Midwall replacement fibrosis with late gadolinium enhancement LGE-CMR imaging as an independent predictor of mortality and utility of Cardiovascular Magnetic Resonance Image

One-third of all patients with heart failure(HF) have nonischemic dilated cardiomyopathy (NIDM). Five-year mortality from NIDM is as high as 20% with sudden cardiac death (SCD) as the cause in 30% of the deaths. Currently, the LVEF is used as the main criteria to risk stratify patients requiring an implantable cardioverter defibrillator (ICD) to prevent SCD. However, LVEF does not necessarily reflect myocardial propensity for electrical instability leading to ventricular tachycardia (VT) or ventricular fibrillation (VF). Due to the differential risk in various subgroups of patients for arrhythmic death, it is important to identify appropriate patients for ICD implantation so that we can optimize healthcare resources and avoid the complications of ICDs in individuals who are unlikely to benefit. NIDCM is identified by progressive dilatation of the LV associated with the absence of obstructive CAD. Histopathologic studies have associated NIDCM with myocardial inflammation and fibrosis, which may be secondary to prior viral infection, toxins, iron overload, or other causes. In single-center experiences, the absence of infarct-appearing LGE of the myocardium excludes CAD as the cause of LV dysfunction. (**McCrohon 2003**) Occasionally, a more specific diagnosis of NIDCM can be reached by observing patchy or linear midwall enhancement that does not follow a coronary artery territory.

Ventricular arrhythmia is a frequent cause of SCD in patients with NIDCM with a depressed LVEF. (**Bardy2005**) The risk of SCD in this population has been shown to be reduced with the implantation of an ICD. The severity of transmural involvement of LGE in patients with NIDCM has been linked with ventricular arrhythmias and may become a risk-stratifying tool in this population.(**Nazarian 2005**)

Memon et al. performed a systematic search and review of clinical trials of NIDM and the use of ICDs and cardiac magnetic resonance imaging(CMR) with late gadolinium enhancement (LGE-CMR) for risk stratification. LGE-CMR identifies patients with NIDM who are at high risk for SCD and enables optimized patient selection for ICD placement,

while the absence of LGE-CMR may reduce the need for ICD implantation in patients with NIDM who are at low risk for future VF/VT or SCD. (**Memon 2016**)

LGE-CMR is a predictor of adverse cardiovascular outcomes in patients with NICM. However, these findings are limited by single-center studies, small sample sizes, and low event rates. Kuruvilla et al. performed a meta-analysis to evaluate the prognostic role of LGE-CMR imaging in patients with NICM. PubMed, Cochrane CENTRAL, and EMBASE were searched for studies looking at the prognostic value of LGE-CMR in patients with NICM. The primary end points included all-cause mortality, HF hospitalization, and a composite end point of SCD or aborted SCD. Pooling of odds ratios was performed using a random-effect model, and annualized event rates were assessed. Data were included from 9 studies with a total of 1488 patients and a mean follow-up of 30 months. Patients had a mean age of 52 years, 67% were men, and the average LVEF was 37% on CMR. LGE was present in 38% of patients. Patients with LGE-CMR had increased overall mortality, HF hospitalization, and SCD/aborted SCD compared with those without LGE-CMR. The annualized event rates for mortality were 4.7% for LGE-CMR + subjects versus 1.7% for LGE-CMR - subjects (P=0.01), 5.03% versus 1.8% for HF hospitalization, and 6.0% versus 1.2% for SCD/aborted SCD. They concluded that LGE-CMR in patients with NICM is associated with increased risk of all-cause mortality, HF hospitalization, and SCD. Detection of LGE-CMR has excellent prognostic characteristics and may help guide risk stratification and management in patients with NICM. (**Kuruvilla 2014**)

Risk stratification of patients with NIDC is primarily based on LVEF. Superior prognostic factors may improve patient selection for ICDs and other management decisions. Prospective, longitudinal study of 472 patients with NIDC referred to a UK center for CMR between November 2000 and December 2008 after presence and extent of midwall replacement fibrosis were determined. Patients were followed up through December 2011. Primary end point was all-cause mortality. Secondary end points included cardiovascular mortality or cardiac transplantation; an arrhythmic composite of SCD or aborted SCD (appropriate ICD shock, nonfatal VF, or S-VF); and a composite of HF death, HF hospitalization, or cardiac transplantation. Assessment of midwall fibrosis with LGE-CMR imaging provided independent prognostic information beyond LVEF in patients with NIDC.

