CARDIOVASCULAR IMAGING IN WOMEN WITH HEART DISEASES, A LOCAL CLINICAL PRACTICE GUIDELINES FOR PAKISTANI POPULATION

Sultana Habib[1], Fateh Ali Tipoo Sultan[1], Saba Hussain[1], Lubna Baqai[1], Saba Sohail[1]
[1]**The Task Force - Go Red for Women-Pakistan**

PREAMBLE

This is the first time that a local preliminary document on gender differences in CVDs has been initiated in Pakistan. International forum has been highlighting significant gender and ethnicity in CVDs. So different countries from world took the initiative to develop their local guideline or clinical scientific statements on gender differences with different socio-cultural and educational background for their own countries. GRFW in collaboration with Scientific Council of Women with Heart Disease PCS Pakistan floated this idea to develop a local guideline in various aspects CVDs for our own women population. In this regard different topics were assigned to different groups including mostly female cardiologists, senior gynecologists/obstetricians and radiologist from all over Pakistan. Primary objectives of this write up on Cardiac Imaging in Women is to provide a local clinical practice guideline for the assessment and management of CVD that will improve and standardize the physicians' decision making for Pakistani women population. In the setting of growing awareness of providing personalized precision medicine, addressing sex differences in CVD is a key goal.

The intention is to inform cardiologists, non-cardiologist physicians', general practitioners, and, obstetrician/gynecologists about the reasonable use and understanding of technologies to help in proper approach to their treating women with HDs and when to send them for cardiac specialist diagnostic center. As we could not find our own local data on cardiac imaging to report at present, most recommendations on cardiac imaging used has been taken from international literatures (which we have found feasible, readily available, and some cost effective approach in our money constraint society which can be followed in our population) and also which were published within the past decade were given priority. In this document, we discuss the role of using different cardiac imaging modalities, with a focus on diseases which are unique/or occur more in women. So, five women specific topics more commonly seen in our population were selected currently, which are (stable/unstable angina and ACS, MINOCA), non-ischemic CMP, HD during pregnancy, cardio-oncology, and connective tissue diseases (CTD). In these topics we have tried to used our own local incidences and prevalence of these diseases in our community/internationally on gender basis and have highlighted the availability/limitations of cardiac imaging in our society. The updated recommendations in women have been taken from international guidelines. Graphs and tables layout has been taken from abroad literatures and made some few changes according to its use in our population. You will find this a preliminary review document which will be simple to read, have updated approach in evaluating the diagnosis of HD in women easily. For current cost effectiveness issues for our population will be taken up by PCS to Health ministries of Pakistan for its making it easily availability with cheap cost so to benefit our female (very neglected and ill informed) with CVD population.

Introduction

Heart disease (HD) is one of the leading cause of death for women in the USA/south Asian countries, killing 1 in 3 women in 2018.[1,2] Despite understanding of CVD in men and women, recognition of sex and gender influences on the clinical care and awareness of women has been slow or absent and there are only limited numbers of sex-specific and age-balanced imaging and management guidelines for women with CVD.[1] The presentation and identification of CVD in women pose unique diagnostic challenges compared to men, and under-recognized conditions in this population may lead to clinical mismanagement. Our population especially women lack in personal care, professional health care and excess in prevalence in coronary risk factors (RFs).

We have discussed the role of using different cardiac imaging modalities, with a focus on diseases which are unique/or occur more in women population. The primary objectives of this write up is to provide a local clinical practice guideline for the assessment and management that will improve and standardize our physicians' decision making for Pakistani women population with CVD.

1 Cardiac Imaging in Women with Coronary Heart Disease (CHD)

1.1 Introduction: This document may help informing knowledge gaps that may recommend/help clinical practice and care that will be truly tailored for our women and eventually would also help in the limited use of resources in Pakistan. Its now well-known that anatomic differences exist between men and women which can affect diagnostic performance of cardiac imaging in women (Table 1).

Table 1: Gender differences in coronary anatomy, patho-physiology, radiation, pregnancy[3]

Challenges	Details
Sex-based differences in anatomy and physiology	Smaller coronary arteries, Smaller LV chamber, Digitalis-like effect of estrogen
Sex based differences in pathogenesis	Older age, atypical seen than typical presentation in women. More non-obstructive lesions micro-vascular, endothelial, and non-ischemic lesions
Radiation	Radiation exposure to breast tissue. Radiation risk in pregnancy
Pregnancy	Maternal and fetal radiation /contrast exposure.

1.2 Atherosclerotic Heart Disease: People of South Asian origin, which include Pakistan also, have an increased risk of ASCVD 4 times higher than the general population in America.[1,2] Women have a bad prognosis from IHD than men despite less prevalence and decrease severity of obstructive CAD. Mechanism is now well understood but over here there is much lack in awareness. We have discussed on the role of contemporary functional and anatomic imaging techniques, including ETT, echocardiography, cardiac magnetic resonance imaging (MRI), coronary computed tomographic angiography (CCTA), single-photon emission computerized tomography (SPECT) and positron emission tomography (PET), myocardial perfusion imaging (MPI), and invasive coronary angiography (ICA) in the detection and risk assessment of the burden of ASCAD in women at risk for IHD. All these technologies with expertise are now available in major cities of Pakistan (Table 2). All the contemporary non-invasive cardiac imaging's have high sensitivity and specificity. With this table it can be helped in selecting tests which has better sensitivity and specificity in women and this can prevent us from its over and unnecessary utilization in women with IHD.

Table 2: Noninvasive Tests Capability to Detect Gender differences in CAD [3]

Test	Sensitivity (%)		Specificity (%)	
	Men	Women	Men	Women
Exercise ECG	61	68	70	77
Stress Echocardiography	79	76	83	88
SPECT MPI	84	89	79	71
PET MPI	81	81	86	89
Cardiac MRI	89	86	84	83
Coronary CT Angiography	90	96	89	

1.3 Introduction to Ischemic Heart Diseases (IHD) in Women: It is well known by now that IHD continues to be a major threat to women across their lifespans misconception on other diseases as number one has been ruled out. Despite the progress, IHD remains the leading cause of death and disability in women all over the world and ¼ population lives in South Asia. In light of the potential sex-based differences, there have been recent efforts to adopt female-specific diagnostic paradigms for the workup of IHD.[4] The commonly used pretest probability assessment underestimate risk in women. With our improved understanding of the ischemic cascade, allow IHD to be diagnosed early and with greater accuracy. Considering the spectrum of IHD in women we encounter diagnostic challenges, it can limit the application of traditional testing strategies which, while adequate to detect obstructive epicardial CAD, may be insufficient for many women and additional investigation beyond standard stress tests is often necessary to define the etiology of symptoms in women. We have in Pakistan limited healthcare services exclusive and limited use of resources in

women of Pakistan. Its knowledge/awareness and availability of local expertise/availability of tests will guide test selection suitable for our populations.

1.4 Cardiac Imaging Tests Which Are More Suitable For Detection Of IHD in Women: ESC document[5] recommended that in every patient with suspected IHD should undergo detailed clinical history, in women must add the pregnancy history on CVD, thorough physical examination then we should do pooled estimate pre-test probabilities (PTP) of significant CAD, it may helps in re-evaluation in the utility of the different diagnostic techniques according to such estimates. So first of all we should estimate the PTP and categorize the patients into low, intermediate and high risk.

The diagnostic approach in woman with suspected IHD includes basic testing like ECG and ETT, and ECHO. A resting TTE is recommended in all patients for exclusion of alternative causes of angina. Then, functional imaging includes MPI with SPECT or PET, stress ECHO, or stress CMR imaging assessing myocardial perfusion and/or wall motion can be performed according to the local expertise and availability of the tests.

Table 3: Use of Non-invasive Imaging modalities for Diagnosis and Prognostic evaluation of Women at Risk for IHD categorized according to PTP [3]

Identification Text		Exercise ECG	Stress RN1	Stress ECHO	Stress CMR	Calcium Scoring	CCTA	Invasive Coronary Angiography
1	• Low PTP of CAD. • And ECG readable **AND** able to exercise.	A	R	M	R	R	R	R
2	• Low PTP of CAD. • And ECG un-interpretable **OR** patient cannot do exercise		A	A	M	R	M	R
3	• Intermediate PTP of CAD. • ECG not readable **AND** patients able to exercise.	A	A	A	M	R	M	R
4	• Intermediate PTP of CAD. • ECG not readable **OR** patient unable to exercise.		A	A	A	R	A	M
5	• High pre-test PTPof CAD. • ECG readable **AND** patient is able to exercise	M	A	A	A	R	M	A
6	• High PTP of CAD. • ECG not readable AND patient cannot exercise		A	A	A	R	M	A

A=appropriate; M=May be appropriate; R=rarely appropriate

For symptomatic female patients with an intermediate pretest risk of IHD, the addition of stress imaging's have shown to improve overall CV risk assessment, and can help in proper clinical management, and can determine need for coronary revascularization.[3] The flow chart shown below from 2014 AHA[3] clinical scientific statement guideline for women with IHD which has highlighted the novel imaging modalities and its expanded role for making the diagnosis and risk stratification in women with different spectrum of IHD easy, besides diagnosing obstructive CAD, it can diagnose non–obstructive CAD associated endothelial and micro vascular disease dysfunction, sub-clinical atherosclerosis for detection of myocardial ischemia Figure 1.

1.5 Radiation-free Imaging: The 2014 AHA consensus statement have discussed the role of noninvasive testing in the clinical evaluation of women with suspected IHD and makes decision that clinicians should carefully weigh the risks and the benefits of radiation-based imaging modalities. The statement adds that for low-risk premenopausal women, no test is preferable or can go for tests without radiation exposure.[4] Pharmacological stress echo is recommended for such patients for identification of obstructive CAD and estimation of prognosis. The role of magnetic resonance imaging (MRI) in cardiac diagnosis is easily available in Pakistan and its utility should increase in our women population.

