Special Imaging for Special Cardiomyopathies

UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA
NATIONAL CARDIAC PET CENTRE

uOttawa

The Ottawa Hospital
L'Hôpital d'Ottawa

Rob Beanlands, MD, FRCP(C), FACC, MASNC, FCCS

Vered Chair and Chief, Division of Cardiology
uOttawa Distinguished Chair in Cardiac Imaging Research
Deputy Director General
University of Ottawa Heart Institute

Conflict of Interest Disclosures

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  Lantheus Medical Imaging

  GE
- **Consulting fees**:

  Jubilant DraxImage

  Lantheus Medical Imaging

  GE
- **Speaker fees**:

  Nil
- **Other**:

  Institution produces Positron Emitting Radiopharmaceutical

  Report SPECT and PET Cardiac Scans

Objectives

- **Special Imaging for Special Cardiomyopathies**
- 1. Describe the role for Nuclear imaging (PET and SPECT) in the diagnosis of cardiac sarcoid and amyloidosis
- 2. Describe the role of Cardiac MRI in defining specific types of cardiomyopathy (highlights from the OUTSMART trial; IMAGE HF project IB)
- 3. Discuss a few potential pitfalls (limitations) of advanced cardiac imaging

Cardiac imaging in patients with suspected or established heart failure (1)

Recommendations	Class	Level
TTE is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of either HFrEF, HFmrEF or HFpEF.	I	C
TTE is recommended to assess LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device (ICD, CRT) treatment recommended for HFrEF.	I	C
TTE is recommended for the assessment of valve disease, right ventricular function and pulmonary arterial pressure in patients with an already established diagnosis of either HFrEF, HFmrEF or HFpEF in order to identify those suitable for correction of valve disease.	I	C
TTE is recommended for the assessment of myocardial structure and function in subjects to be exposed to treatment which potentially can damage myocardium (e.g. chemotherapy).	I	C
Other techniques (including systolic tissue Doppler velocities and deformation indices, i.e. strain and strain rate), should be considered in a TTE protocol in subjects at risk of developing HF in order to identify myocardial dysfunction at the preclinical stage.	IIa	C
CMR is recommended for the assessment of myocardial structure and function (including right heart) in subjects with poor acoustic window and patients with complex congenital heart diseases (taking account of cautions/contra-indications to CMR).	I	C
CMR with LGE should be considered in patients with dilated cardiomyopathy in order to distinguish between ischaemic and nonischaemic myocardial damage in case of equivocal clinical and other imaging data (taking account of cautions/contra-indications to CMR).	IIa	C
CMR is recommended for the characterization of myocardial tissue in case of suspected myocarditis, amyloidosis, sarcoidosis, Chagas disease, Fabry disease non-compaction cardiomyopathy, and haemochromatosis (taking account of cautions/ contra-indications to CMR).	I	C

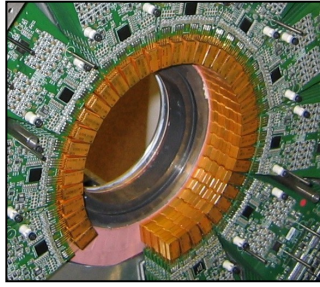
Cardiac imaging in patients with suspected or established heart failure (2)

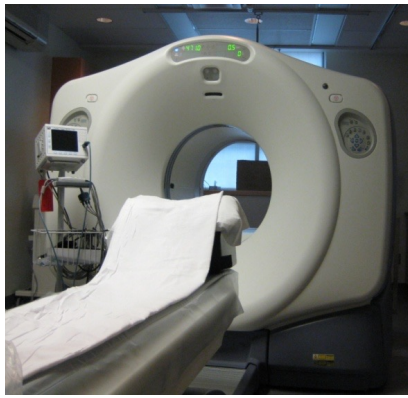
Recommendations	Class	Level
Non-invasive stress imaging (CMR, stress echocardiography, SPECT, PET) may be considered for the assessment of myocardial ischaemia and viability in patients with HF and CAD (considered suitable for coronary revascularization) before the decision on revascularization.	IIb	B
Invasive coronary angiography is recommended in patients with HF and angina pectoris recalcitrant to pharmacological therapy or symptomatic ventricular arrhythmias or aborted cardiac arrest (who are considered suitable for potential coronary revascularization) in order to establish the diagnosis of CAD and its severity.	I	C
Invasive coronary angiography should be considered in patients with HF and intermediate to high pre-test probability of CAD and the presence of ischaemia in non-invasive stress tests (who are considered suitable for potential coronary revascularization) in order to establish the diagnosis of CAD and its severity.	IIa	C
Cardiac CT may be considered in patients with HF and low to intermediate pre-test probability of CAD or those with equivocal non-invasive stress tests in order to rule out coronary artery stenosis.	IIb	C
Reassessment of myocardial structure and function is recommended using non-invasive imaging: – in patients presenting with worsening HF symptoms (including episodes of AHF) or experiencing any other important cardiovascular event; – in patients with HF who have received evidence-based pharmacotherapy in maximal tolerated doses, before the decision on device implantation (ICD, CRT); – in patients exposed to therapies which may damage the myocardium (e.g. chemotherapy) (serial assessments).	I	C

European Heart Journal (2016) **37**, 2129-2200 - doi:10.1093/eurheartj/ehw 128

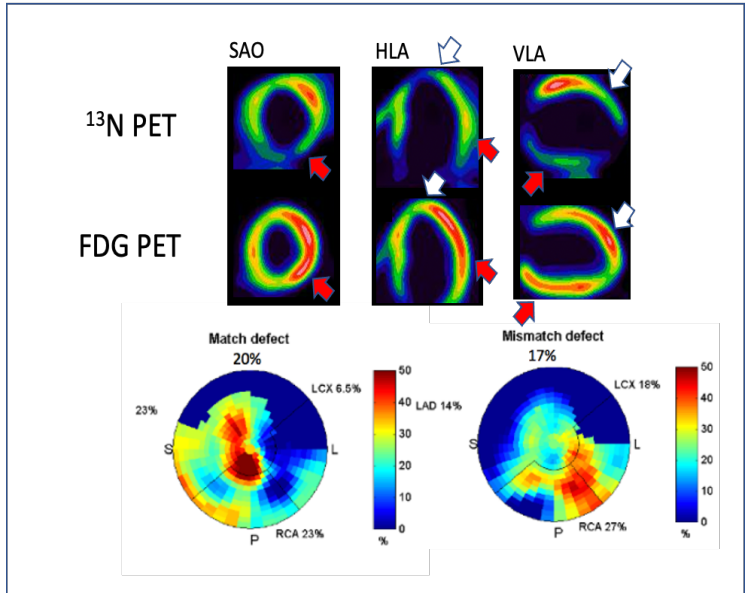
EUROPEAN SOCIETY OF CARDIOLOGY®

Advantages of Cardiac PET



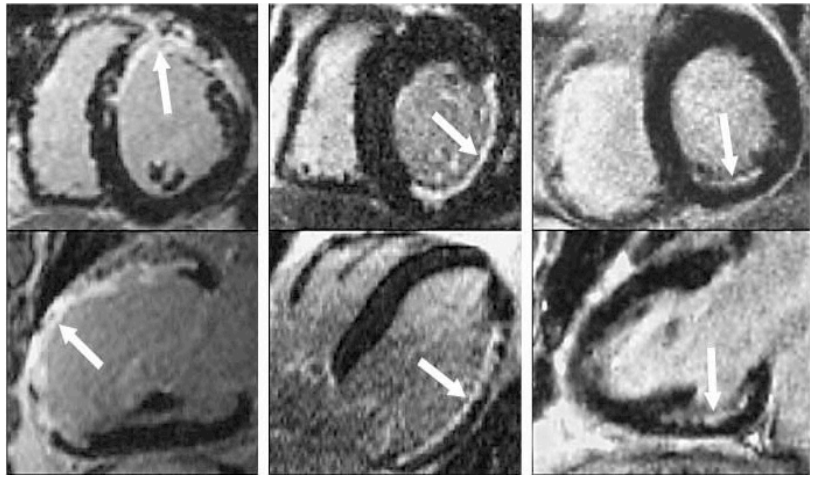


- **Superior ‘Functional’ Accuracy**
- **Measure and Track Molecular and Functional Processes [*picomol*]**
  - ***Flow, Metabolism-Inflammation, Neurohormonal function***
- **Biological Quantification Capability**
- **Diagnostic and Prognostic Value**



Advantages of Cardiac MR

- **Superior Anatomic Accuracy and Resolution**
- **Detailed Structure, Function and Tissue Characterization**
  - ***Size, EF, Regional wall motion, Edema / Scar, Iron***
- **Quantification Capability**
- **Diagnostic and Prognostic Value**



Kim et al, NEJM 2000;343:1445-53

Disadvantages of PET

• **Access / Cost**	• ***Low-cost PET***
• **Resolution**	• ***Supra-Resolution PET (PET-MR; PET-CT)***
• **Cyclotron dependence**	• ***Generators (Rb-82, Ga-68)*** • ***F-18 tracers***
• **Radiation**	• ***ALARA (< 2mSv)***