The role of LGE-CMR in the risk stratification of NIDC requires further investigation. (**Gulati 2013**)

Neilan et al studies sought to determine whether the extent of late gadolinium enhancement (LGE-CMR) can provide additive prognostic information in patients with a NIDC with an indication for ICD therapy for the primary prevention of SCD. Data suggest that the presence of LGE-CMR is a strong discriminator of events in patients with NIDC. Limited data exist on the role of LGE-CMR quantification. The extent of LGE-CMR and clinical follow-up were assessed in 162 patients with NIDC prior to ICD insertion for primary prevention of SCD. LGE-CMR extent was quantified using both the standard deviation-based (2-SD) method and the full-width half-maximum (FWHM) method. They al studied 162 patients with NIDC (65% male; mean age: 55 years LVEF: 26 ± 8% and followed up for major adverse cardiac events (MACE), including cardiovascular death and appropriate ICD therapy, for a mean of 29 ± 18 months. Annual MACE rates were substantially higher in patients with LGE-CMR (24%) than in those without LGE-CMR (2%). By univariate association, the presence and the extent of LGE-CMR demonstrated the strongest associations with MACE; LGE extent, HR: 1.15 per 1% increase in volume of LGE-CMR. Multivariate analyses showed that LGE-CMR extent was the strongest predictor in the best overall model for MACE, and a 7-fold hazard was observed per 10% LGE extent after adjustments for patient age, sex, and LVEF. LGE-CMR quantitation by 2-SD and FWHM both demonstrated robust prognostic association, with the highest MACE rate observed in patients with LGE involving >6.1% of LV myocardium. They concluded that LGE-CMR extent may provide further risk stratification in patients with NIDC with a current indication for ICD implantation for the primary prevention of SCD. Strategic guidance on ICD therapy by cardiac magnetic resonance in patients with NIDC warrants further study. (**Neilan 2013**)
Figure 1

Table 1

Sequence name	Sequence function

Cine SSFP or fast gradient echo	Myocardial structure and function
T1-weighted black blood	Myocardial fat imaging
T2-weighted black blood	Tissue edema
Inversion recovery late enhancement	Late gadolinium enhancement
T2*	Myocardial iron content

Typical CMR sequences for evaluation of cardiomyopathies

Table 2

CMR approach to cardiomyopathies

	Sequences			
Cardiomyopathy	**SSFP**	**LGE**	**T1 black blood**	**T2 black blood**
Ischemic	•	•		•
DCM	•	•		•
Myocarditis	•	•		•
Takatsubo	•	•		•
Amyloidosis	•	•		•
Sarcoidosis	•	•		•
Iron overload	•			
HCM	•	•		
ARVC	•		•	
Noncompaction	•	•		
Transplant	•	•		•

The application of CMR in the diagnostic evaluation of cardiomyopathy of unknown origin has been identified as an appropriate use of this technology (**Hendel 2006**). The unique features of CMR, including exceptional temporal and spatial resolution, tissue characterization, perfusion analysis, and ability to image in any tissue plane, make it an ideal tool for use in this clinical setting. Cardiomyopathy sequencing protocols have been published to standardize and streamline the approach to the clinical scan(http://www.scmr.org/documents/scmr_protocols_2007.pdf). An experienced staff can perform a thorough study within 30 minutes and provide a multimodality cardiac survey to help the clinician determine therapies that may ultimately improve patient outcomes.

Mordi et al. studied the incremental prognostic value of global circumferential strain (GCS), as measured using CMR tagging, in addition to baseline clinical characteristics, LVEF, and LGE-CMR, in the prediction of MACE in an unselected cohort of patients. LVEF is a powerful predictor of mortality and is used for guiding treatment decisions. It is, however, subject to limitations. The value of GCS measured by CMR tagging in patients with suspected cardiac disease has not been fully explored despite its being considered as the gold standard noninvasive method of assessment of LV deformation. They prospectively evaluated data from 539 consecutive patients referred for CMR who underwent a CMR protocol that included cine imaging, tagging, and LGE. The primary endpoint was the prevalence of MACE, defined as a composite of all-cause mortality, HF-related hospitalization, and aborted SCD. MACE occurred in 62 of 539 patients (11.5%) over a mean follow-up period of 2.2 years. History of coronary heart disease (CHD) and β-blocker use were both significant clinical predictors of adverse outcomes. All 3 CMR parameters were significant multivariate predictors of the primary outcome when added to significant clinical predictors (LVEF, hazard ratio [HR]: 0.96 [95% confidence interval [CI]: 0.94 to 0.99; p = 0.005]; presence of LGE, HR: 2.07 [95% CI: 1.03 to 4.14; p = 0.04]; GCS, HR: 1.11 [95% CI: 1.02 to 1.21; p = 0.041]). Global chi-square increased significantly with the addition of both LGE-CMR, and GCS. Both the presence of LGE-CMR and reduced GCS had independent prognostic value in the overall cohort. Patients with LVEF ≥35% but LGE-CMR present and reduced GCS had a poor outcome similar to that in those with LVEF <35%. The authors found, in a large-scale cohort of patients, that GCS, in addition to clinical variables, LVEF, and LGE-CMR, had incremental independent prognostic value. This measure could

provide further risk stratification, especially in patients with mild LV impairment. (**Mordi 2015**)