1.6 Chronic/Stable IHD:[6] The diagnosis of chronic/stable angina is difficult in women due to a more atypical angina presentation.

a) Symptomatic Intermediate-Risk Women: Table 5 Patients who are at intermediate pre-test probability for IHD should undergo ETT if there are no contraindications. If ECG not interpretable, ETT with nuclear MPI or ECHO is recommended.[4] CTA is also reasonable in this situation.[4] It is reasonable to perform CTA for patients who are at the decrease range of intermediate PTP for CAD to rule out CAD, while

an imaging ETT carries a Class 1 recommendation for patients who are intermediate risk (65–85% PTP) for evaluation of CAD. PET-MPI has improved accuracy compared to SPECT-MPI for diagnosing underlying vascular dysfunction.[4,7] The advantage of CTA is its increased sensitivity and negative predictive value although exposure to radiation may attenuate its benefit in pregnant and/or young women. CT also exclude other causes of life threatening chest pain due to dissection and pulmonary embolism. CTA can also provide plaque characterizations.[8,9]

b) Symptomatic Low-Risk Women: For patients who are at low PPT of having IHD, ETT is an initial test if the ECG is interpretable, exercise stress ECHO can also be a reasonable test. However, in those patients with decrease PTP of IHD who cannot exercise, pharmacologic stress ECHO, CTA, or stress CMR are all reasonable for further workup if available in Pakistan (Table 4).[8]

c) Asymptomatic Intermediate-Risk Women: Table 4 Currently, ETT is recommended in assessing CV risk for asymptomatic patients with intermediate risk, while Calcium score (CAC) by CT is better test if available.[10] Stress ECHO, CTA, and CMR are not recommended for asymptomatic low- or intermediate-risk patients.[11] CAC is a useful tool to help detect subclinical atherosclerosis and provides valuable prognostic information for asymptomatic patients.[12]

d) Asymptomatic Low-Risk Women: CAC may be reasonable for risk assessment for patients at low-to-intermediate risk, while CTA, stress ECHO, nuclear MPI, and stress MRI are not recommended in this patient population (Table 4 and 5).[13,14]

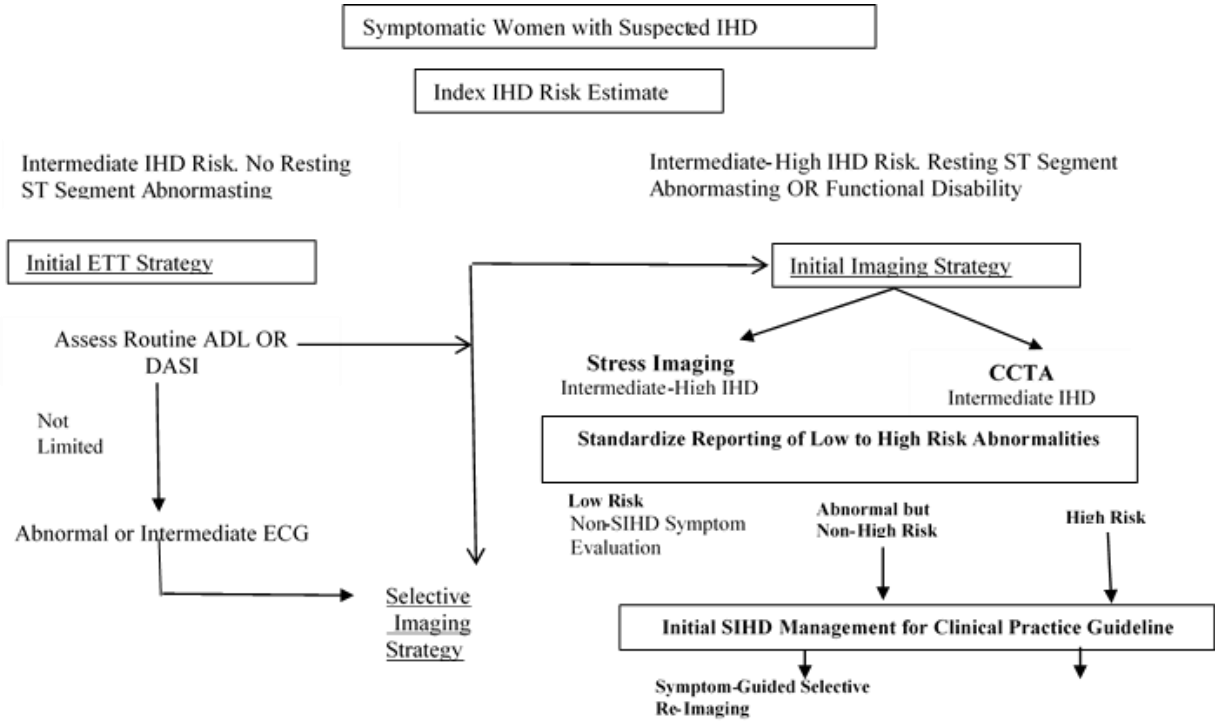

Figure 1: Diagnostic evaluation algorithm for women presenting with suspected IHD symptoms and intermediate IHD risk and intermediate-high IHD risk[3]

Table 4: Class of recommendation for Cardiac Imaging for Detection of CAD in Asymptomatic Women[8]

	Asymptomatic Intermediate Risk[1]	Asymptomatic Low Risk[1]
Exercise Stress Test	IIb	
Stress Echocardiography	III	III
Stress Myocardial perfusion imaging (MPI)	IIb	III
Coronary Artery Calcium (CTA)	IIa	IIb
Computer Tomography Angiography (CTA)	III	III
Stress Magnetic Resonance Imaging (MRI)	III	III

Table 5: Class of Recommendation for Cardiac Imaging for detection of CAD in Symptomatic Women able to exercise[4]

	Symptomatic		
	High Risk	Intermediate Risk	Low Risk
Exercise Stress Test		I	IIa
Stress Echocardiography	I	I	
Stress Myocardial Perfusion Imaging (MPI)	I	I	III
Coronary Artery Calcium (CAC)			IIb
Computer Tomography Angiography (CTA)		IIa	
Stress Magnetic Resonance Imaging (MRI)	IIa	IIa	

1.7 Acute Coronary Syndrome (ACS):[6] Table 6. Most imaging techniques have high sensitivity and specificity for the diagnostic and prognostic evaluation of the full spectrum of IHD in women Presentation of ACS is different in both gender. Women have different presentation of ACS due to different mechanisms such as MVD and SCAD[12] and less likely to have obstructive CAD[13] Demirkiran et al.[15] showed the role of CMR if available in tissue characterization after AMI and utility of CMR in detected microvascular injury in AMI. Park et al.[16] reported on LV remodeling and functional impairment in women with non-obstructed CAD using data from the WISE-CVD study. Kanaya et al.[17] showed an interesting insight into the composition of high-intensity coronary plaques observed by CMR compared with non-high intensity plaques using optical coherence tomography (OCT). IVUS and OCT (IVUS is available in major cities of Pakistan but unfortunately being used in only 20% of cases: OCT is only available in some institutions of in Punjab) have shown to provide high image resolution of the coronary artery and can guide clinical decision-making in .Women presenting with ACS have different composition of atherosclerotic plaque, including decrease plaque rupture, less necrotic core, and ↓ calcium,2 making these lesions harder to detect using traditional CA. IVUS detected calcium in 73%. While in those same vessels angiography had a sensitivity of 39%.[18] IVUS and OCT can assess arterial wall to visualize intimal tears, intra-luminal thrombi, false lumens, and intramural hematomas, therefore can help in making correct diagnosis. Experts have recommended using IVUS and OCT to assess arterial wall integrity to improve diagnosis especially when it is uncertain in women.[19]

Table 6: Class of Recommendation for Cardiac Imaging for detection of CAD in Symptomatic Women Unable to Exercise

	Symptomatic		
	High Risk[2]	Intermediate Risk[2]	Low Risk[2]
Exercise Stress Test	III	III	III
Stress Echocardiography			IIa
Stress Magnetic Perfusion Imaging (MPI)	I	I	
Coronary Artery Calcium (CAC)			IIb
Computer Tomography Angiography (CTA)		IIa	IIa
Stress Magnetic Resonance Imaging (MRI)	IIa	IIa	

1.8 Non-obstructive/Microvascular disease (MVD):[6] It is seen mostly in women a mismatch b/w the severity of obstructive CAD and the prognosis. Women have a decrease burden of obstructive CAD compared with men, but prevalence of angina and mortality from IHD is increasing for women than men. There are certain non-ischemic conditions have shown to have sex-specific differences in them in clinical presentation and occurrence. PET and CMR (these modalities are available in most part of our country and usually not utilized for such issues if we encounter in our women population) can be used to measure and quantify myocardial blood flow (MBF) and coronary flow reserve (CFR), although PET is currently considered the gold standard.[20] We should be careful in using these test in pregnant women. CMR in

pregnancy is helpful in documenting better diagnosis which can help management and that CMR should be offered to pregnant women when indicated. Further, CMR has been used to assess for sub-endocardial ischemia given its ability to distinguish sub-endocardial from epi-cardial perfusion[21] CMR not only has the advantage of lack of ionizing radiation, making it an attractive modality for women testing for myocardial ischemia, but it is a useful modality for patients who are obese. Specifically, perfusion CMR was not only feasible in more than 95% of patients with a BMI [30 kg/m^2], but provided good negative prognostic value in a 2-year follow-up period in women. The 2014 AHA Consensus Statement highlighted the development of novel diagnostic tools that have an expanded role in the evaluation of symptomatic female patients to detect not only focal epi-cardial coronary stenosis, but also non-obstructive atherosclerosis as well as the identification of ischemia resulting from MVD.