Disadvantages of Cardiac MR

- **Access / Cost**
- ***Availability increasing***

- **NSF Risk in Renal Failure**
- ***Risk is low especially with newer agents***

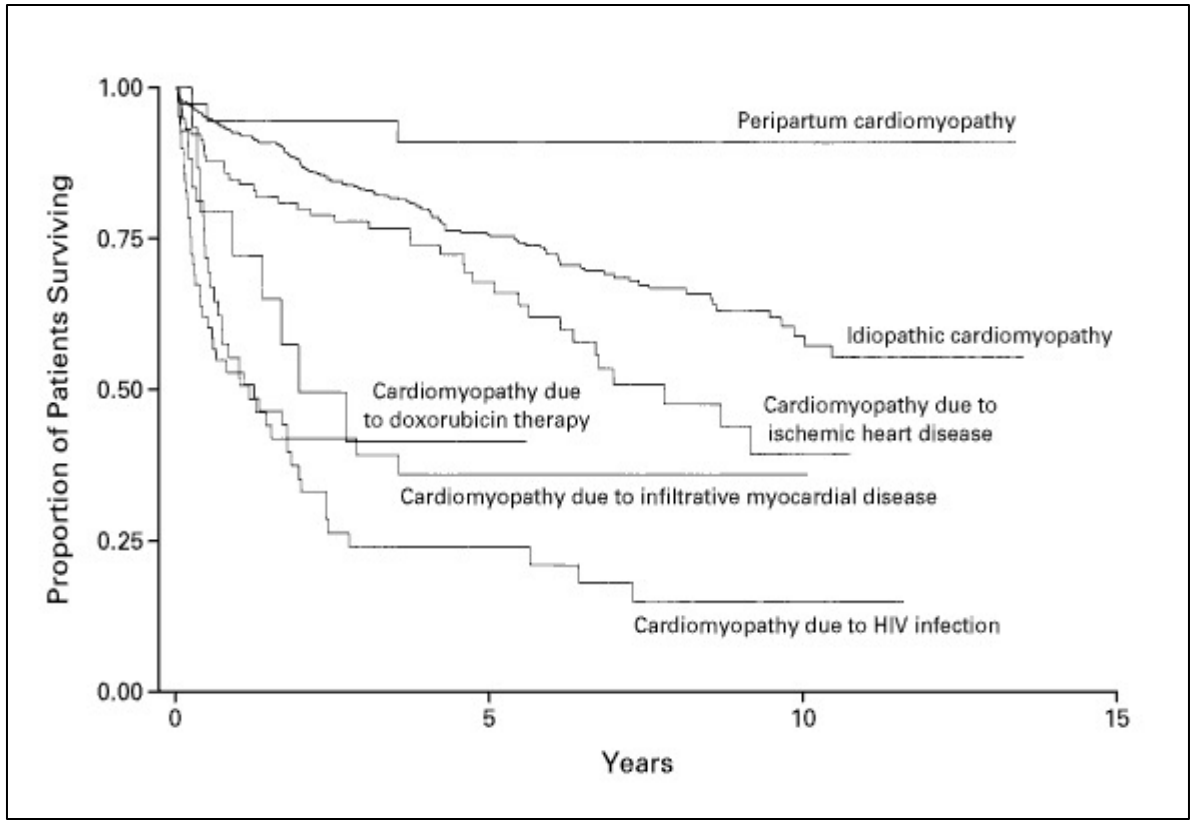
- **Devices**
- ***MR compatible devices***
- ***Device programing***
- ***Canadian Guidelines developed***

Known/Suspected NICM

- Tissue Diagnosis – does it matter
- Role of CMR
- Echo + selective CMR vs routine CMR

Outcomes According to the Underlying Cause of Cardiomyopathy

1230 Patients, 1982-1997, biopsy in all
50% Idiopathic ; 15% Specific histological diagnosis



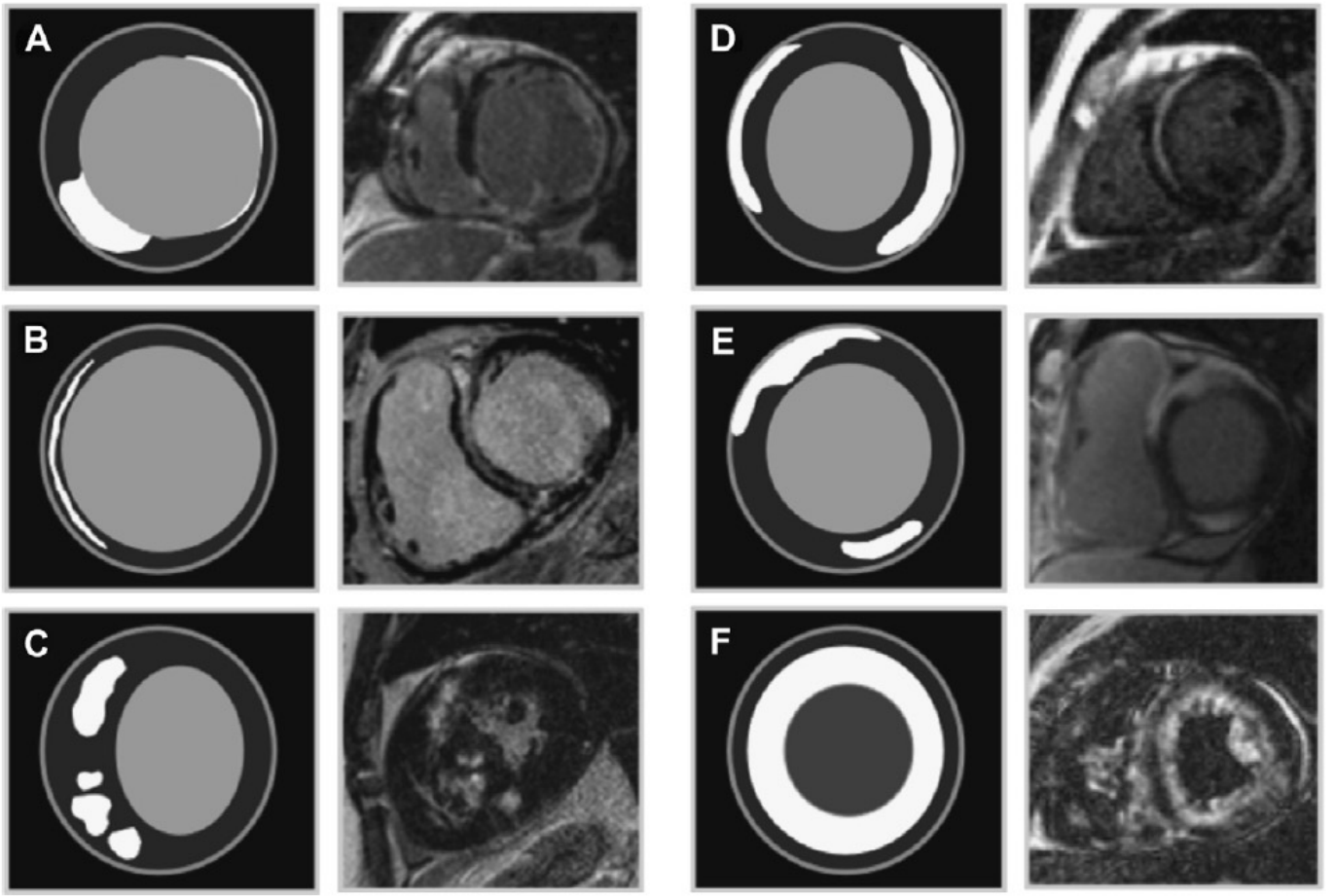
Felker GM. *N Engl J Med* 2000. 342:1077-1084

CMR for Cardiomyopathies

Ischemic CM

Dilated CM

Hypertrophic CM



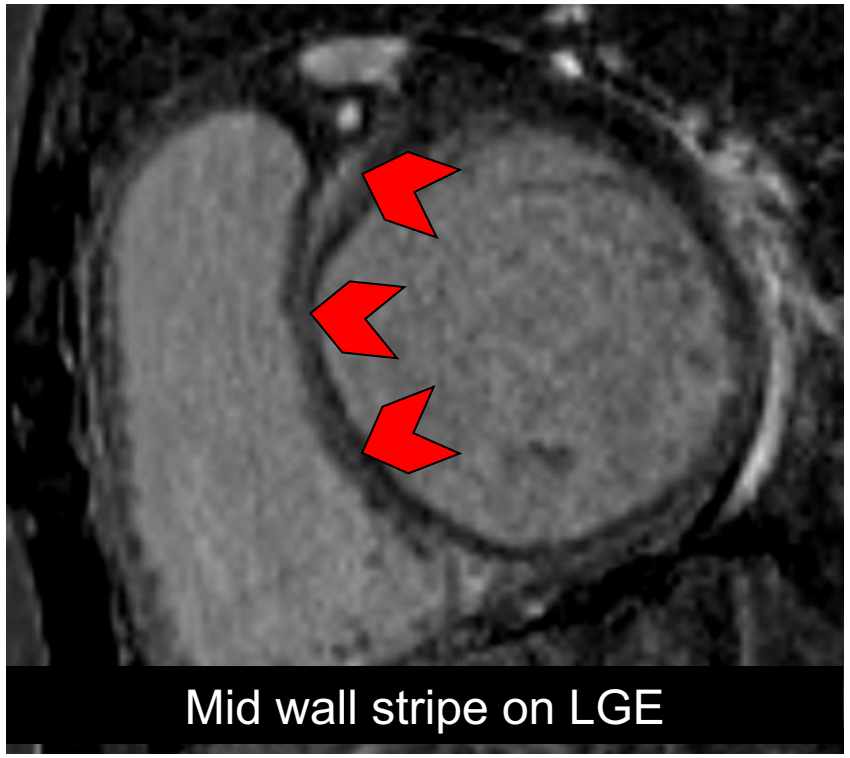
Myocarditis

Sarcoidosis

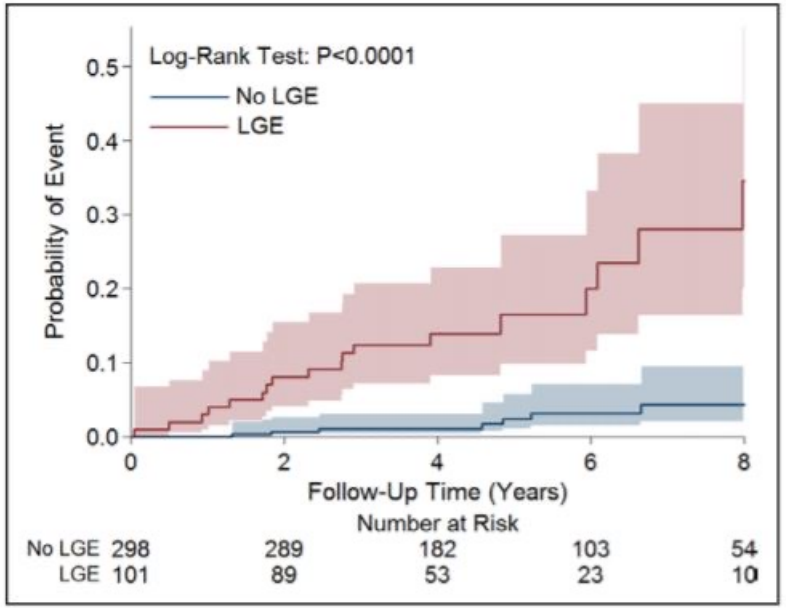
Amyloidosis

Stirrat J, White J. CJC 2013. 29:329-336.