Current risk stratification for SCD in (NIDC relies on LV dysfunction, a poor marker of ventricular electrical instability. Contrast- LGE-CMR has the ability to accurately identify and quantify ventricular myocardial fibrosis To evaluate the impact of the presence and amount of myocardial fibrosis on arrhythmogenic risk prediction in NIDC Perazzolo Marra et al studied 137 consecutive patients with angiographically proven NIDC were enrolled for this study. All patients were followed up for a combined arrhythmic end point including sustained S-VT, appropriate ICD intervention, VF, and SCD.

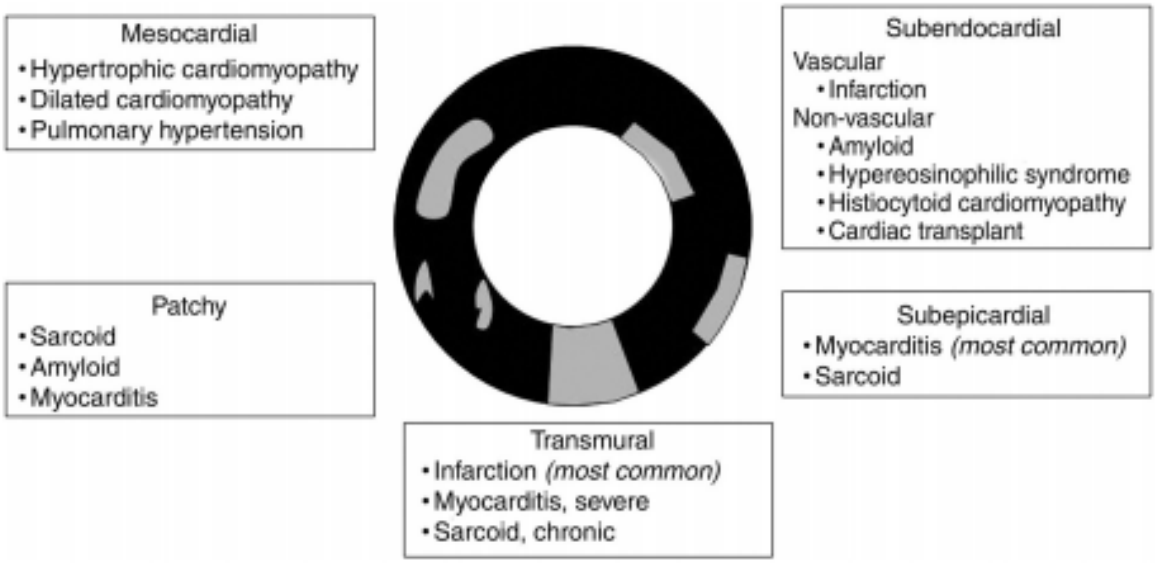
LV-LGE was identified in 76 (55.5%) patients. During a median follow-up of 3 years, the combined arrhythmic end point occurred in 22 (16.1%) patients: 8 (5.8%) S-VT, 9 (6.6%) appropriate ICD intervention, either against VF (n = 5; 3.6%) or VT (n = 4; 2.9%), 3 (2.2%) aborted SCD, and 2 (1.5%) died suddenly. Kaplan-Meier analysis revealed a significant correlation between the LV-LGE presence (not the amount and distribution) and malignant arrhythmic events. In univariate Cox regression analysis, LV-LGE (hazard ratio [HR] 4.17; 95% confidence interval [CI] 1.56-11.2; P = .005) and LBBB (HR 2.43; 95% CI 1.01-5.41; P = .048) were found to be associated with arrhythmias. In multivariable analysis, the presence of LGE was the only independent predictor of arrhythmias. The authors concluded that LV-LGE is a powerful and independent predictor of malignant arrhythmic prognosis, while its amount and distribution do not provide additional prognostic value. Contrast-enhanced MCR may contribute to identify candidates for ICD therapy not fulfilling the current criteria based on LVEF.(**Perazzolo Marra 2014**)