1.9 Referral to Cardiac Specialist from GPs and Non-cardiologists Treating Physician

1. Women with high and intermediate risk PTP.
2. Women with ACS.
3. Dilemma in etiology of chest pain in-stable angina and non-responding to medical therapies or change in clinical scenario from pregnant lady with chest pain.
4. Need for use of advance cardiac technologies.
5. Use of diagnostic imaging is a responsibility.

2 Cardiovascular Diseases and Cardiovascular Imaging during Pregnancy

2.1 CVDs during pregnancy: Prevalence of HD in pregnancy varies considerably between countries. According to the most recent information, 1-4% of all pregnancies in industrialized countries are complicated by CVD.[22] In Pakistan, 1% of all pregnancies are complicated by HD and 69% are caused by rheumatic heart disease (RHD).[23] According to another study from Pakistan the most common cardiac disease in pregnancy is RHD.[24]

a) Valvular heart disease (VHD): In Pakistan, patients with mitral stenosis or with heart valve replacement are the most common cases of HD during pregnancy.[24] Most women with less severe valve disease tolerate pregnancy well, some valve lesions are considered contraindicated: severe mitral stenosis MS, severe symptomatic aortic stenosis (AS), and any valve disease associated with LV dysfunction and/or PH. All such women should be diagnosed preconception and if diagnosed antepartum should be women with these conditions should receive stringent f/u with cardiac imaging and treatment.

b) Complex congenital heart disease (CHD): Such as Fontan circulation, systemic right ventricle and uncorrected cyanotic CHD are associated with increased maternal and fetal risk.

c) Peri-partum cardiomyopathy (PPCM): In Pakistan, younger women with higher parity and pregnancy-induced HTN are at increased risk of PPCM.[25] Although prognosis is more favorable in PPCM than in other CMP, it is associated with significant mortality (<5-50%) and morbidity.

2.2 CV Imaging during pregnancy: Number of diagnostic cardiac imagings are available for the pregnant woman to evaluate cardiac anatomy and function. These include Echo, cardiac MRI, CT scanning, nuclear imaging, and Right heart catheterization (RHC) /Left heart catheterization (LHC). In case of non-cardiologist physicians and obstetricians they should take clinical history and do physical examinations and can make a provisional diagnosis. What we have described in this is how and when such suspected HD patients should be sent to cardiologist for advance imaging to confirm the existing diagnosis and severity, so future management plan on the disease and obstetric/obstetrics plan could be finalized for such patients.

2.3 Ionizing radiation and pregnancy: Side effects of ionizing radiation include 1) genetic consequences 2) carcinogenesis and 3) teratogenic effects on the developing embryo or fetus. The reported dose of radiation with consequent increase incidence of birth defects or miscarriage is above 200 mSv. An important determinant of the consequence of radiation exposure in pregnancy is the stage in which the radiation exposure occurs.[26,27] The accepted cumulative dose of ionizing radiation during pregnancy is 5 rad (equal to 50 mSv).[28] CV diagnostic studies involving radiation do not reach these levels but should be avoided if possible.

a) Echocardiography:

TTE: TTE is by far the preferred diagnostic test for cardiac imaging[29] during pregnancy, when a cardiac diagnosis is suspected.

TEE: TEE is relatively safe during pregnancy[30] although its uses should be restricted to circumstances where a TEE study is necessary. Pregnant women have increased risk of vomiting and aspiration. Sedation may best be handled with the help of anesthesiologist.

b) Cardiac Magnetic Resonance (CMR) Imaging: In case of technically difficult ultrasonography which is unable provide adequate diagnostic information, and better imaging is required to optimize management in the pregnancy, CMR can be performed during pregnancy.[31-33] No untoward side effects of MRI on the fetus have been reported. CMR should be avoided in the first trimester if possible. The use of gadolinium, a class C drug, should be avoided.[34-36]

c) Cardiac Computed Tomography (CCT): Safety issues with CT differ with gestational age in context with radiation exposure/contrast agent effect of the mother and the fetus. Fetal risks of anomalies, growth restriction, or spontaneous abortions do not appear to be ↑ with radiation exposure of less than 50mSv, a level that is above the range of exposure for the diagnostic procedures.[36] Currently used low-osmolality iodinated contrast agents are category B drugs and can be used when needed.[37]

d) Cardiac Catheterization:

RHC: RHC may be necessary to accurately measure the PAP and the pulmonary vascular resistance if management of the patient is to be altered. RHC requires minimal or no fluoroscopy.

LHC: LHC would be required in women with VHD undergoing mitral balloon valvuloplasty or aortic valvuloplasty. Such procedure should only be taken in high risk pregnant women presenting with HF.

Coronary angiography (CA): During pregnancy its use is not frequently required except in ACS and spontaneous coronary artery dissection if it occurs in pregnant women.[36,37] Higher age during pregnancy can increase in the prevalence of cardiac RFs which can increase risk of complications during pregnancy, delivery and peripartum period.

e) Nuclear Imaging: Most of nuclear imaging studies are not performed during pregnancy due to the concern for exposure to radiopharmaceuticals, except for ventilation–perfusion imaging for the diagnosis of pulmonary embolism.

f) Stress testing: Exercise ECHO is preferred over nuclear imaging studies as stress testings due to radiation exposure and radiopharmaceutical agents required.[32,35] Use of dobutamine stress echocardiography (DSE) during pregnancy is debatable(its use can be associated with hemodynamic complications) and can only be used for women who are unable to exercise. Dobutamine is a class B drug.[37] During pregnancy DSE should be avoided, whenever possible.[32] Diagnosis of this entity is cornerstone for the improved outcomes of the females with HF.

Table 7: Cardiovascular Imaging during pregnancy

Test	Safety	Trimester	Indication
Echo (TTE)	Safe	Safe in all trimesters	Cardiac symptoms - SOB, CP, Syncope, Palpitation (Class I, Level C) Arrhythmias Known HD (Class I, Level C) Stroke of unknown etiology Prior history of chemotherapy or radiation
TEE	Safe	Safe in all trimesters	Before or during PTMC (Class I, Level C) Aortic dissection (Class I, Level C)
CMR	Safe	Should be avoided in the first trimester if possible. Gadolinium should be avoided	When echo is insufficient for a definite diagnosis (Class IIa, Level C) Myocarditis, CMP Complex congenital heart disease Aortic dissection (Class I, Level C)
Cardiac CT	Relative	Should be avoided in all if possible (especially before 20 weeks, 8-15weeks is the most sensitive period)	Suspected pulmonary embolism Aortic dissection (when TEE or CMR not available) Trauma involving aorta
Cath (Fluoroscopy)	Relative	Should be avoided in all if possible (especially before 20 weeks, 8-15weeks is the most sensitive period)	RHC when accurate measurement of pulmonary artery pressure is necessary for management. (Class I, Level C) LHC for mitral balloon valvuloplasty or aortic valvuloplasty during pregnancy, only in highly symptomatic women presenting with HF. Coronary angiography in case of coronary dissection or STEMI. (Class I, Level C)
SPECT/PET	Relative	Should be avoided in all if possible (especially before 20 weeks, 8-15weeks is the most sensitive period)	Ideally should be avoided except the ventilation perfusion scan for suspected PE as an alternative to CTPA
Stress test	Safe with exercise	Safe in all trimesters	Chest pain or cardiac symptoms with suspicion of ischemia Exercise echo is preferred when imaging is required DSE should be avoided whenever possible

Table 8: Cardiac diseases during pregnancy and recommended Cardiovascular Imaging

Diseases	Echocardiography	Additional tests
Pre-existing heart disease	Evidence of pre-existing valve disease or congenital defects	May consider CMR
PPCMP	LV and/or RV dysfunction	May consider CMR
Pulmonary embolism	RV dysfunction and elevated pulmonary pressures, McConnell's sign	CTPA or ventilation perfusion scan
Pregnancy associated MI	Regional wall motion abnormalities	Coronary angiography
Myocarditis	Global or regional hypokinesis	CMR for confirmation

Computed tomographic pulmonary angiography; MI: Myocardial infarction, CMR: Cardiac magnetic resonance imaging; LV: Left ventricle; RV: Right ventricle; CTPA

3 Cardiac Imaging in Women with Non-Ischemic Cardiomyopathy (CMP)

3.1 Introduction: CMP is a group of diseases affecting myocardium leading to clinical manifestation of HF. It has been broadly divided as ischemic and non-ischemic on the basis of presence or absence of obstructive CAD. Its classified as shown in figure below by ESC.[38] Figure 2 shows the European classification of the non-ischemic CMP.

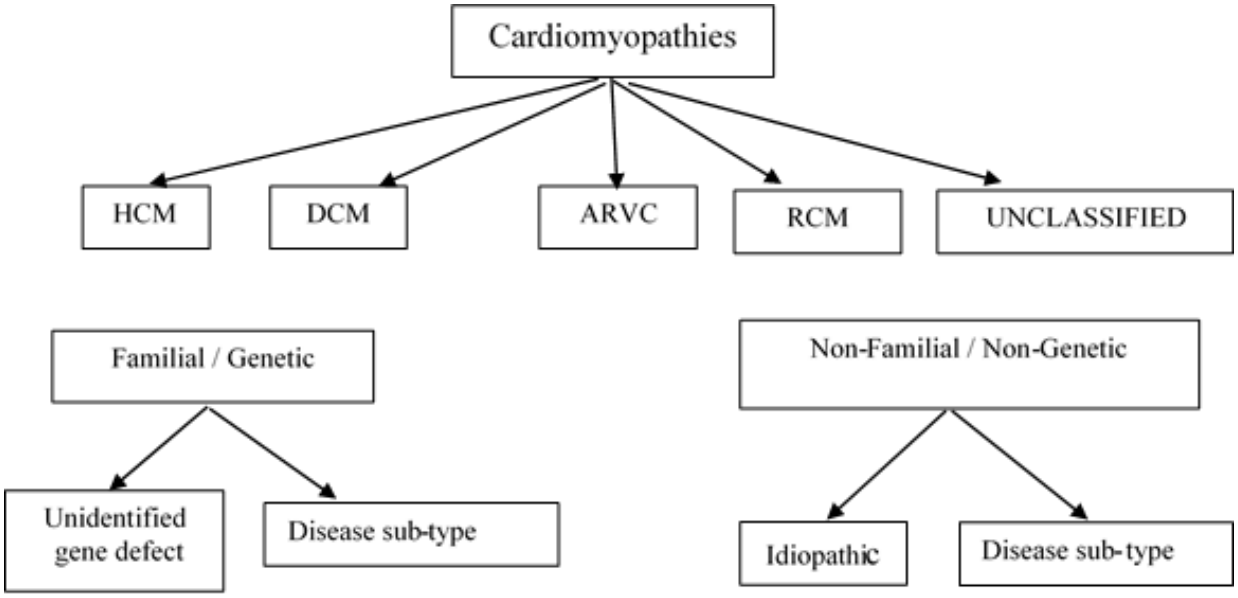

Figure 2: The European classification of the non-ischemic CMP
ARVC, arrhythmogenic RV CMP; DCM, dilated CMP; HCM, hypertrophic CMP; RCM, restrictive CMP