Dilated cardiomyopathy

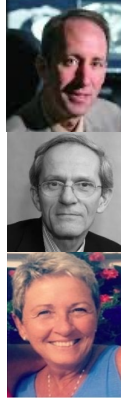


The predicted 5-year risk of aborted and actual SCD using a model including both LGE and LVEF was markedly different than a model using LVEF alone (Figure 3). For example, a patient with an LVEF of 45% had a 5-year predicted risk of 7.8% on the basis of LVEF alone, which fell to 3.2% in the absence of LGE but increased to 20.2% if LGE was present.



Halliday et a. Circulation. 2017;135:2106–2115.

OUTSMART HF: A Randomized Controlled Trial of Routine Versus Selective Cardiac Magnetic Resonance in Non-Ischemic Heart Failure (IMAGE-HF project 1B)



Paterson I, Erthal F, Garrard L, Mielniczuk L, O'Meara E, White J, Connelly K, Knuuti J, Radja M, Laine M, Chow B, Chen L, Wells G, Ezekowitz J, Beanlands R, Chan K

Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, AB, Canada; Ottawa Heart Institute, Ottawa, ON, Canada; Université de Montréal, Montreal, QC, Canada; University of Calgary, Calgary, AB, Canada; University of Toronto, Toronto, ON, Canada;. Turku University, Turku, Finland; Dalhousie University, Halifax, NS, Canada; Helsinki University, Helsinki, Finland.

Primary Aim

- In patients with non-ischemic HF, determine if a strategy using routine CMR yields more specific diagnoses of the underlying HF etiology compared to a strategy using CMR selectively

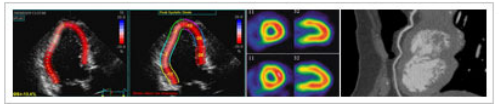
Design

- Randomized, controlled multi-centre trial – 518 patients
- Two arm, 1:1 allocation routine versus selective CMR in patients with non-ischemic HF
- Analyzed as intention to treat

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

TEKES

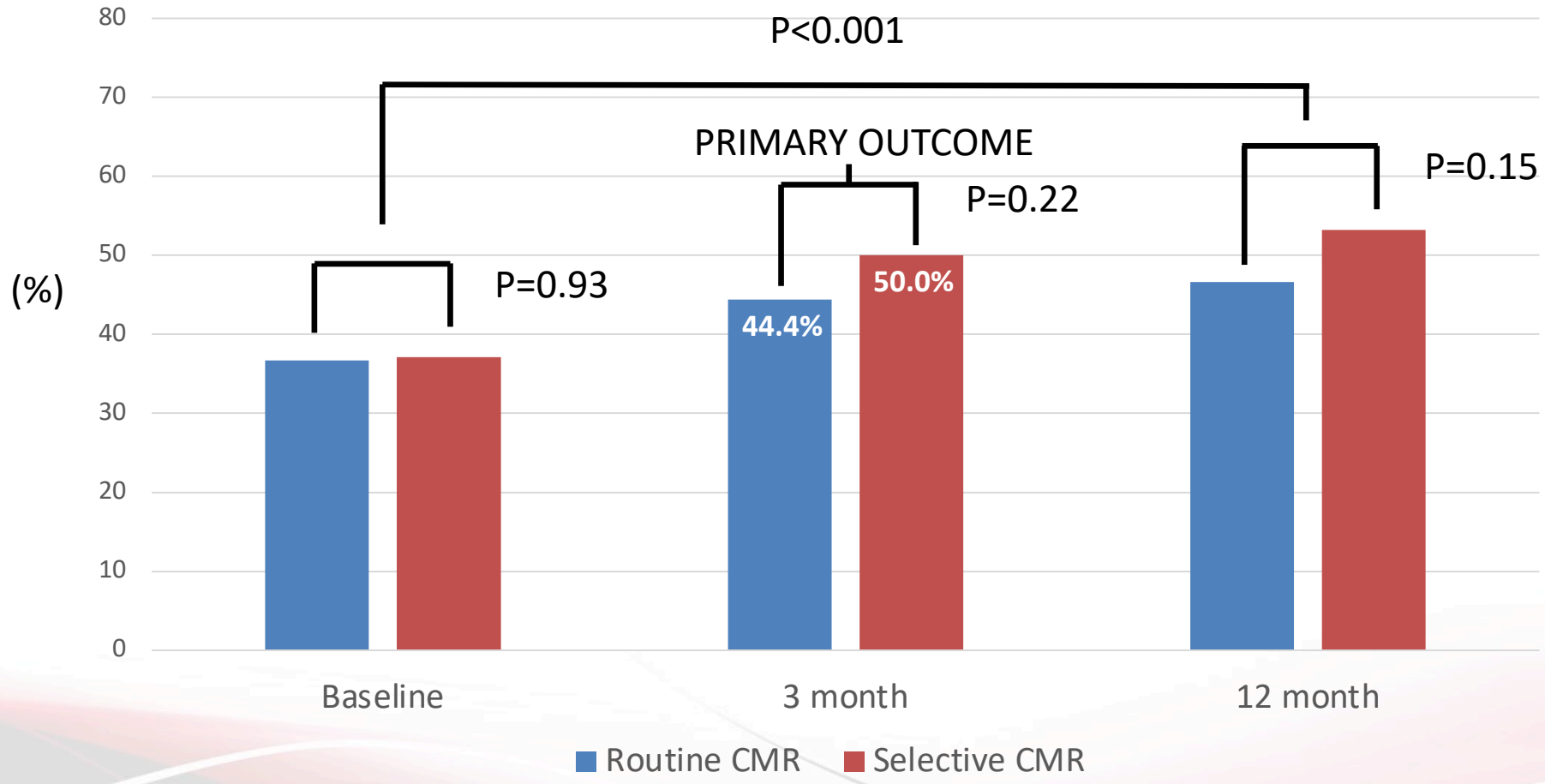
IMAGE-HF



ClinicalTrials.gov: NCT01283659

Circulation. 2020 Mar 10;141(10):818-827

PRIMARY OUTCOME
Clinical Assessments of Specific HF Etiologies



Courtesy of Ian Paterson

Circulation. 2020 Mar 10;141(10):818-827

HF Etiology by Imaging Test (Paired Analysis in Routine CMR)

Suspected HF Etiology	Echo N=224	CMR N=224
HFpEF	21 (9%)	11 (5%)
Dilated	149 (67%)	122 (54%)
Inflammatory	2 (1%)	20 (9%)
Infiltrative	3 (1%)	6 (3%)
Hypertrophic	1 (0.5%)	4 (2%)
Ischemic	17 (8%)	5 (2%)
Valvular	1 (0.5%)	1 (0.5%)
Mixed	8 (4%)	17 (8%)
Other	11 (5%)	17 (8%)
No HF	2 (1%)	10 (4%)
Unknown	9 (4%)	11 (5%)
Specific HF Causes ‡	**45 (20%)**	**80 (36%)‡**

‡ $p < 0.001$

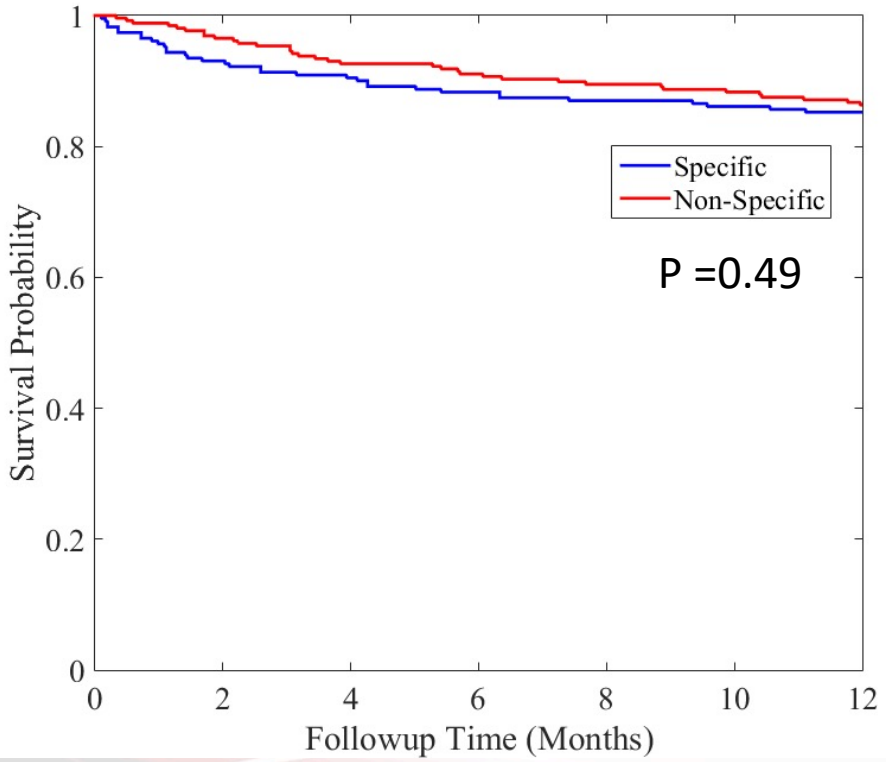
Courtesy of Ian Paterson

Circulation. 2020 Mar 10;141(10):818-827

Clinical Events
(Death or CV hospitalization)