Ventricular tachycardia in patients with cardiomyopathy originates in scar tissue. Intramural or epicardial scar may result in ineffective ablation if mapping and ablation are limited to the endocardium. Njeim et al. investigate whether preprocedural CMR is beneficial in patients with failed endocardial VT ablations in determining an appropriate ablation strategy. A CMR was performed in 20 patients with a failed ablation procedure and cardiomyopathy (NIDCM n = 12, ischemic n = 8). A subsequent ablation strategy was determined by a LGE-CMR and an epicardial subxyphoid access was planned only in patients with epicardial or intramural free-wall scar. CMRs were performed in all patients with or without an ICD. The location of

scar tissue in the CMR predicted the origin of VT in all patients. In 9/20 patients an epicardial procedure was performed based on the result of the CMR. An endocardial procedure was performed in the remaining 11 patients who had either endocardial or septal scarring and one patient in whom the CMR only showed artifact. Five patients remained inducible postablation and 4 patients had VT recurrence within a follow-up period of 17 ± 22 months. All of the latter patients had an intramural scar pattern. They concluded that Imaging with CMR prior to VT ablation in patients with previously failed endocardial ablation procedures is beneficial in identifying an ablation strategy, helps to focus on an area of interest intraprocedurally, and provides valuable outcomes information. (**Njeim 2016**)

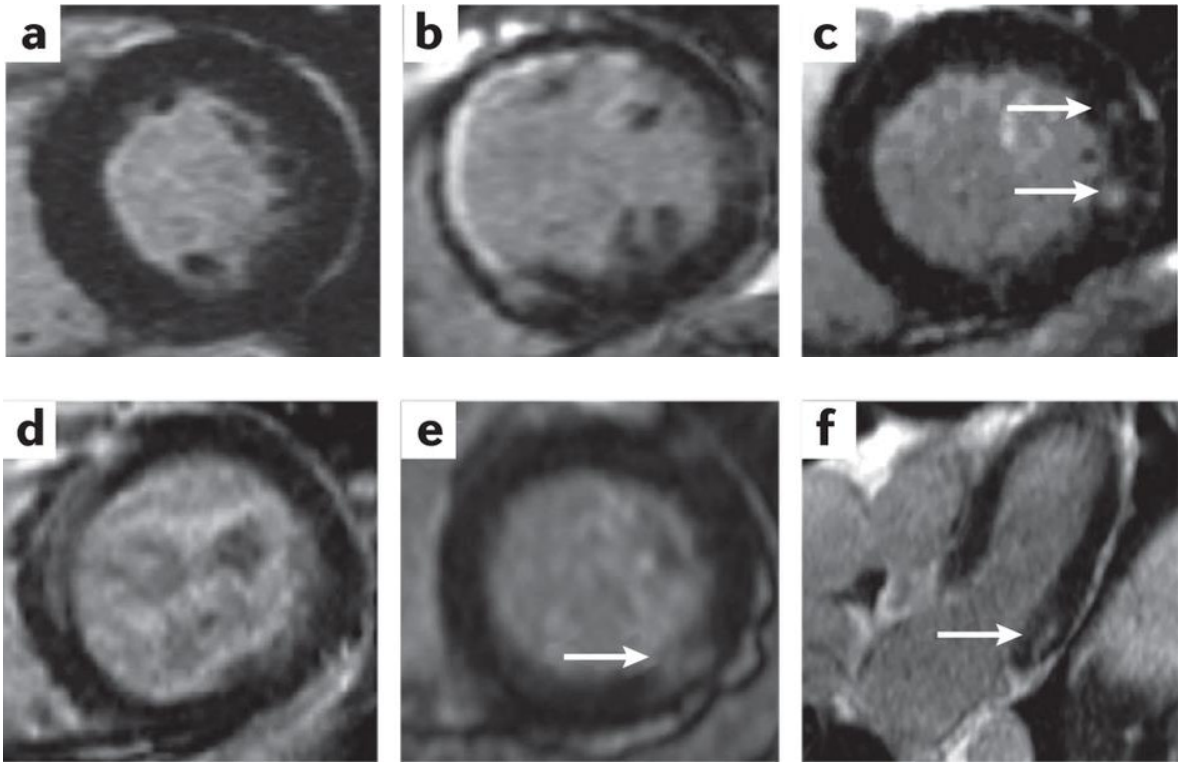
Dweck et al studied the prognostic significance of midwall and infarct patterns of LGE-CMR in aortic stenosis. Myocardial fibrosis occurs in aortic stenosis as part of the hypertrophic response. It can be detected by LGE-CMR, which is associated with an adverse prognosis in a range of other cardiac conditions.Between January 2003 and October 2008, consecutive patients with moderate or severe aortic stenosis undergoing CMR with administration of gadolinium contrast were enrolled into a registry. Patients were categorized into absent, midwall, or infarct patterns of LGE-CMR by blinded independent observers. Patient follow-up was completed using patient questionnaires, source record data, and the National Strategic Tracing Service. A total of 143 patients (age 68 ± 14 years; 97 male) were followed up for 2.0 ± 1.4 years. Seventy-two underwent aortic valve replacement, and 27 died (24 cardiac, 3 sudden cardiac deaths). Compared with those with no LGE-CMR (n = 49), univariate analysis revealed that patients with midwall fibrosis (n = 54) had an 8-fold increase in all-cause mortality despite similar aortic stenosis severity and CAD burden. Patients with an myocardial infarct pattern (n = 40) had a 6-fold increase. Midwall fibrosis (hazard ratio: 5.35; 95% confidence interval: 1.16 to 24.56; p = 0.03) and LVEF (hazard ratio: 0.96; 95% confidence interval: 0.94 to 0.99; p = 0.01) were independent predictors of all-cause mortality by multivariate analysis. Midwall replacement fibrosis with late gadolinium enhancement LGE-CMR imaging was an independent predictor of mortality in patients with moderate and severe aortic stenosis. It has incremental prognostic value to ejection fraction and may provide a useful method of risk stratification. (**Dweck 2011**) Figure 2