3.2 Prevalence, Prognosis and Gender Differences: Prevalence of non-ischemic CMP is different in different geographical areas, study population subtypes and the type of CMP, ranging from 2% to 15%.[39] Data from Pakistan shows 1.57% prevalence of CMP with dilated CMP being the most frequent type (66%) followed by HCM (8%).[40] Although CMP is found to be more common among the males but restrictive CMP is more prevalent among the females.[40] Peripartum cardiomyopathy(PPCMP) is frequent CMP in females with prevalence rate of 11% among Pakistani population.[41] The overall prognosis of non-ischemic CMP is better than ischemic CMP. So, the more quickly and accurate diagnosis of this entity is cornerstone for the improved outcomes of the females with HF.

3.3 Imaging Recommendation in Different Non Ischemic CMP Sub-types: Imaging recommendation for non- ischemic CMP starts with good history taking and physical examinations. After this GPs and non-cardiologist physicians can go for ECG, laboratory test (for confirming the diagnosis and exclusion of HF) X-ray chest once a provisional diagnosis of HF is made, proceed to confirming the etiology/ severity. For this it needs more sophisticated imaging's for establishing the management of the patients. So GPs and non-cardiologist physicians can think of referring it to cardiac centers.

X-ray: X-rays are of limited use in CMP. They are mainly performed to rule out pulmonary pathology for the symptoms. X-rays should be avoided in females whenever possible to reduce radiation exposure.

a) **Dilated CMP:** TTE is appropriate initial modality for the diagnosis and etiologic evaluation of female with suspected dilated CMP.[42,43] Repeat TTE is appropriate in the case of change in clinical status or for the determination of therapy response.[43] TTE is also appropriate before planning the device therapy in female patients with OMT of DCM.[43] Stress imaging and CT are appropriate to rule out obstructive CAD in patients with intermediate pre-test probability.[43] CMR with gadolinium enhancement is appropriate to differentiate different etiologies and determining the prognosis of DCM.[43] It is reasonable to prefer CMR in female patients on other imaging modalities requiring radiation to reduce radiation exposure.[44] FDG PET scan combined with other imaging modalities e.g.

CMR, CT is reasonable for the diagnosis in suspected cases of myocarditis and sarcoidosis with inconclusive other testing and high clinical suspicion.[45] Coronary angiogram (CA) is reasonable to rule out obstructive CAD in females with intermediate or high pre-test probability in patients with suspected dilated CMP.

b) HOCM (Hypertrophic Obstructive CMP): TTE with strain imaging is appropriate initial test in female patients with suspected HOCM.[42,46,47] Repetition of TTE at periodic interval in genotype positive phenotype negative females is appropriate.[48] TTE is appropriate screening tool for the first degree relatives of with HCM.[46] Periodic TTE (1-2 years in adolescent and 3-5 year in adults) is appropriate for children of patients with HCM, starting from puberty or before participating in intense competitive sports or with f/o of SCD.[45] Repetition of TTE is appropriate in case of change in clinical status.[46] Repetition of TTE is appropriate after alcohol septal ablation or surgical myomectomy. Exercise TTE is reasonable for the quantification of dynamic LVOT obstruction in the absence of significant LVOT gradient.[44] TEE is reasonable in cases of inconclusive TTE.[46] CMR is appropriate in cases of inconclusive ECHO.[45] CMR is reasonable for the risk stratification of SCD in cases of inconclusive conventional RFs.[45,46] CMR imaging is reasonable to differentiate the different causes of hypertrophy (e.g. cardiac amyloidosis and Fabry disease) if the clinical suspicion is high.[46,47] CT scan may be done in cases with high suspicion of HOCM when other tests are either inconclusive or contraindicated.[47] Invasive angiography or coronary cardiac CT should be done before surgical myomectomy.[46]

c) Restrictive CMP: Echo with diastology is an appropriate initial modality for the diagnosis and subtype evaluation of RCM.[42,46] Tissue tracking and speckle Doppler ECHO is reasonable for the diagnosis and subtype evaluation of RCM.[42,47] CMR is appropriate for the diagnosis and subtype evaluation in patients with inconclusive ECHO.[46] CMR is also appropriate to differentiate restrictive CMP from restrictive physiology cause by constrictive pericarditis in patients with inconclusive ECHO.[46] CMR should be preferred over invasive imaging for hemodynamic assessment in female patient to decrease radiation exposure.[46] CCT may be used to determine pericardial thickness and so to differentiate restrictive CMP from constrictive pericarditis.

d) Arrhymogenic Right Ventricular Cardiomyopathy (ARVC): TTE is appropriate initial test in female patients with suspected ARVC.TEE is appropriate in females with suspected ARVC with inconclusive TTE. CMR is appropriate for the confirmation of echo diagnosis of ARVC or with the inconclusive ECHO in females with suspected ARVC.[44] CT scan may be done in cases with high suspicion of ARVC when other tests are either inconclusive or contraindicated.[44]

e) Takotsubo CMP: TTE is appropriate initial modality in post-menopausal females with clinical presentation of ACS to rule out Takotsubo syndrome.[49] Repeat TTE is appropriate in the case of change in clinical status or for the determination of therapy response and improvement of LV function.[47] TTE is appropriate in females with Takotsubo syndrome for the evaluation of complications like LVOT obstruction and MR.[47] Strain imagining is appropriate for the assessment of regional dysfunction and its recovery.[47] CMR with gadolinium is reasonable to differentiate ischemic versus non-ischemic aetiology of regional wall motion abnormalities.[47] CA is reasonable to rule out obstructive CAD in patients with suspected Takotsubo syndrome.[47]

f) Peripartum Cardiomyopathy (PPCMP): TTE is appropriate initial modality in female with last month of pregnancy and post-delivery for the five months if presenting with shortness of breath to rule out PPCMP.[47] Repeat TTE is appropriate in the case of change in clinical status or for the determination of therapy response and improvement of LV function.[47] CMR is appropriate modality for the diagnosis and differential diagnosis of PCMP in the cases with inconclusive ECHO.[47]

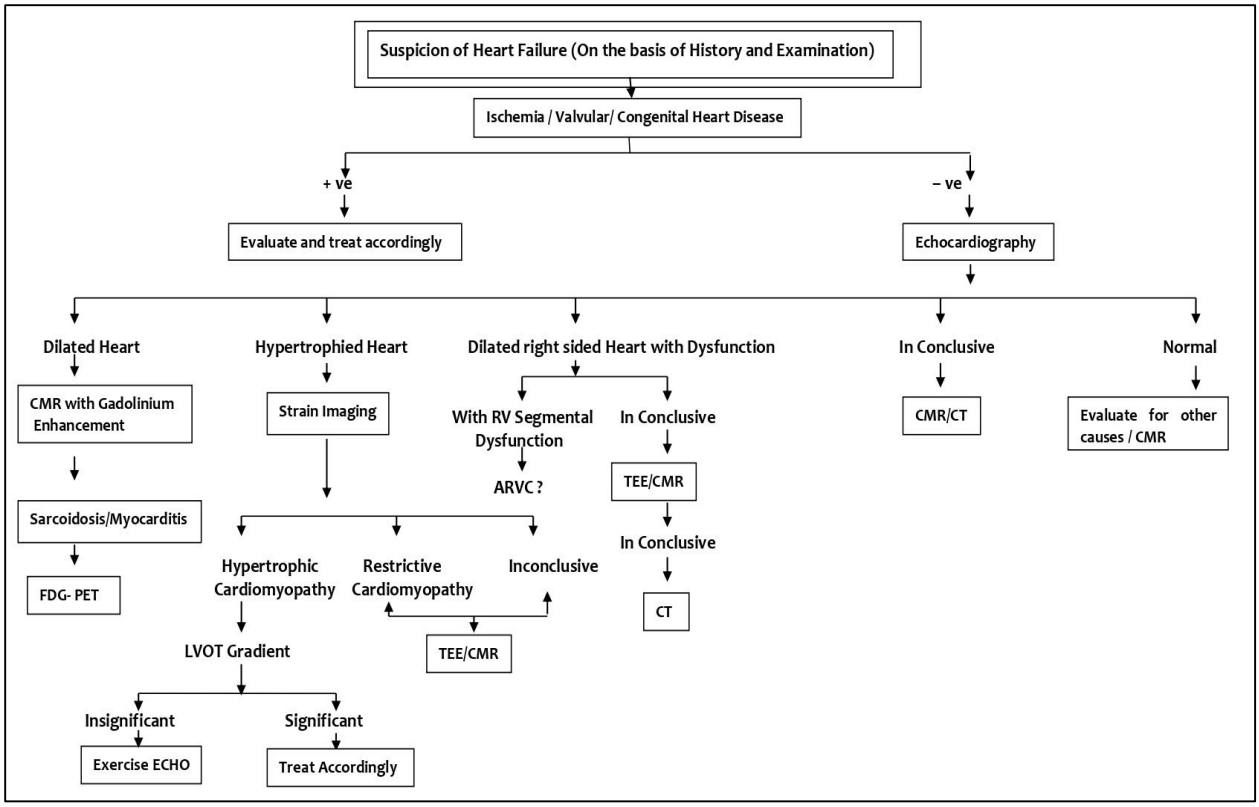

Figure 3: Schematic representation of imaging guidelines in non-ischemic cardiomyopathy