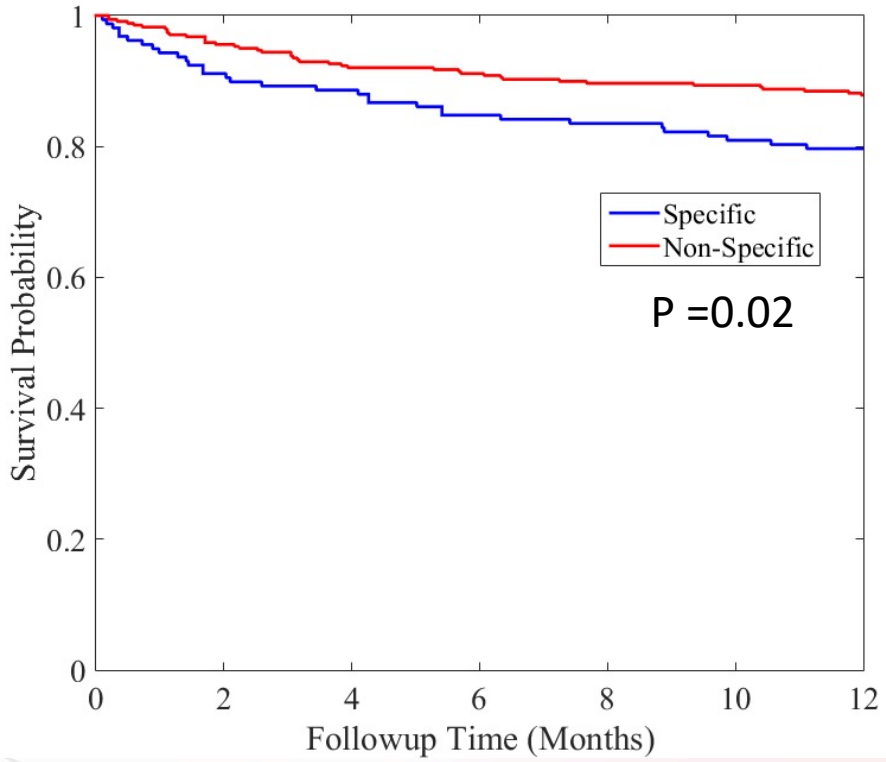
CLINICALLY assigned (3 month)

Specific vs. Non-specific HF etiology



IMAGING assigned

Specific vs. Non-specific HF etiology



Survival adjusted to MAGGIC score

Courtesy of Ian Paterson

Circulation. 2020 Mar 10;141(10):818-827

Interpretation: OUTSMART (IMAGE HF 1B)

In patients with non-ischemic HF,

- CMR increases Specific Imaging diagnoses but does not change Specific Clinical diagnoses
- Imaging-based diagnoses appear to enable stratification of risk
- Greater attention to use of CMR and HF diagnoses from Imaging in general should be considered

Courtesy of Ian Paterson

Circulation. 2020 Mar 10;141(10):818-827

Cardiac Sarcoidosis

	Japanese Society of Sarcoidosis (2017)	Heart Rhythm Society (2014)
Histologic diagnosis	• EMB: non-caseating granulomas, and • Histologic or clinical diagnosis of extracardiac sarcoidosis	• EMB: non-caseating granuloma

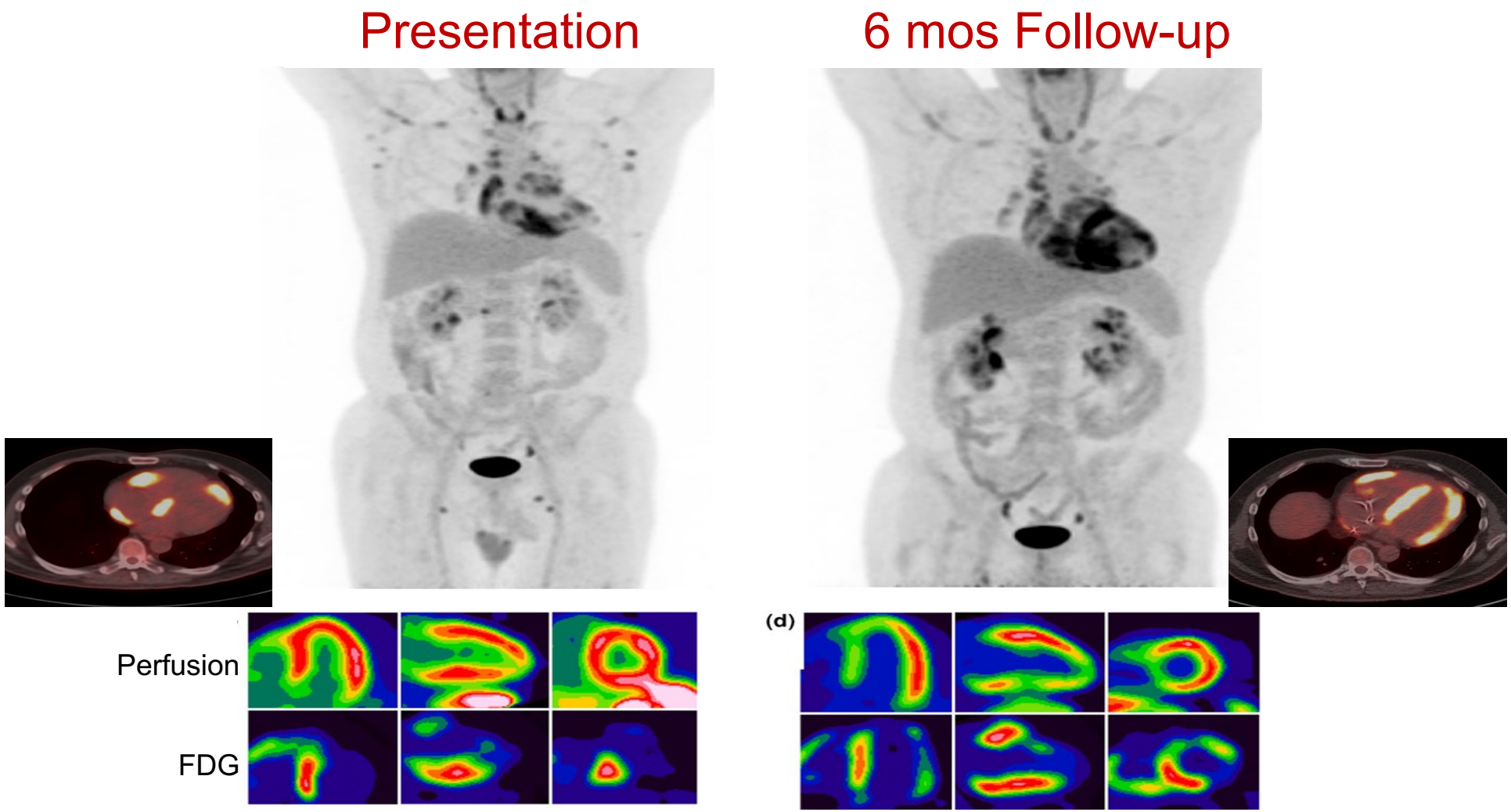
Clinical diagnosis	• Clinical/histologic extracardiac sarcoidosis, and
	  • ≥2 major criteria, or
	  • 1 major and ≥2 minor criteria
		• Histologic diagnosis of extracardiac sarcoidosis, and ≥1 clinical criteria = "probable" CS

Clinical criteria	• Major
	  ▫ High-grade AV block or fatal VT/VF
	  ▫ Basal septal thinning or abnormal wall anatomy
	  ▫ LVEF<50%
	  ▫ Abnormally high ♥Ga-67 or ♥F-18 FDG uptake
	  ▫ MRI ♥LGE
	• Minor
	  ▫ ECG: NSVT, RBBB, LAD, RAD, Qwave
	  ▫ SPECT perfusion defects
	  ▫ EMB: Monocyte infiltration and moderate or severe myocardial interstitial fibrosis
		• Cardiomyopathy or heart block responsive to steroid ± immunosuppressive therapy
		• Mobitz type II 2° or 3°AV block
		• Unexplained LVEF<40%
		• Spontaneous or induced VT
		• Positive ♥^{67}Ga uptake
		• CMR LGE c/w cardiac sarcoidosis
		• Patchy ^{18}FDG uptake on PET c/w cardiac sarcoidosis
		• Exclusion of other causes of ♥manifestations

Birnie DH et al. Heart Rhythm 2014;11:1304–1323.