Figure 1



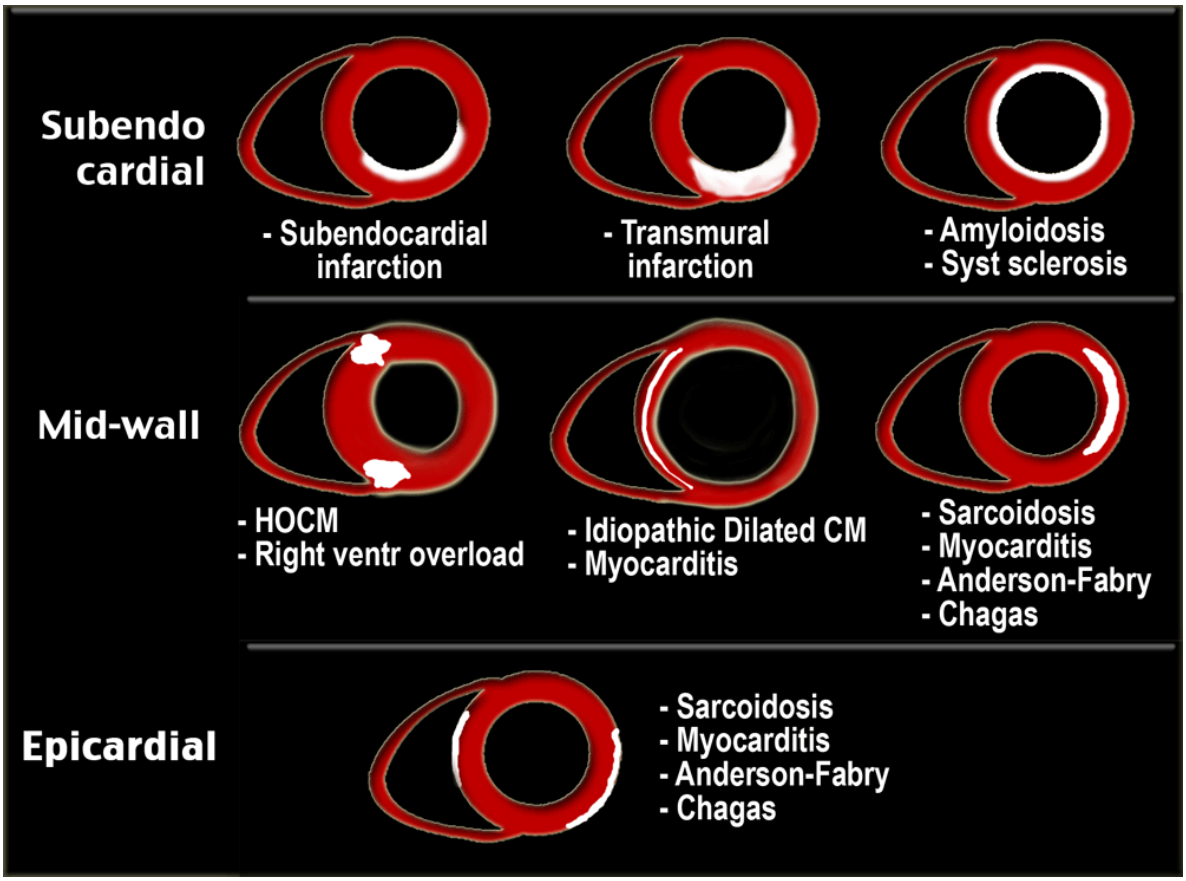
A pattern-based approach to assessment of delayed enhancement in NIDC using CMR imaging. (**Cummings 2009; Karamitsos2009**)