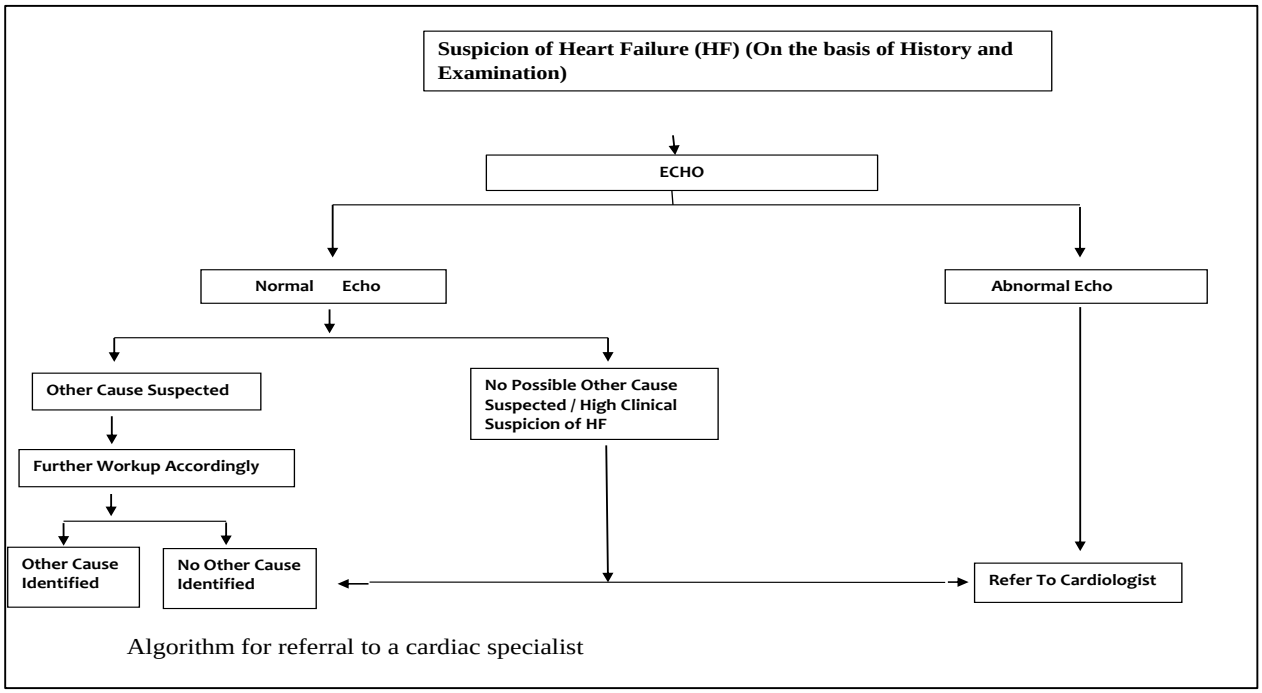

Figure 4: Algorithm for referral to a cardiac specialist

4 Use of Cardiac Imaging Techniques in Women with Cancer Treatments and Cardiovascular Toxicity

4.1 Introduction: Cancers are seen to increase its incidence in both the genders in Pakistani population include breast (23%), lip and oral cavity (8.6%), lung (4.6%), non-hodgkin lymphoma (4%) and colorectum (3.6%). Deaths due to different cancer include breast (16.1%), lip and oral cavity (7.2%), lung (5.9%), esophagus (4.7%) and non-hodgkin lymphoma (4.3%). The most prevalent, frequently diagnosed and top most cause of cancer death in female population is breast cancer.[48] CV complications of cancer therapy are, myocardial dysfunction and HF, CAD, VHD, Arrythmias, HTN, Thromboembolic disease, PAD, stroke and PAH.

Cardiac dysfunction is now a growing health issue during and after cancer treatment therapy. Its recommended now that it should be dealt with in some multidisciplinary center. Current advance cancer therapies have significantly improved the survival rate in cancer patients in women with breast cancer; the 5-year survival for early stage breast cancer increase from 79% in 1990 to 88% in 2012.[49,50] In a recent comprehensive review of breast cancer survivors, deaths due CVD is seen more in women to their chemo and radiations treatment and exceeding their risk of death from the initial cancer itself or from recurrent disease.[48,51] Doxorubicin-induced cardiotoxicity is widely known to occur at cumulative doses exceeding 450 mg/m^2 however local data suggest, the incidence of subclinical cardiac dysfunction was increase with doxorubicin in the cumulative dose range of 300–450 mg/m^2.[52,53] Concomitant use of cyclophosphamide, low BMI (<20 kg/m^2) and preexisting cardiac disease showed a trend towards increase risk of cardiac dysfunction.[54,55] Another issue we encounter is the long delay b/w exposure and clinical manifestation of HD, the use of concomitant cardiotoxic chemotherapy, continuous improvements in radiation techniques and changes in the treated population and failure to attribute cardiac disease to previous radiotherapy despite increase awareness of CV physicians of its long-term side effects. In patients with breast cancer treated in the era 1980–2000, the risk of cardiotoxicity was increase in patients treated with both left breast radiotherapy and cardiotoxic chemotherapy, suggesting a synergistic effect on cardiac risk.[48,51] Marked interstitial myocardial fibrosis had evidence of DD, systolic dysfunction is generally observed when radiotherapy is combined with anthracyclines. HF may aggravate with associated VHD and CAD, which may have developed later on in these treated patients.

Table 9. The incidences of LV dysfunction with different anti-cancer drugs

Chemotherapeutic agent	Incidence
Anthracyclines(dose dependent)	
Low dose	3-5%
High dose	18-48%
Alkalating agents	
Cyclophosphamide	7-28%
Ifosamide	17%
Antimetabolites	
Clofarabine	27%
Antimicrotubules agents	
Docetaxel	2.3-10%
Paclitaxel	<1%
Monoclonal antibodies	
Trastuzumab	1.7 to 20%
Small molecules tyrosine kinase inhibitors	
Dosatinib	2-4%
Imitanib	0.5-1.5%
Lapatinib	1.5-2.2%
Sunitinib	2.7-11%
Proteosome inhibitors	
Carfilzomib	11-25%
Bortezomib	2-5%
Miscellenious	
Everolimus	<1%
Temsirolimus	<1%

4.2 Definition of cancer therapeutics–related cardiac dysfunction (CTRCD): CTRCD as a decrease in the LVEF of >10 percentage points, to a value <53% (normal reference value for 2D) 2DE. The repeat study should be performed 2 to 3 weeks after the baseline diagnostic study showing the initial decrease in LVEF.[54] Repeat ECHO is needed at different interval to detect LVEF decrease which may be further categorized as symptomatic or asymptomatic, or with regard to reversibility.

4.3 Vascular complications of chemotherapeutics: The newer anti-cancer drugs which inhibit vascular endothelial growth factor signaling are also associated with CV pathology, especially HTN, thromboembolism, MI, and proteinuria.[55]

4.4 Risk Assessment of Cardiac Dysfunction: A baseline CV risk assessment is essential.[56] Many strategies have had been developed in previous decades. Two of them evolved over time to be very useful: endo-myocardial biopsies and monitoring of LVEF by cardiac imaging. Echo is now widely available, cheap in Pakistan. CT is very helpful for the assessment of coronary anatomy, MRI to detected MPI abnormalities, scarring and early signs of myocardial damage such as edema and beginning fibrosis. Nuclear medicine can image perfusion abnormalities, cell death and alterations in metabolism and innervation.[57] Myocardial deformation imaging

and 3D volumetric analysis seem to be optimal techniques to address temporal structural and functional changes during cancer therapy.[58] very important that the same imaging modality should be used for all screening throughout the treatment pathway. Switching b/w modalities or assays should be avoided.

It's very important to have awareness on the cardiotoxicity effects of chemotherapeutic agents and radiation CV RFs control is important in mitigating cardiotoxicity risk in our female patients. Assessment of patient- and treatment-specific risk with appropriate CV surveillance is another key component of care. Mismatch between baseline cardiotoxicity risk and intensity of cardiotoxicity surveillance can lead to an unnecessary downstream testing, increase healthcare expenditure, and interruption or discontinuation of potentially life-saving treatment.

4.5 Echo evaluation of cardiac structure and function in the cancer patient: Echo is the method of choice for the evaluation of patients before, during and after cancer therapy. Calculation of LVEF ideally by 3DE, when using 2DE, the modified biplane Simpson technique is the method of choice.

- In the absence of global longitudinal strain (GLS) by STE, quantification of LV longitudinal function using mitral-annulus displacement by M-mode echocardiography, and/or peak systolic velocity (s') of the mitral annulus by pulsed-wave DTI is recommended.
- The use of myocardial contrast agents could be potentially useful in chemotherapy patients when endocardial drop out occurs.
- Other parameters to be measured by echocardiography are diastolic function, RV assessment, valvular pathologies, pericardial diseases like constriction, effusion and tamponade due to metastasis and radiotherapy should be addressed.
- Stress echocardiography may be helpful in the evaluation of patients with intermediate or high pre-test probability for CAD.