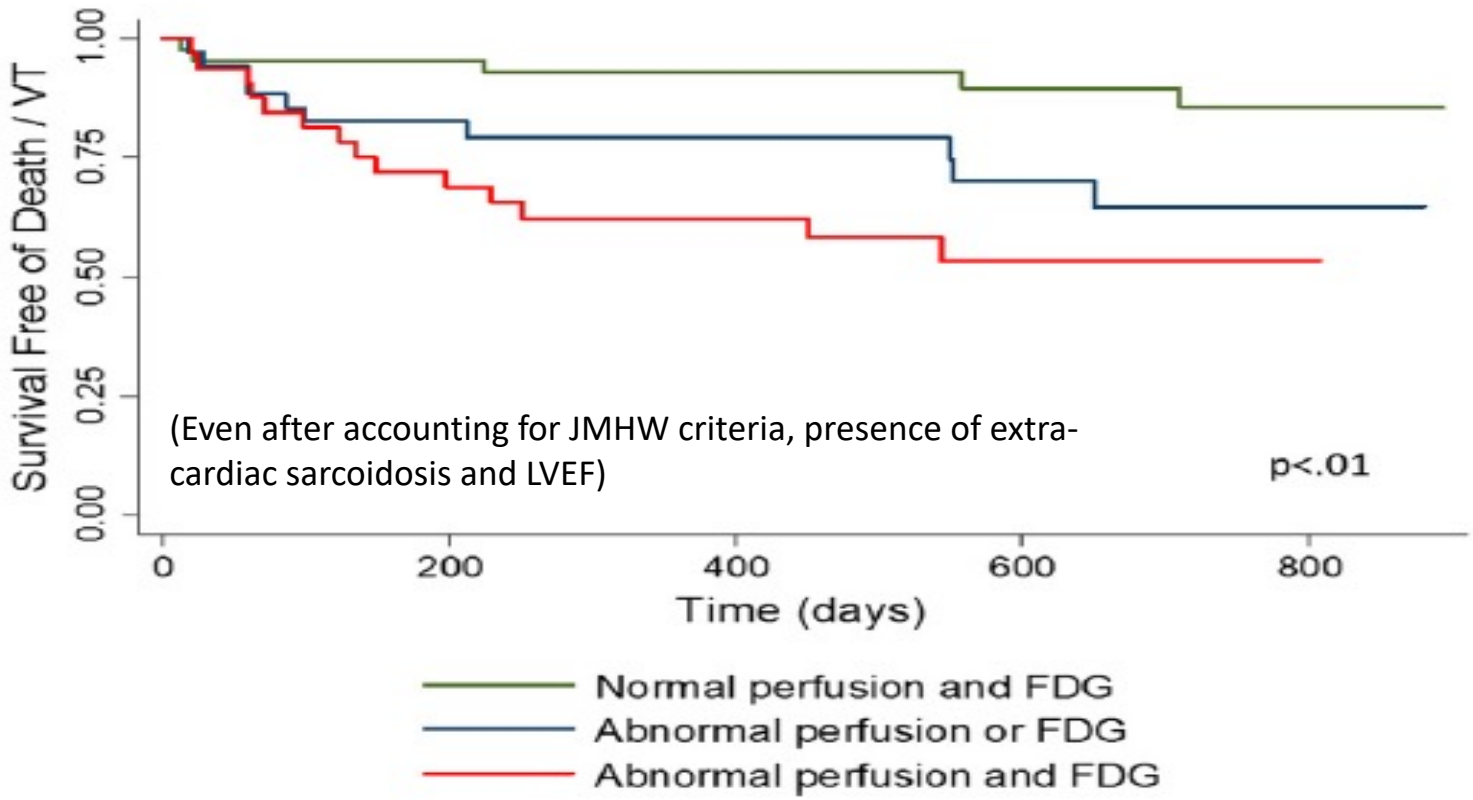
Tersaki F et al. Ann Nucl Cardiol 2017;3(1) doi: 10.17996/anc.17-00042

44 year old man with syncope – complete heart block



In patients with Suspected Cardiac Sarcoidosis: Abnormal Cardiac PET identifies patients at risk for SCD/VT

Survival Free of Death or VT Stratified by Cardiac PET Examination Results

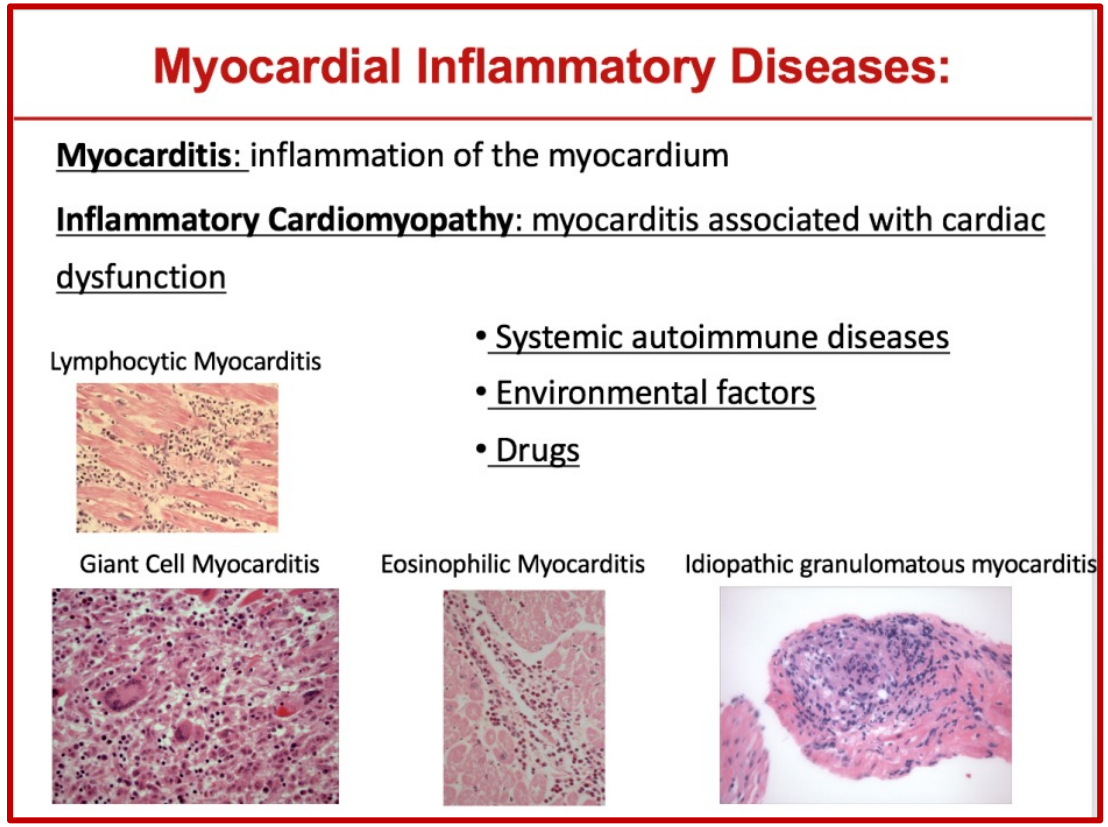


Blankstein et al. J Am Coll Cardiol. 2013;63(4):329-36

Challenges with FDG PET

- Increased FDG in heart is not specific for CS
  - Hibernating myocardium
  - Other inflammatory cardiomyopathies
  - Myocarditis (only some forms)
  - "Physiologic" uptake (poor prep)

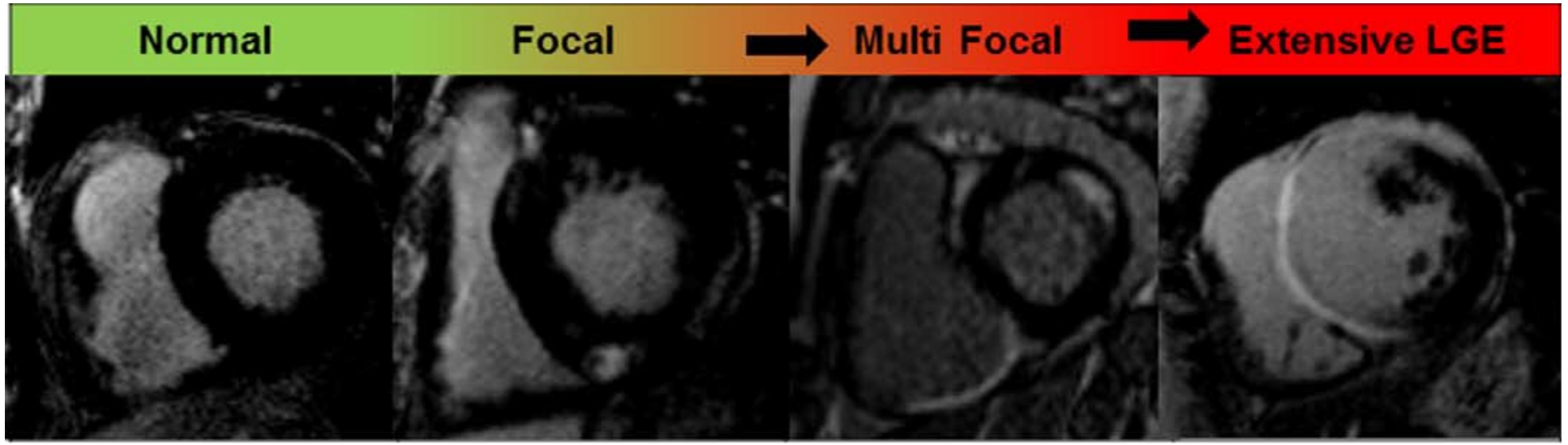
- Requires patient preparation
  - High fat low carb diet
  - Fasting
  - +/- heparin pre-scan

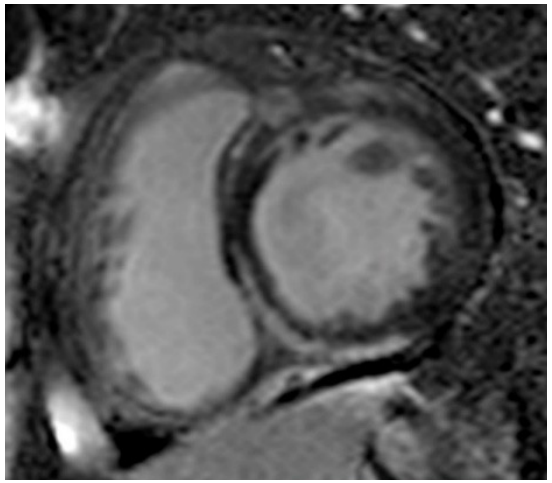


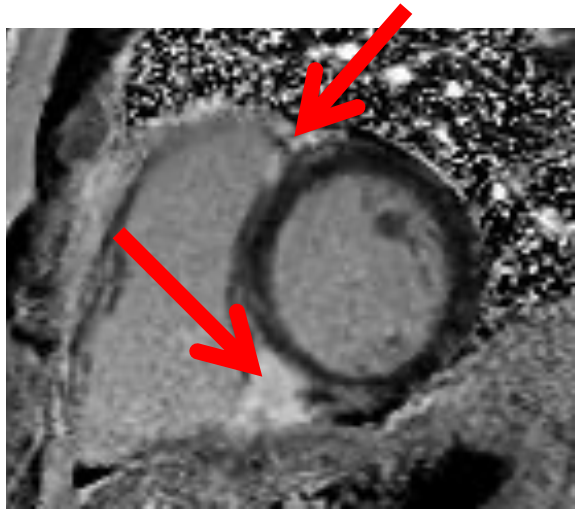
(Blankstein, Lundbye, Heller. JNC 2015)