Figure 2



Several patterns of LGE-CMR can be observed in patients with severe aortic stenosis, from a | no LGE, to b | infarct-like replacement fibrosis with subendocardial scar, or c–f | midwall fibrosis. The arrows indicate the presence of LGE.

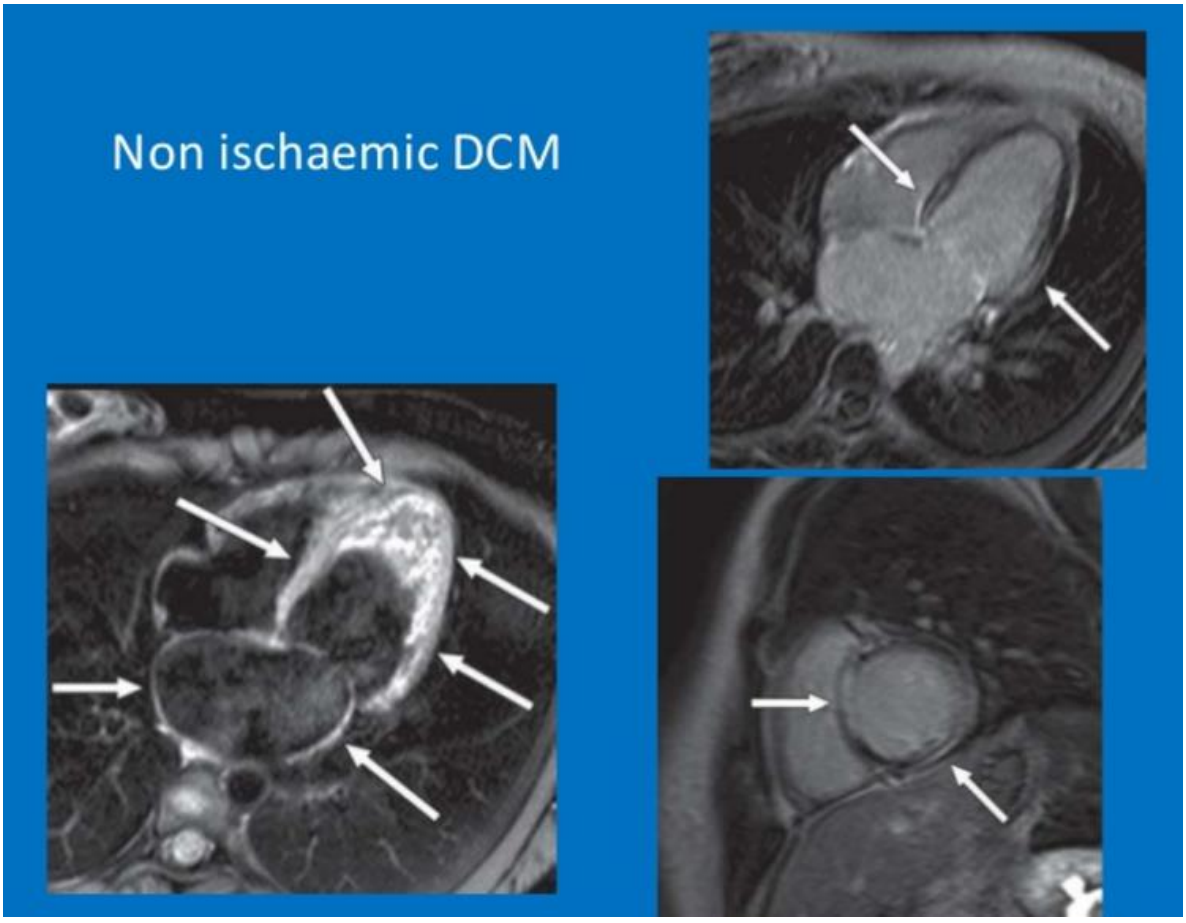
Figure 3


Subendo cardial
- Subendocardial infarction
- Transmural infarction
- Amyloidosis
- Syst sclerosis
Mid-wall
- HOCM
- Right ventr overload
- Idiopathic Dilated CM
- Myocarditis
- Sarcoidosis
- Myocarditis
- Anderson-Fabry
- Chagas
Epicardial
- Sarcoidosis
- Myocarditis
- Anderson-Fabry
- Chagas