Of those exposed, some will develop abnormalities in myocardial strain early on, and then an ↑ in extracellular volume (ECV). A subset of patients will progress to a ↓ of LVEF, and a subset of these will have a ↓ left ventricular mass with the worst outcome.[59]

4.6 Valvular disease: VHD is frequently observed in patients with cancer due to radiotherapy, infective endocarditis, pre-existing valve lesion, or secondary to LV dysfunction.[53,57] Approximately 10% of patient treated with radiation develop a relevant VHD during lifetime.[57] In patients with Hodgkin lymphoma, a relationship b/w radiation dose to the heart and development of valvular events after treatment has been described, especially at doses >30 Gy.[60] Echo is useful modality in making its diagnosis.

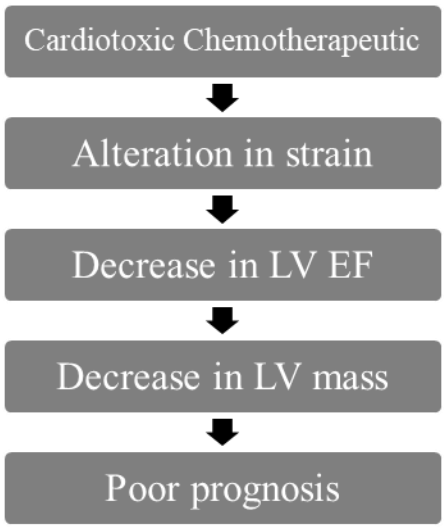

Figure 5: Progression in LV dysfunction in adult patients undergoing anthracycline therapy

4.7 Detection of sub-clinical LV dysfunction

- LVEF assessed by 2DE, often fails to detect small changes in LV contractility.
- A 10% to 15% early decrease in GLS by STE appears to be the most useful parameter for the prediction of cardiotoxicity, defined as a drop in LVEF or heart failure.[52,60]
- Myocardial deformation (strain) can be measured using Doppler tissue imaging or 2D STE.
- GLS is the optimal parameter of deformation for the early detection of sub-clinical LV dysfunction.[61,62]

Other imaging modalities

- The calculation of LVEF by MUGA is highly reproducible. The main limitations are radiation exposure and the lack of ability to report on pericardial and VHD and RV function.
- The newer and most commonly used dual head gamma cameras are not frequently used due to its debatable reproducibility.
- Main issue with CMR is its limited availability in our country. It's the gold standard for the evaluation in the evaluation of LV and RV volumes and LVEF. Its particularly helpful in situations where discontinuation of chemotherapy is being entertained, and/or when there is concern

regarding echo or equilibrium radionuclide angiocardiography calculation of LVEF.

- Electromagnetic interference from CMR should be kept in mind especially in patients with breast cancer in whom tissue expanders placed for breast reconstruction may represent a hazard.
- It is important to important to remember that the same technique should be performed for baseline assessment and follow-up studies during and after cancer treatment.
- CT scan if suspected metastasis or pericardial involvement.

Now we have greatly advanced in developing field of cardio- oncology in Pakistan too which can provide highly sensitive methods for timely diagnosis of cardiotoxicity. Cardiac dysfunction is a growing health concern during and after well-developed cancer therapy and should be addressed in a multidisciplinary setting. Advanced modalities like myocardial deformation imaging and 3D volumetric analysis seem to be optimal techniques to address temporal structural and functional changes during cancer therapy. The intensity of echo monitoring, coordination with cardiac biomarkers monitoring, should be based on the individual risk of cardiotoxicity, all these requires collaborative evaluation by the cardio- oncology team.

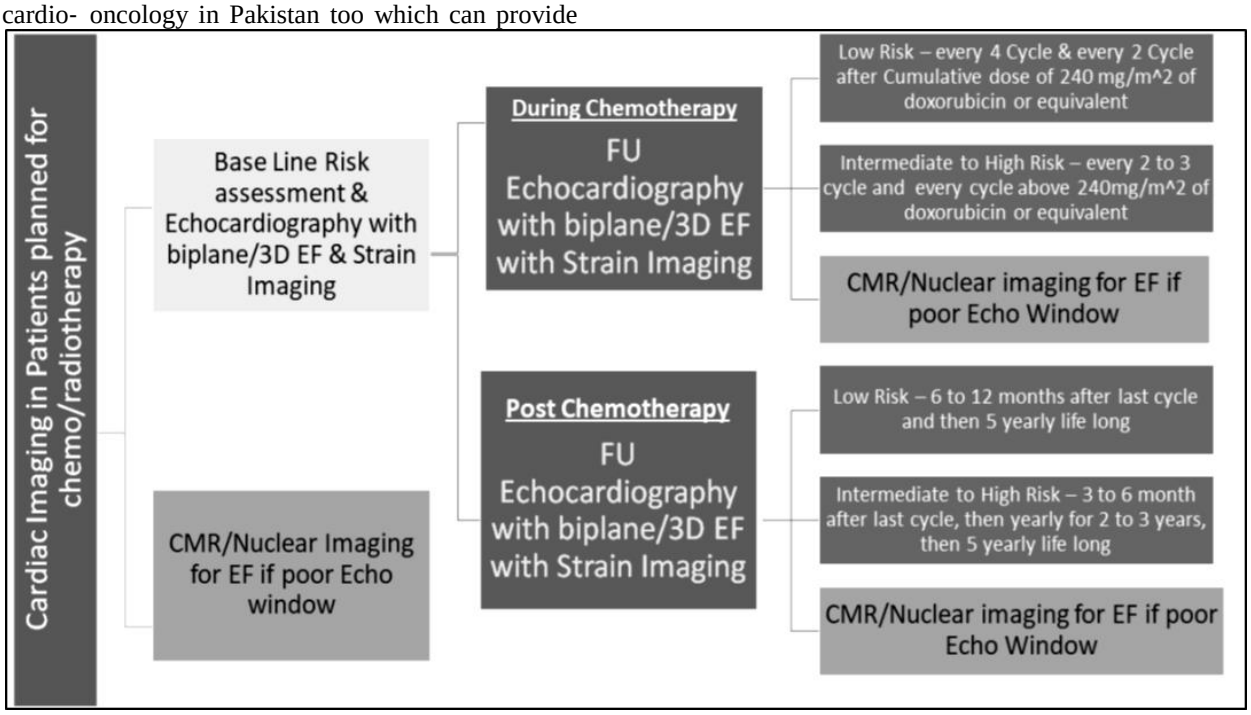

Figure 6: Strategies for screening and detection of cardiotoxicity

5 Cardiac imaging in women with Connective Tissue Disorders (CTD)

5.1 PICO Question: P- In women with Cardiac disease solely due to Connective Tissue disorders I+C- How various imaging modalities should be utilized O- for optimum evaluation of cardiac disease.

CTD also called collagen vascular disorders are a heterogenous group of over 300 immunologically mediated multisystem disorders while sharing some fascinatingly common clinical dermatologic, arthritic, pulmonary and cardiac, and laboratory features.[63] The relative frequency and distribution of these features divides them into some distinctive groups of conditions of arthritides namely rheumatoid arthritis, ankylosing spondylitis, vasculitides- such as mixed connective tissue disorder, dermatoses such dermato-myositis, polymyositis, progressive systemic sclerosis, and miscellaneous conditions such as Sjogren syndrome, Sarcoidosis and Systemic lupus erythematosus.[63] The prevalence of these conditions in Pakistan is 0.55- 1% according to hospital-based studies with a female preponderance and RA, SLE and PSS being the commonest.[64] The ↑ frequency in women is considered to be an estrogenic effect, ↑ the CV mortality risk.[65] The pathophysiology is a myriad and variable combination of direct immune/ vasculitis mediated damage to myocardium and pericardium, premature atherosclerosis- mediated myocardial damage, valvular vegetation, and PH resulting from interstitial lung disease, the end result is a HF with preserved left ventricular ejection (PLVEF) at a relatively younger age.[66] The manifestations themselves and their optimum imaging are therefore complex, interrelated and overlapping.

Many modalities may be used for the purpose depending upon the clinical manifestations. Echo is often the baseline investigation utilized for the purpose of visualizing the structure of chambers, valves, origin of great arteries, wall movement, Doppler flow and EF%. Though it is operator dependent, the modality is radiation- free. Recently, s speckle- tracking strain echo technique was reported to be able to demonstrate the LV systolic dysfunction in systemic sclerosis.[67]

5.2 Imaging modalities for evaluation of cardiac disease in rheumatic heart disease (RHD): Myocardial perfusion defects presence extent and reversibility are classically studied by various kind of nuclear studies which include MPS, MIBI and Thallium SPECT. These have been utilized for evaluation of women with SLE at risk of premature atherosclerosis with success.[68] Cardiac MRI (CMR) is rapidly assuming the position of one-stop solution for evaluation of myocardium, pericardium, great vessels and coronary abnormalities despite its cost. This is due to excellent tissue characterization, combined with functional and perfusion evaluation. There is a growing body of evidence that MRI provides the details of myo-pericarditis, vasculitis, CAD including spontaneous dissection, myocardial fibrosis, PH, aortic valvular and vascular lesions and HF.[66,67] Even silent disease can be unraveled.[69] Mapping of myocardial disease is also feasible.[70] PH is basically caused by the ILD and the vasculitis. The best modality for evaluation of ILD is CT scan, particularly HRCT. Hence studies have advocated early -stage echocardiography and CT scan should be used to detect potential CV including PH in patients with CTDs.[70] Premature atherosclerosis contributes to the CV morbidity risk in patients with CTD. The recommended screening modality for those with suspected atherosclerotic CAD is carotid artery Doppler ultrasound which evaluates the intimal plaques and their morphology quite nicely, predicting the risk of CAD.[71,72] There is no difference in the imaging modalities used for this purpose in men and women except that evaluation of a pregnant woman would require the use of non-ionizing radiation studies such as echo and cardiac MRI.