Cardiac MRI

- CMR → myocardial late gadolinium enhancement in regions of fibrosis / edema







(Blankstein, Waller, Circ CV Imaging 2016)

Magnetic Resonance Imaging

Presence of Late Gadolinium Enhancement by Cardiac Magnetic Resonance Among Patients With Suspected Cardiac Sarcoidosis Is Associated With Adverse Cardiovascular Prognosis

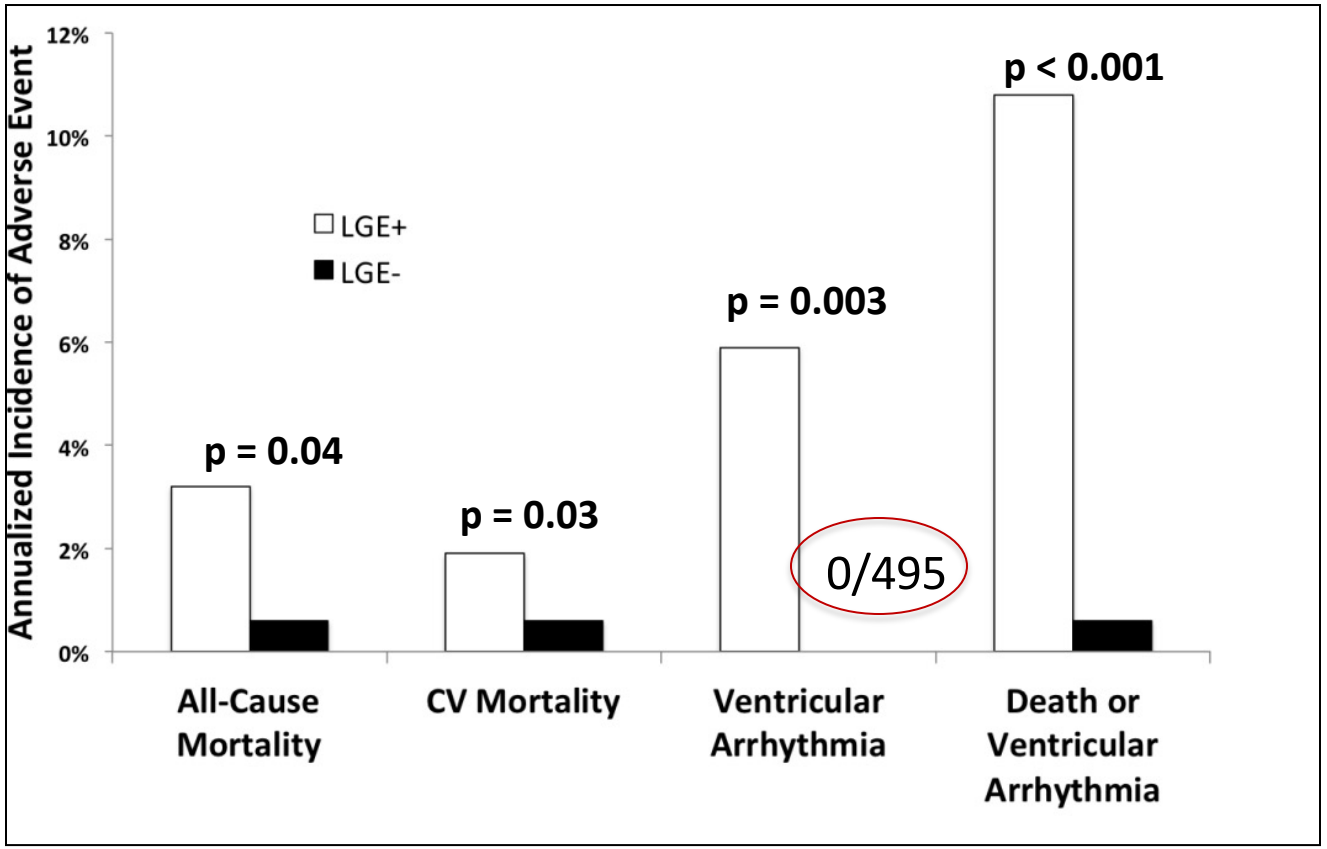
A Systematic Review and Meta-Analysis

Edward Hulten, MD, MPH;* Vikram Agarwal, MD, MPH;* Michael Cahill, MD; Geoff Cole, MD; Tomas Vita, MD; Scott Parrish, MD; Marcio Sommer Bittencourt, MD; Venkatesh L. Murthy, MD, PhD; Raymond Kwong, MD, MPH; Marcelo F. Di Carli, MD, Ron Blankstein, MD

No LGE →

excellent prognosis

Meta-analysis of 7 studies
694 patients

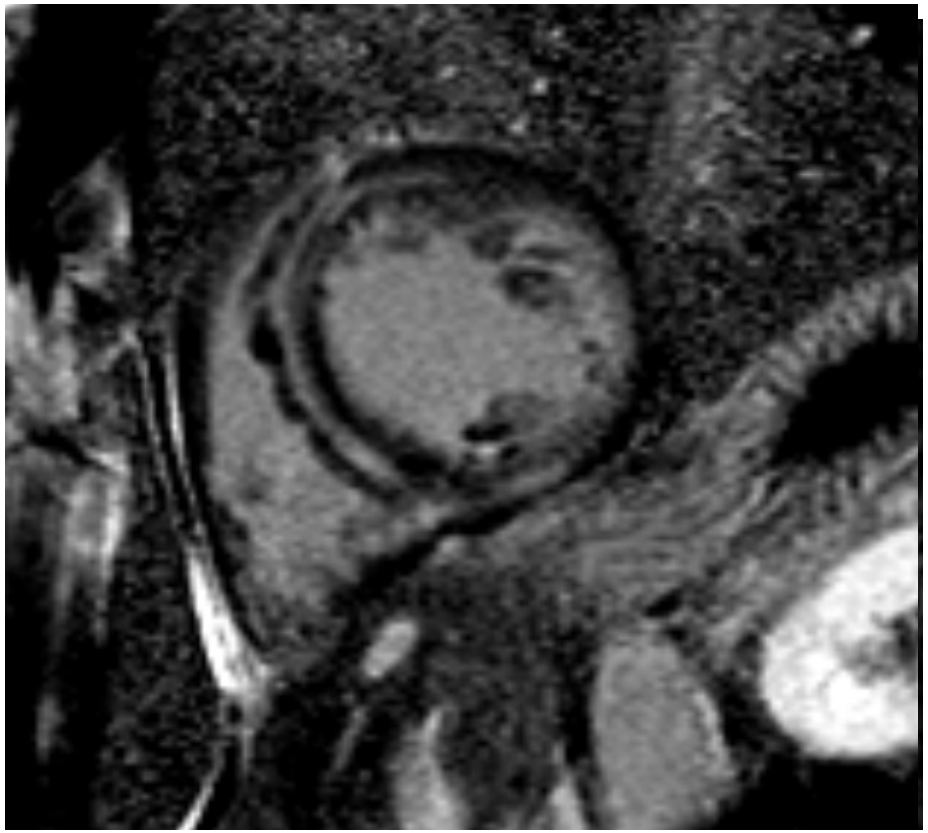


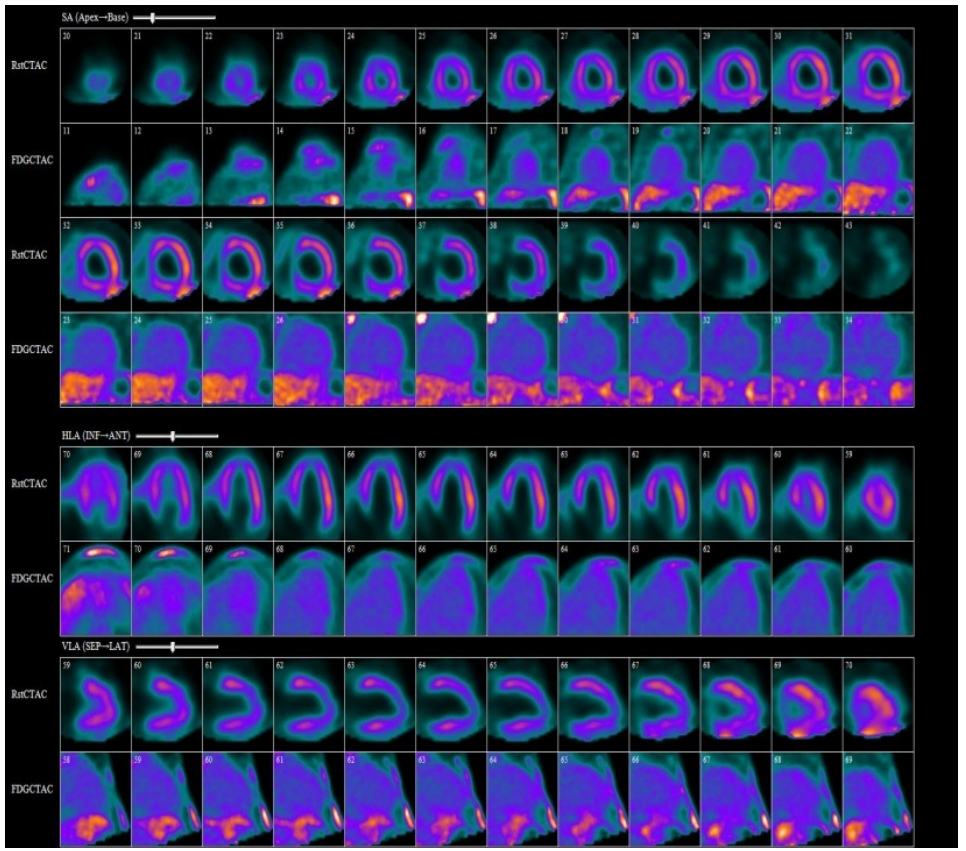
(Slide Courtesy of Ron Blankstein)

(Circulation: CV Imaging, September 2016)

Limitations of CMR

In patients with LGE, difficult to distinguish scar from inflammation





Perfusion

FDG

Perfusion

FDG

Perfusion

FDG

(Slide Courtesy of Ron Blankstein)

When to suspect CS (Who should be screened for CS ?)