NIDM

Cardiac Magnetic Resonance features

- **black blood images**: enlarged cardiac chambers and thin myocardial walls
- **Cine images**: show LV hypokinesia, increased volumes, (end-diastolic volumes that constitute a dilated CMP: > 140 mL for the LV and > 150 mL for the RV
- **Phase-contrast sequences**: impaired diastolic function. transvalvular flow may be characterized by a restrictive pattern
- **Late gadolinium-enhancement**



	Idiopathic dilated cardiomyopathy (DCM)	Ischemic dilated cardiomyopathy(IDCM)
Past history of CAD	Should be absent	Present in most
Antecedent fever , systemic illness ,	May be present	Not relevant
Symptoms	Angina uncommon	Angina may be present
ECG (Q waves, LBBB, low voltage QRS , slurred ,notched QRS, Fascicular blocks ,Non specific ST/T changes)	*Generally not useful* . Q waves are more common in IDCM. Diffuse q waves not confining to an arterial territory may suggest idiopathic DCM .Please remember q waves are not synonymous with infarct. It can occur with scars, fibrosis , extreme atrial enlargement (Cavity potential)	
X ray chest	Global Cardiomegaly	More of LV configuration
ECHO	*4 chamber dilatation Common* (Can be made as essential criteria)	*LV , LA dilatation* predominant
Wall motion defect	*Uniform Global hypokinesia*	*Global hypokinesia with regional variation*
Myocardial scars	Less common (More of thinning)	Significant scars , Random and patchy. (Makes CRT difficult)
Mitral regurgitation	Usually present (Central jet)	Often present (Eccentric jet common due to differential pap muscle involvement.)
Diastolic dysfunction	*Often restrictive*	Grade 1 or 2 (Rarely restrictive)
RV dysfunction (RVD)	High incidence (True myopathies do not differentiate RV and LV)	Less common (RVD is due to spiral muscle sharing between RV and LV)

	Idiopathic dilated cardiomyopathy (DCM)	Ischemic dilated cardiomyopathy(iDCM)
Coronary angiogram (Considered Gold standard)	Usually normal . Minor lesions may be present.	Extensive lesions common
Management	*Response to medical therapy better.* (Digoxin , diuretics ACEI, ARBs, BBs, ± Statins). Diastolic function more difficult to tackle.	Medical management + A revascularisation procedure must be done whenever possible.
Response to CRT (Cardiac resynchronisation)	*Fare better* (Desynchrony is uniform And predictable .Hence easy to tame it by wires)	Less favorable (Desynchrony is random and chaotic. scar interference an issue)
Natural history	Highly variable *Complete recovery to rapid downhill possible* Mean prognosis better	Usually predictable Progressive . (Response to revascularisation not uniform)
Risk of Sudden cardiac death	No major difference. VTs more common with scarred IDCM. Severity of LV dysfunction primary determinant.	
Survivial *(Mayo clinic data 2010 with CRT)*	77%	55%

*Diagnosis of Idiopathic DCM depends upon the ***efforts we make*** to arrive at a specific diagnosis. *What is idiopathic DCM in a peripheral hospital can become a specific cardiomyopathy in a teaching hospital .Hence the primary aim in every patient with DCM is to identify reversible cause (Connective tissue disorder ,Alcohol, toxins, etc)*

** ***Coronary angiogram is probably indicated in every patient with DCM*** to rule out potential ischemic etiology . (Sliced MDCT is a good option in patients at low risk of CAD)

***Presence of diabetes HT, and chronic kidney disease modifies the behavior of myocardium to a great extent .In fact , there can be an important overlap between DCM/IDCM if the above conditions are associated .

**** Many times differentiation between these two entities is purely ***an academic pursuit*** , as management strategies and outcome are more similar than different .