Table 10: Cardiac manifestations of CTD and optimal imaging modalities

Manifestation	Imaging Modality	Main use
Pericardial effusion	Echo, CT scan	Detection, quantification
Ventricular dysfunction, myocardial ischemia and myocardial fibrosis	CMR	Detection, evaluation of extent, Better for subclinical disease
	Nuclear studies	Reversibility of ischemia
Pulmonary embolism (PE)	CTPA	Contrast imaging for suspected PE only
MPA dilatation	CMR, CT scan	Diagnosis, follow up of ILD which are the root cause
Premature atherosclerotic CAD	Carotid ultrasound and CTCCS	Screening for premature atherosclerosis
Spontaneous coronary artery dissection	MRI	Good for subclinical disease
Aortic valvular and vascular disease	Echo, MRI	

Table 10 summarizes the main CV abnormalities which may be imaged in patients with CTD and the optimal imaging modality for the purpose. One potential limitation is that RA, SLE and SS have been the most studied and imaged conditions among the group and extrapolation on other less common conditions requires careful consideration of costs, risks and benefits.

For the non-cardiologist physician, a thorough history, physical examinations, laboratory test and preliminary diagnostic picture should be obtained. Once the diagnoses of CTD is made and there is suspicion of cardiac disease, basic cardiac imaging like x-ray, and echo should be requested. For specialized imaging requirements, make a referral to specialist cardiologist or the specialized tertiary care cardiac imaging center.

The suspicious findings that need further evaluation by a specialist are presence of;

- Large pleural effusion on baseline x-ray requiring drainage,
- Pericardial effusion,
- Acute chest pain with dyspnea that requires exclusion of pulmonary embolism and acute coronary syndrome, and
- Progressive dyspnea without orthopnea, requiring HRCT for evaluation of pulmonary fibrosis or diffuse interstitial lung disease

5.3 Conclusion: This local practice guideline document has been endorsed by Council members of GRW-P and PCS. Our intent was that this preliminary review detailed document on cardiac imaging for our local female population with HD may serve as a foundation and prototype for future local clinical practice recommendations and if possible may develop local statement guidelines. This document may help in transformation to clinical practice and care for our women and eventually would also help in the limited use of resources in Pakistan. Our next aim is to review/ and write every 1 to 2 years for adding on our own local data if available and any new data from international literatures on cardiac imaging's for women.

REFERENCES

1. Rybicki FJ, Udelson JE, Peacock WF, Goldhaber SZ, Isselbacher EM, Kazerooni E, et al. 2015 ACR/ACC/AHA/AATS/ ACEP/ASNC/NASCI/SAEM/SCCT/SCMR/SCPC/SNMMI/ STR/STS appropriate utilization of CV imaging in emergency department patients with chest pain. J Am Coll Cardiol. 2016;67(7):853-79.
2. Chow CK, Patel AA. Women's cardiovascular health in India. Heart. 2012;98(6):456-9.
3. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of cardiology Foundation appropriate use criteria Task force, American heart association, American Society of echocardiography, American Society of nuclear cardiology, heart failure Society of America, heart rhythm Society, Society for cardiovascular angiography and interventions, society of cardiovascular .... J Am Coll Cardiol. 2014;63(4):380-406.
4. Mieres JH, Gulati M, Bairey Merz N, Berman DS, Gerber TC, Hayes SN, et al. Role of noninvasive testing in the clinical evaluation of women with suspected IHD: a consensus statement from the AHA. Circulation 2014;130:350-79.
5. Edvardsen T, Haugaa KH, Petersen SE, Gimelli A, Donal E, Maurer G, et al. The year 2019 in the European Heart Journal—Cardiovascular Imaging: part I. Eur Heart J Cardiovasc Imaging. 2020;21(11):1208-15.
6. Paynter NP, Chasman DI, Paré G, Buring JE, Cook NR, Miletich JP, et al. Association between a literature-based genetic risk score and cardiovascular events in women. JAMA. 2010;303(7):631-7.
7. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012 Dec 18;126(25):e354-471.
8. Jaarsma C, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. J Am Coll Cardiol. 2012;59(19):1719-28.
9. Nakazato R, Shalev A, Doh J-H, Koo B-K, Dey D, Berman DS, et al. Quantification and characterisation of coronary artery plaque volume and adverse plaque features by CCTA: a direct comparison to intravascular ultrasound. Eur Radiol. 2013;23(8):2109-17.
10. Park HB, Heo R, o´ Hartaigh B, Cho I, Gransar H, Nakazato R, et al. Atherosclerotic plaque characteristics by CT angiography identify coronary lesions that cause ischemia. JACC Cardiovasc Imaging. 2015;8(1):1-10.
11. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the AHA Foundation/AHA task force on practice guidelines. J Am Coll Cardiol. 2010;56(25):e50-103.
12. Church TS, Levine BD, McGuire DK, LaMonte MJ, FitzGerald SJ, Cheng YJ, et al. CAC score, RFs, and incident CAD events. Atherosclerosis. 2007;190(1):224-31.
13. Shaw LJ, Bugiardini R, Merz CNB. Women and IHD. J Am Coll Cardiol. 2009;54(17):1561-75.
14. Zhou W, Lodhi F, Srichai MB. Role of Cardiac Imaging in Cardiovascular Diseases in Females. Curr Radiol Rep. 2017;5(10):1-5.
15. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, et al. Emergence of nonobstructive CAD. J Am Coll Cardiol. 2015;66(17):1918-33.
16. Prati F, Regar E, Mintz GS, Arbustini E, Di Mario C, Jang I-K, et al. Expert review document on methodology, terminology, and clinical applications of OCT: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. Eur Heart J. 2010;31(4):401-15.
17. Demirkiran A, Everaars H, Amier RP, Beijnink C, Bom MJ, Go¨ tte MJW et al. CV magnetic resonance techniques for tissue characterization after acute myocardial injury. Eur Heart J Cardiovasc Imaging. 2019;20:723-34.
18. Park S-M, Wei J, Cook-Wiens G, Nelson MD, Thomson L, Berman D, et al. Left ventricular concentric remodelling and functional impairment in women with ischaemia with no obstructive CAD and intermediate coronary flow reserve: a report from the WISE-CVD study. Eur Heart J Cardiovasc Imaging 2019;20:875-82.
19. Lansky AJ, Ng VG, Maehara A, Weisz G, Lerman A, Mintz GS, et al. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in ACS. JACC Cardiovasc Imaging. 2012;5(3 Suppl):62-72.
20. Mann DL, Zipes DP, Libby P, Bonow RO, Braunwald E. Braunwald's heart disease. 10th ed. Philadelphia: Elsevier Saunders; 2015.
21. Bratis K, Mahmoud I, Chiribiri A, Nagel E. Quantitative myocardial perfusion imaging by CV magnetic resonance and . J Nucl Cardiol. 2013;20(5):860-70.
22. Weiss BM, von Segesser LK, Alon E, Seifert B, Turina MI. Outcome of CV surgery and pregnancy: a systematic review of the period1984-1996. Am J Obstet Gynecol. 1998;179:1643-53.
23. Wasim T, Amer W, Majrooh A, Siddiq S. Foetomaternal outcome of pregnancy with cardiac disease. JPMA. 2008;58:175-8.
24. Nassar AH, Bobeika EM, Abd Essamad HM, Taher A, Khalil AM, Usta IM. Pregnancy outcome in women with prosthetic heart valve. Am J Obstet Gynecol 2004;19:1009-13.
25. Munir R, Hussain S, Kayani AM. Peripartum CMP in a Pakistani cohort. J Coll Physicians Surg Pak. 2016;26:740-3.
26. ACOG Committee on Obstetric Practice. ACOG Committee Opinion. Number 299, September 2004 (replaces No. 158, September 1995).Guidelines for diagnostic imaging during pregnancy. Obstet Gynecol. 2004;104(3):647-51.
27. Streffer C, Shore R, Konermann G, Meadows A, Holm LE, Stather J, et al. Biological effects after prenatal irradiation (embryo and fetus). A report of the International Commission on Radiological Protection. Ann Int Comm Radiol Protect. 2003;33(1–2): 5-206.
28. Brent RL. Utilization of developmental basic science principles in the evaluation of reproductive risks from pre- and post-conception environmental radiation exposure. Teratology. 1999;59:182-204.
29. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. European Society of Gynecology (ESG); Association for European Paediatric Cardiology (AEPC); German Society for Gender Medicine (DGesGM); ESC Committee for Practice Guidelines. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the task force on the Management of cardiovascular diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(24):3147-97.
30. Kanal E, Barkovich AJ, Bell C, Borgstede JP, Bradley Jr WG, Froelich JW, et al. ACR Guidance for safe MR Practices: 2007. Am J Roentgenol. 2007;188:1447-74.
31. Baysinger CL. Imaging during pregnancy. Anesth Analg. 2010;110:863-7.
32. Wang PI, Chong ST, Kielar AZ, Kelly AM, Knoepp UD, Mazza MB, et al. Imaging of pregnant and lactating patients: part 1,