Biopsy proven extra-cardiac sarcoidosis

- Symptoms (palpitations, pre-syncope, syncope)
- Abnormal EKG
- Abnormal echocardiogram

Specific presentations with no prior history of sarcoidosis

- Unexplained Mobitz II or 3rd degree AV block; age<60
- Sustained Monomorphic VT of Unknown Etiology
- ARVC (with AV block)
- Unexplained HFrEF

Birnie DH, Sauer WH et al. Heart Rhythm. 2014;11:1305-23
Blankstein, Waller. Circulation : CV Imaging 2015
Roberts WC et al AJC 2014;113:706-12

Suggested Use of Advanced Imaging

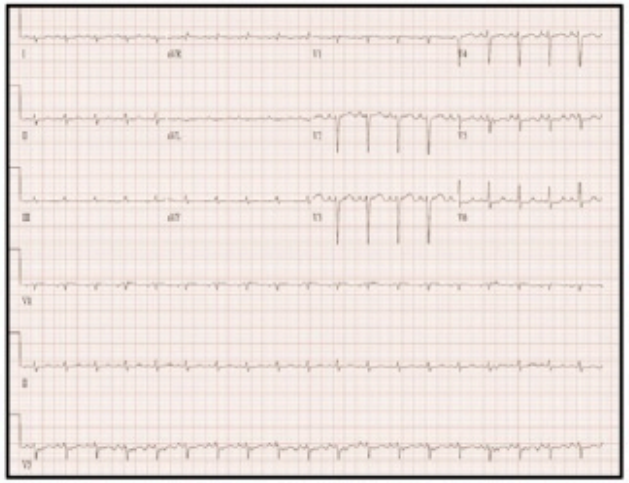
Table 1
Suggested use of advanced imaging modalities in various clinical scenarios

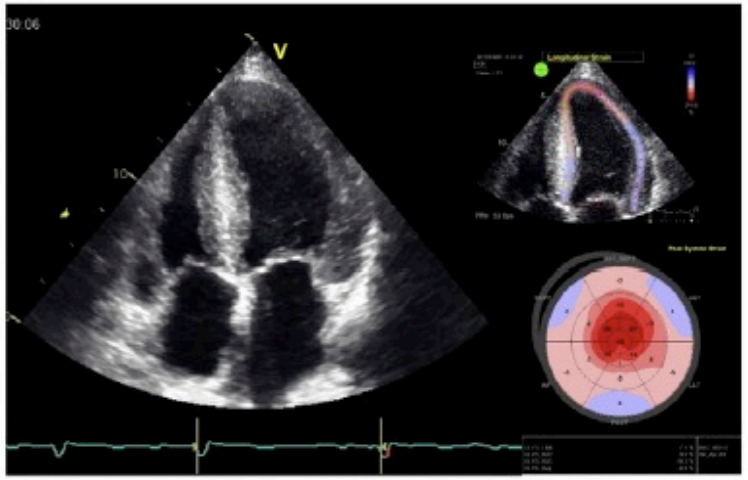
Clinical Scenario	Suggested Test
Screening younger patients (age <60 y) with acute presentation of idiopathic advanced conduction system disease	FDG–PET
Screening for cardiac involvement in patients with extracardiac sarcoidosis and 1 initially abnormal screening test	MRI
To follow response to steroids or immunosuppression	FDG–PET
To assess for active disease in patients with manifest CS and increased ventricular arrhythmia burden	FDG–PET

Birnie DH et al. Heart Rhythm (2014);11:1304–1323
Birnie DH et al. Clin Chest Med (2015; 36:: 657–668

Findings on cardiovascular investigations associated with cardiac amyloidosis

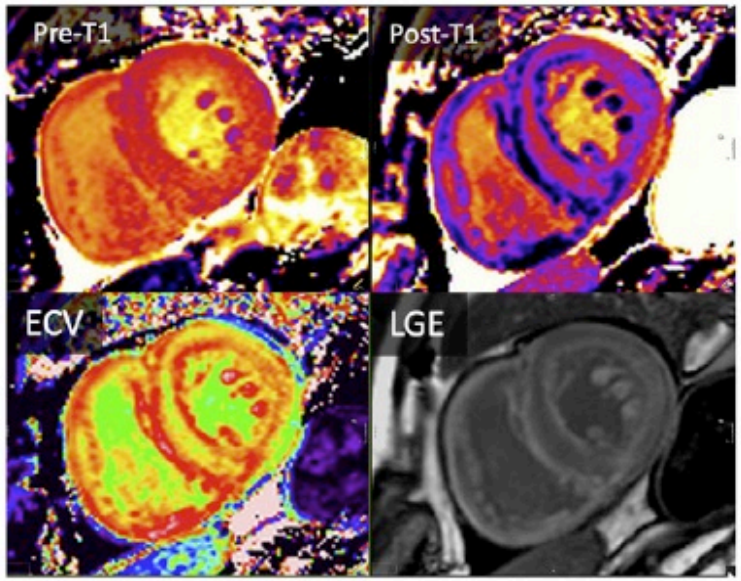
-Low voltage (especially limb leads)
-Pseudo-infarct pattern
-Atrial arrhythmia
-Conduction system disease
-Ventricular ectopy

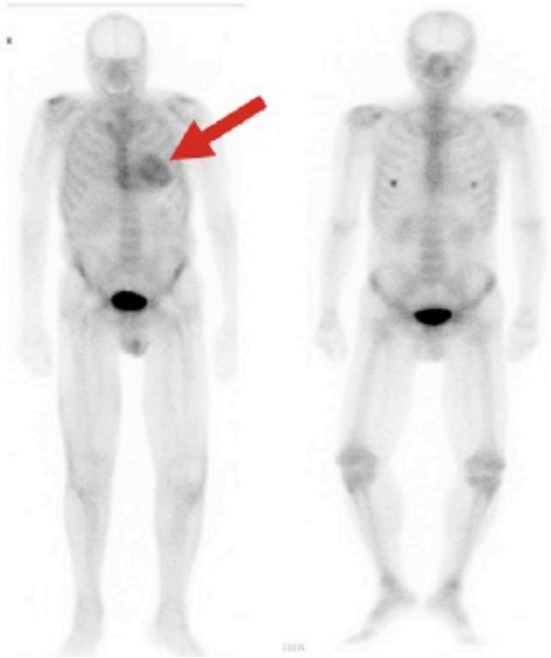




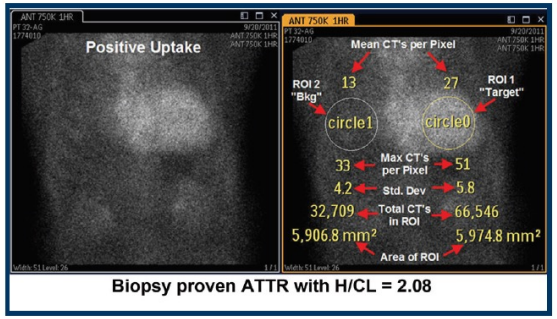
-Increased LV and RV wall thickness
-Preserved ventricular size, biatrial enlargement
-Diastolic dysfunction
-Increased valvular and interatrial septum thickness
-Small pericardial effusion
-Reduced LV GLS, preserved apical strain (basal-apical gradient)

-Diffuse transmural or subendocardial pattern LGE
-Left atrial LGE
-Elevated native (non-contrast) T1 relaxation time
-Shortened post-contrast T1 relaxation time
-Elevated extracellular volume (ECV) fraction





-Increased myocardial radiotracer uptake equal to or greater than bone (≥Grade 2), or quantitative comparison with the contralateral lung (HCL ratio ≥1.5) is consistent with ATTR cardiac amyloidosis



Biopsy proven ATTR with H/CL = 2.08

Fine NM, Davis MK et al. CCS/CHFS Joint Position Statement on the Evaluation and Management of Patients with Cardiac Amyloidosis. Canadian Journal of Cardiology 36 (2020) 322-334

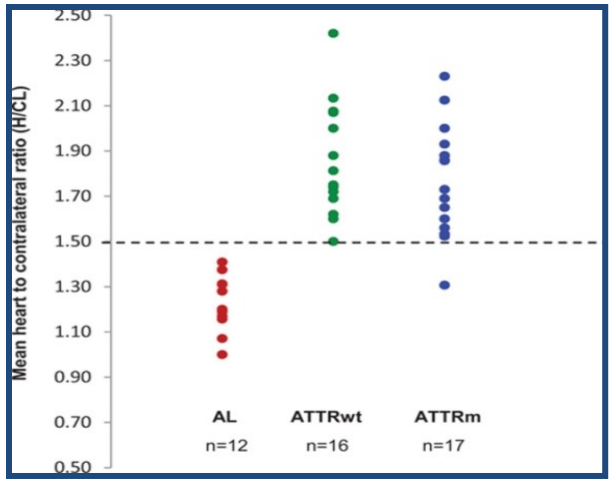
^{99m}Tc-DPD and ^{99m}Tc-PYP : Highly sensitive and specific for cardiac ATTR

Table 2. Scintigraphic Findings in the Patient Population and Control Group

	Group A TTR-Related CA (15 Patients)	Group B AL CA (10 Patients)	Unaffected Control Patients (10 Patients)
Heart tracer retention (%)			
Median	7.3*†	3.8‡	2.9
Interquartile range	6.7–8.4	3.4–4.05	2.7–3.5
Whole-body tracer retention (%)			
Median	70.1†	67.6‡	56
Interquartile range	63.6–77.3	61.8–71.3	52–60
Heart/whole-body ratio			
Median	10.0*†	5.4	5.4
Interquartile range	8.9–11.2	5.2–5.5	5.0–5.7
Visual cardiac score			
0	0 (0%)	10 (100%)	10 (100%)
1	0 (0%)	0 (0%)	0 (0%)
2	3 (20%)	0 (0%)	0 (0%)
3	12 (80%)	0 (0%)	0 (0%)

*$p < 0.05$ group A vs. B. †$p < 0.05$ group A vs. control group. ‡$p < 0.05$ group B vs. control group.
CA = cardiac amyloidosis; TTR = transthyretin.