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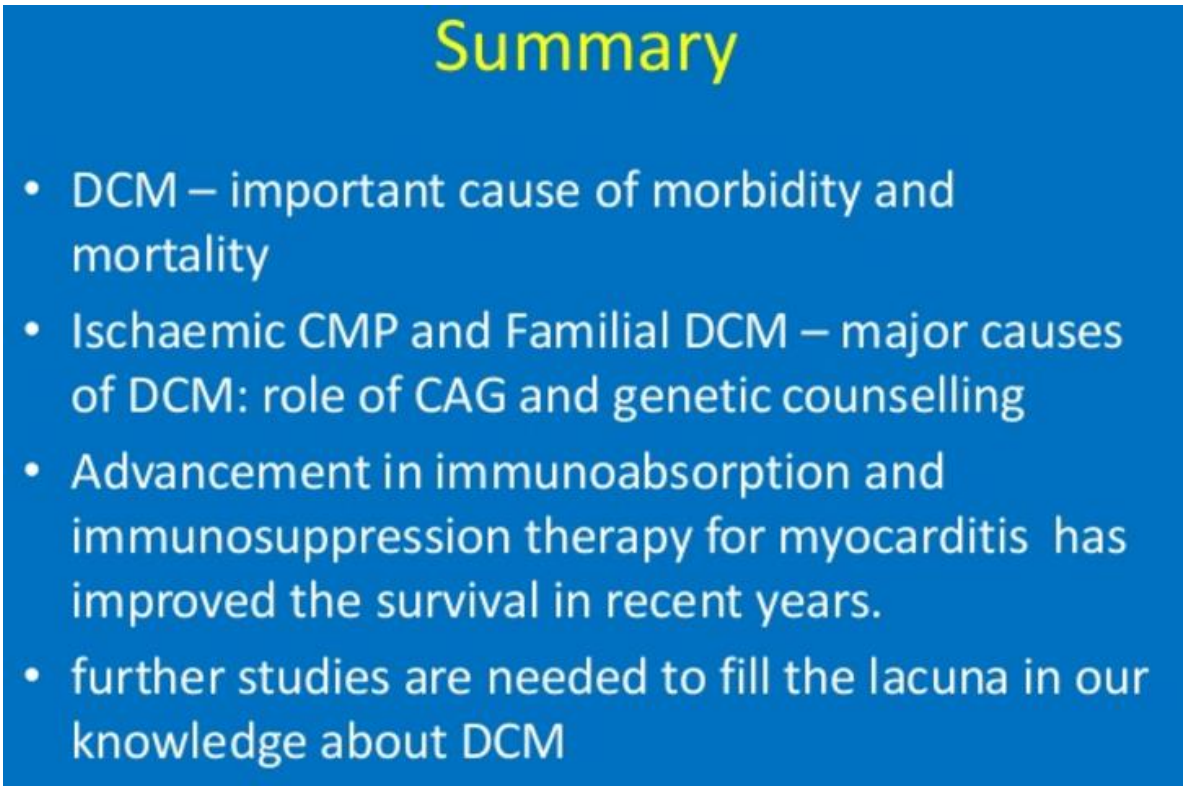

Summary Determination of exact etiology of cardiomyopathy can be difficult but remains important for both treatment and prognosis. CMR imaging allows comprehensive assessment of patients suspected to have NIDM and is therefore being increasingly used in diagnosis and follow-up of these patients. CMR offers a comprehensive assessment of HF patients and is now the gold standard imaging technique to assess myocardial anatomy, regional and global function, and viability. Furthermore, it allows assessment of perfusion and acute tissue injury (edema and necrosis), whereas in nonischemic HF, fibrosis, infiltration, and iron overload can be detected. LGE-CMR extent may provide further risk stratification in patients with NIDC with a current indication for ICD implantation for the primary prevention of SCD.

Conclusions CMR has become one of the most accurate techniques (the gold standard) in quantification volumes, mass, study of the right ventricle, serial assessment of biventricular structure, size, and function (anatomy, LV/RV volumes, global and regional systolic

function, mass and the most complete in the diagnosis of ischemic diseases, NIDM (differentiation of ischemic versus NIDM), determination of the location and extent of acute (including no-reflow regions) and chronic myocardial necrosis, viability assessment before revascularization (LGE or low-dose dobutamine, determination of the area at risk in patients with acute myocardial infarction and the salvageable area post-revascularization with percutaneous coronary intervention, identification of the presence and quantification of the extent of inducible ischemia (vasodilator perfusion or high-dose dobutamine stress CMR), ARVC/D, LV noncompaction, HCM, Anderson-Fabry disease, cardiac sarcoidosis, amyloidosis, iron overload cardiomyopathy, evaluation of suspected anomalous coronary origins (MR coronary angiography) and others congenital diseases, patients with technically limited images from echocardiogram, Discordant information that is clinically significant from prior tests and assessment of mechanical dyssynchrony before resynchronization therapy and risk stratify patients requiring an ICD. Finally, in patients with structural heart disease and previously failed endocardial VT ablation procedures, preprocedural cardiac MRIs are helpful in identifying an ablation strategy, even in patients with previously implanted ICDs

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