evidence-based review and recommendations. Am J Roentgenol. 2012;198:778-84.
33. Colletti PM, Lee KH, Elkayam U. CV imaging of the pregnant patient. Am J Roentgenol. 2013; 200:515-21.
34. Nallamothu BK, Saint M, Daint S, Mukherjee D. Double jeopardy. N Engl J Med. 2005; 353:75-80.
35. Sabatine MS, JAffer FA, Staats PA, Stone JR. Case 28-2010: a 32-year-old woman, 3 weeks postpartum, with sub-sternal chest pain. N Engl J Med. 2010;363:1164-73.
36. Follath F. Nonischemic heart failure: epidemiology, pathophysiology and progression of disease. J Cardiovasc Pharmacol. 1999;33:S31-5.
37. lyas S, Fawad A, Ilyas H, Hameed A, Awan ZA, Zehra A, et al. Echomorphology of CMP: review of 217 cases from 1999 to 2010. JPMA. 2013;63(4):454-8.
38. Jan MF, Tajik AJ. Modern imaging techniques in cardiomyopathies. Circ Res. 2017;121(7):874-91.
39. Mitropoulou P, Georgiopoulos G, Figliozzi S, Klettas D, Nicoli F, Masci PG. Multi-Modality Imaging in Dilated CMP: With a Focus on the Role of CMR. Front Cardiovasc Med. 2020;7:97.
40. Kramer CM, Chandrashekhar Y. Multiparametric CMR in CMP: Beyond Diagnosis and Toward Prognosis. JACC Cardiovasc Imaging. 2019;12(8):1712-4.
41. Greenwood JP, Motwani M, Maredia N, Brown JM, Everett CC, Nixon J, et al. Comparison of CV magnetic resonance and SPECT in women with suspected CAD from the Clinical Evaluation of MRI in Coronary Heart Disease (CE-MARC) Trial. Circulation 2014;129:1129-38.
42. Wicks EC, Menezes LJ, Barnes A, Mohiddin SA, Sekhri N, Porter JC, et al. Diagnostic accuracy and prognostic value of simultaneous hybrid 18F-fluorodeoxyglucose PET/MRI in cardiac sarcoidosis. EHJ Cardiovasc Imaging. 2018;19(7):757-67.
43. ASCI Practice Guideline Working Group, Beck KS, Kim JA, Choe YH, Hian SK, Hoe J, et al. 2017 Multimodality Appropriate Use Criteria for Noninvasive Cardiac Imaging: Expert Consensus of the Asian Society of CV Imaging. Korean J Radiol. 2017;18(6):871-80.
44. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2020;76(25):3022-55.
45. Rammos A, Meladinis V, Vovas G, Patsouras D. Restrictive CMP: The Importance of Noninvasive Cardiac Imaging Modalities in Diagnosis and Treatment-A Systematic Review. Radiol Res Pract. 2017;2017:2874902.
46. Citro R, Okura H, Ghadri JR, Izumi C, Meimoun P, Izumo M, et al. Multimodality imaging in takotsubo syndrome: a joint consensus document of the European Association of CV Imaging (EACVI) and the JSE. J Echocardiogr. 2020;18(4):199-224.
47. Ricci F, De Innocentiis C, Verrengia E, Ceriello L, Mantini C, Pietrangelo C, et al. The Role of Multimodality CV Imaging in Peripartum CMP. Front Cardiovasc Med. 2020;7:4.
48. Sarwar MR, Saqib A. Cancer prevalence, incidence and mortality rates in Pakistan in 2012. Cogent Medicine. 2017;4(1):1288773.
49. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. CA. 2012;62(4):220-41.
50. Howlader N, Ries LA, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved estimates of cancer-specific survival rates from population-based data. JNCI. 2010;102(20):1584-98.
51. Bodai BI, Tuso P. Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. Perm J. 2015;19(2):48.
52. Khattry N, Varma S, Malhotra P, Grover A, Sharma S. Doxorubicin induced cardiotoxicity in adult Indian patients on chemotherapy. J Clin Oncol. 2005;23(16_suppl):2123.
53. Khattry N, Malhotra P, Grover A, Sharma SK, Varma S. Doxorubicin-induced cardiotoxicity in adult Indian patients on chemotherapy. Indian J Med Paediatr Oncol. 2009;30(01):9-13.
54. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. EHJ Cardiovasc Imaging. 2014;15(10):1063-93.
55. Cameron AC, Touyz RM, Lang NN. Vascular complications of cancer chemotherapy. Can J Cardiol. 2016;32(7):852-62.
56. Tajiri K, Aonuma K, Sekine I. Cardio-oncology: a multidisciplinary approach for detection, prevention and management of cardiac dysfunction in cancer patients. Jpn J Clin Oncol. 2017;47(8):678-82.
57. Mahabadi AA, Rischpler C. Cardiovascular imaging in cardio-oncology. J Thorac Dis. 2018;10(Suppl 35):S4351.
58. Čelutkienė J, Pudil R, López- Fernández T, Grapsa J, Nihoyannopoulos P, Bergler- Klein J, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the H eart F ailure A ssociation (HFA), the E uropean A ssociation of C ardiovascular I maging (EACVI) and the Cardio- Oncology C ouncil of the E uropean S ociety of C ardiology (ESC). Eur J Heart Failure. 2020;22(9):1504-24.
59. Herrmann J, Lerman A. An update on cardio-oncology. Trends Cardiovasc Med. 2014;24(7):285-95.
60. Cutter DJ, Schaapveld M, Darby SC, Hauptmann M, Van Nimwegen FA, Krol AD, et al. Risk for valvular heart disease after treatment for Hodgkin lymphoma. JNCI. 2015;107(4):djv008.
61. Laufer-Perl M, Arnold JH, Mor L, Amrami N, Derakhshesh M, Moshkovits Y, et al. The association of reduced global longitudinal strain with cancer therapy-related cardiac dysfunction among patients receiving cancer therapy. Cli Res Cardiol. 2020;109(2):255-62.
62. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol. 2014;63(25 Part A):2751-68.
63. Danhnert W. Radiology Review Manual. 8th edition 2017: Wolters Kluwer. p 30- 31
64. Ahsan T, Khowaja D, Jabeen R, Erum U, Ali H, Farooq MU, et al. Burden of rheumatological disorders in a tertiary care Hospital. JPMA. 2016;66(5):563-7
65. Khalid Y, Dasu N, Shah A, Brown K, Kaell A, Levine A, et al. Incidence of CHF in RA: a review of literature and meta-regression analysis. ESC Heart Fail. 2020;7(6):3745-53
66. Mavrogeni S, Markousis-Mavrogenis G, Koutsogerropoulou L, Dimitroulas T, Vartela V, Riogopoulos A, et al. Pathophysiology and imaging of HF in women with autoimmune rheumatic disease. HF Reviews. 2019;24:489-98
67. Wingaarden SE, Said- Bouyeri SB, Ninaber MK, Huizinga TWJ, Schalalij MJ, Bax JB, et al. Progression of left ventricular myocardial dysfunction in systemic sclerosis; a Speckle-tracking strain echo study. J Rheumatol. 2019;45(4):405-15
68. Sandevska E, Gjorcheva DP, Vavlukis M, Sandevski A, Kafedizka I, Krstik-Damjanovska L, et al Myocardial perfsuin abmormalities in yound ang premenopausal women with SLE, detected with 99MTC MIBI myocardial perfusion scintigraphy-prevalence and correlation with proatherogenic factors. Pril. 2018;39:79-92.
69. Mavrogeni S, Markousis-Mavrogenis G, Koutsogerropoulou L, Kolovou G. CV magnetic resonance imaging: clinical implications in the evaluation of CTD. J Inflam Res. 2017;10:55-61.
70. Mayr A, Kitterer D, Latus J, Steubing H, Henes J, Vecchio F, et al. Evaluation of myocardial involvement in patients with connective tissue disorders: a multi-parametric cardiovascular magnetic resonance study. J Cardiovasc Magn Reson. 2017;18(1):1-3.

71. Wang X, Lou M, Li Y, Ye W, Zhang Z, Jia X, et al. Cardiovascular involvement in connective tissue disease: the role of interstitial lung disease. PLoS One. 2015;10(3):e0121976.
72. Agca R, Heslinga SC, Rollefsted S, Heslinga M, McInnes IB, Peters MJL, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders.2015/2016 update. Ann Rheumatic Dis. 2016;76(1):17-28

Disclaimer

These recommendations are written in best of shared professional knowledge and experience of the "Task Force - Go Red for Women-Pakistan" members and Pakistan Cardiac Society and all members agree to be accountable for all aspects of work ensuring integrity and accuracy.

Authors' Contributions:

1. Cardiac Imaging in Women with Coronary Heart Disease (CHD) by Prof. Dr. Sultana Habib
2. Cardiovascular Diseases and Cardiovascular Imaging during Pregnancy by Prof. Dr. Fateh Ali Tipoo Sultan
3. Use of Imaging in Women with Non-Ischemic Cardiomyopathy (CMP) by Dr. Saba Hussain
4. Use of Cardiac Imaging Techniques in Women with Cancer Treatments and Cardiovascular Toxicity by Dr. Lubna Baqai
5. Cardiac imaging in women with Connective Tissue Disorders (CTD) by Prof. Dr. Saba Sohail

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Address for Correspondence:

Secretariat Pakistan Cardiac Society (PCS) and Go Red Program for Women - Pakistan (GRW-P). Office# 102, 1st, Speedy Towers, D.H.A. Phase 1 Phase 1 Defence Housing Authority, Karachi, Karachi City, Sindh 75500
Phone: (021) 35388459
Email: prokhalidasoomro@hotmail.com

THE TASK FORCE

The Patron: Prof. Dr. Khalida Soomro, Co-ordinator of the Go Red Program for women in Pakistan, Chairperson Scientific Council of Women with Heart Disease

Writing Committee Members

Chair-person: Prof. Dr. Sultana Habib, Consultant Interventional Cardiologist, Postgraduate Institute of Kidney Centre, Karachi

Co-chairperson: Prof. Dr. Fateh Ali Tipoo Sultan, Consultant Cardiologist, Agha Khan University Hospital, Karachi, Pakistan

Dr. Saba Hussain, Assistant Professor Consultant Cardiologist, National Institute of Cardiovascular Diseases, Karachi

Dr. Lubna Baqai, Consultant Cardiologist, Tabba Heat Institute Karachi, Pakistan

Prof. Dr. Saba Sohail, Professor of Radiology, Dow University of Health Sciences, Principal Dow Medical College

Other contributors

Dr. Alisha Shakeel, Jinnah Sindh Medical University

Dr. Aiman Ather, Jinnah Sindh Medical University

Reviewers

Dr. Parveen Akhter, Associate Professor and Consultant Cardiologist and Cardiac Imaging, National Institute of Cardiovascular Diseases, Karachi

Prof. Dr. Shahbaz A Kureshi, Professor of Cardiology and HOD, Watim Medical and Dental College Rawat, Rawalpindi