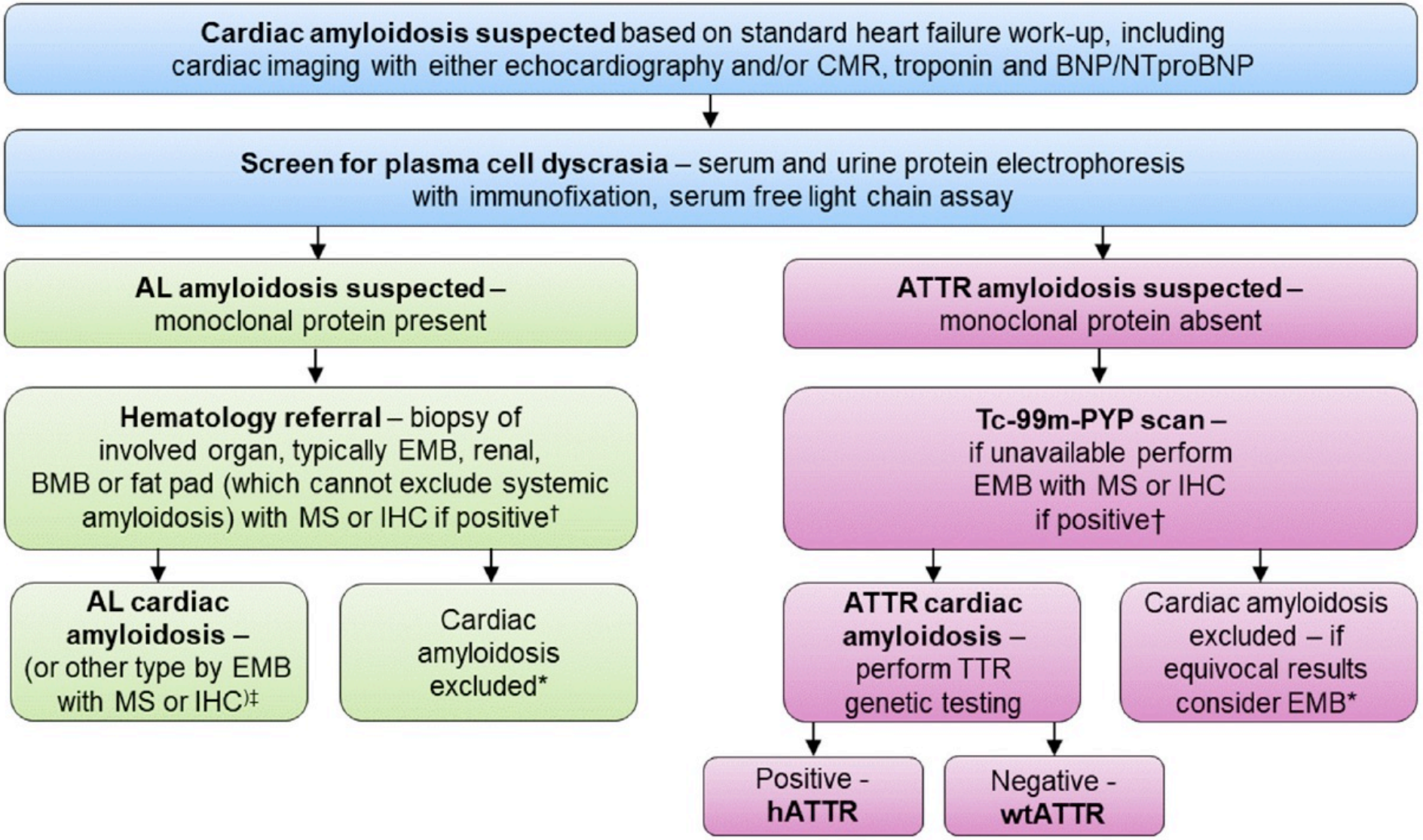
Perugini E et al. J Am Coll Cardiol 2005;46:1076–84



Bokhari S et al. Circ CVIM 2013;6:195-2013

Courtesy of Sharmila Dorbala

Diagnostic algorithm for the evaluation of suspected cardiac amyloidosis



Fine NM, Davis MK et al. CCS/CHFS Joint Position Statement on the Evaluation and Management of Patients with Cardiac Amyloidosis. Canadian Journal of Cardiology 36 (2020) 322-334

Special Imaging for Special Cardiomyopathies. What do we know?

- **Imaging integral to heart failure diagnosis & management**
  - ***Echo Mainstay – there is a role for 'Special' Imaging***
- **Guidelines support Imaging but we need more high quality evidence studies**
- **Special Imaging with PET and CMR have increased costs and specific limitations but are effective, generally safe and have increasing availability**
- ***NICM etiology appears important for prognosis***
  - ***CMR can increase specific Dx vs Echo, and appears to enable risk stratification***
  - ***need more attention to the Imaging in making the Diagnosis***
- **Vast array of emerging imaging biomarkers**
  - ***FDG for Cardiac Sarcoid / PYP for Cardiac Amyloid have changed our approach to these disease***
  - ***Others require further evaluation***

Paterson et al, Circ 2020

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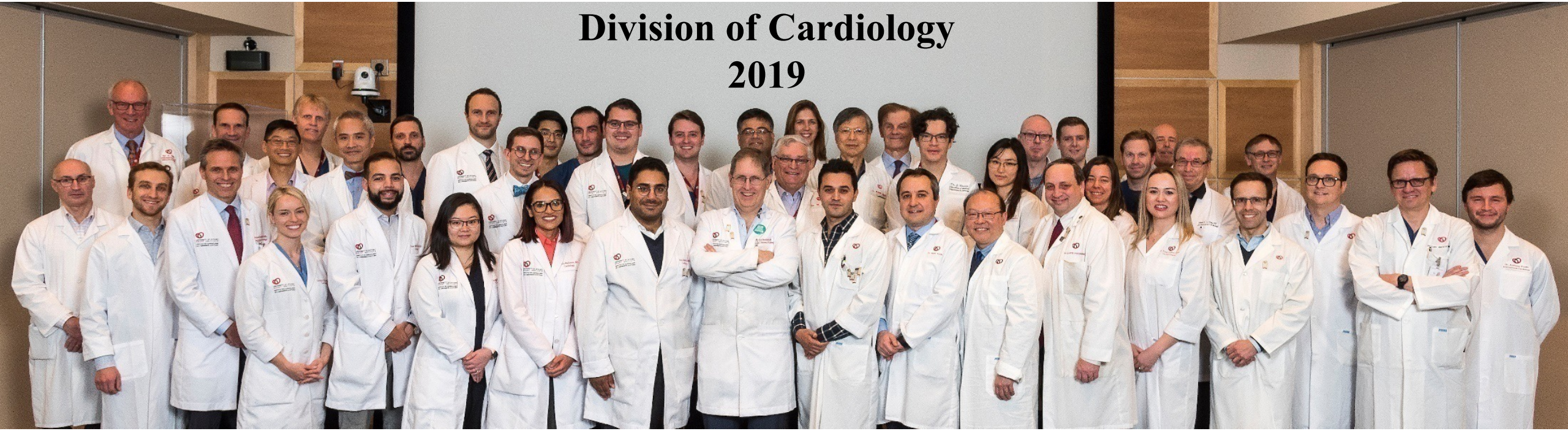
Thank you!



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Thank you!

Division of Cardiology 2020

Special Imaging for Special Cardiomyopathies. What do we know?

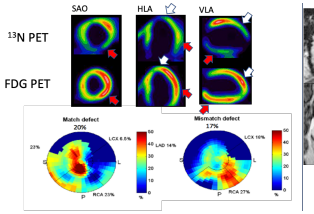
- **Imaging integral to heart failure diagnosis & management**
  - ***Echo Mainstay – there is a role for 'Special' Imaging***

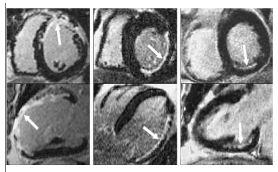
TTE is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of either HFrEF, HFmrEF or HFpEF.	I	C

- **Guidelines support Imaging but we need more high quality evidence studies**

CMR is recommended for the assessment of myocardial structure and function (including right heart) in subjects with poor acoustic window and patients with complex congenital heart diseases (taking account of cautions/contra-indications	I	C

- **Special Imaging with PET and CMR have increased costs and specific limitations but are effective, generally safe and have increasing availability**





Kim et al, NEJM 2000

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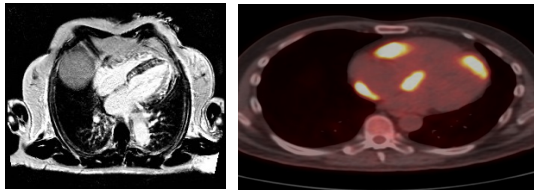

Paterson et al, Circ 2020

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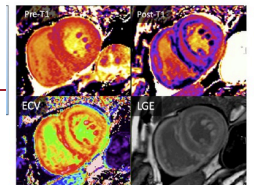

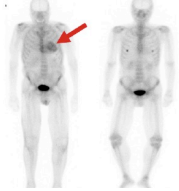

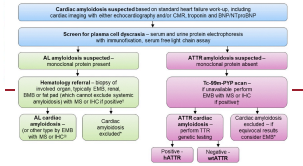

CCS/CHFS Joint Position St. CJC 2020