tafinlar®) <sup>2</sup>	2-13 <sup>^</sup>	++++
Dasatinib (Sprycel) <sup>1</sup>	< 1-3 <sup>#</sup>	++++
Lapatinib (Tykerb®) <sup>1</sup>	16 <sup>#</sup>	++++
Nilotinib (Tasigna®) <sup>1</sup>	< 1-4.1 <sup>b</sup>	++++
Trametanib (Mekinist®) <sup>2</sup>	4-13 <sup>^</sup>	++++
Vandetanib (Caprelsa®) <sup>2</sup>	8-14 <sup>b</sup>	++++
Vemurafenib (Zelboraf®) <sup>2</sup>	NR**	++++

\*The incidence of QT prolongation varies widely in the literature for arsenic due to the differences in study design, definition of QT prolongation, and numbers of patients.

<sup>#</sup>Listed as a warning/precaution in package insert

<sup>^</sup>Incidence of QT prolongation was 2% when dabrafenib given as monotherapy; 4-13% when dabrafenib was given with trametanib

<sup>b</sup>Black box warning in package insert

NA= no usage for the time period specified

## References

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ISBN 978-1-944785-94-9



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