Special Cardiomyopathies: Focus on Treatment

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Objectives

- Evaluate treatment options for distinct cardiomyopathies (Amyloid, Sarcoid and Peripartum cardiomyopathies)
- Review international guideline recommendations for the above-mentioned cardiomyopathies
- Discuss algorithms to facilitate monitoring response to treatment

Cardiac Sarcoidosis: Different Faces of a Case

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Conflict of Interest Disclosures

- **Consultancy/speaking fees**: Bayer, Janssen, Novartis, Boehringer-Ingelheim, Takeda, Pfizer, Akcea, Alnylam, Amgen, Ferring

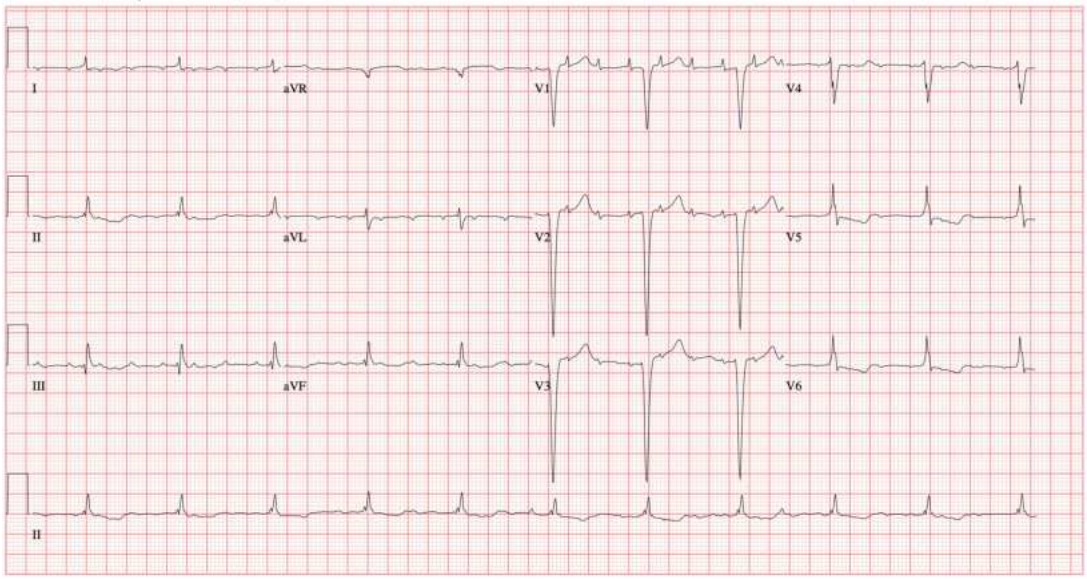
- **Grant funding**: Pfizer, Takeda, Boehringer-Ingelheim, Servier, Akcea

Case: Mr. F

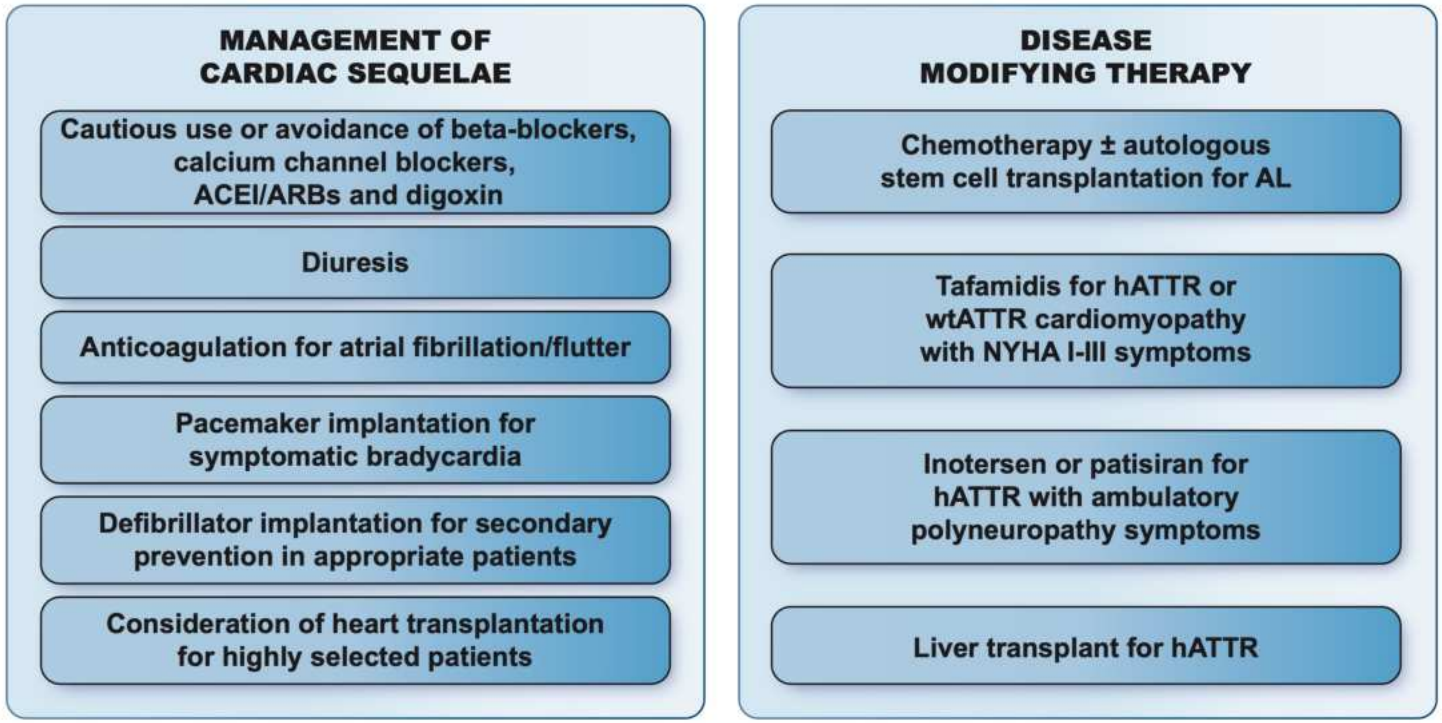
- 74-year-old man referred to Cardiac Amyloid Clinic with possible amyloid after presenting with new-onset HF and atrial flutter
- PMHx:
  - HFpEF; LVEF 50% on recent echo
  - Atypical atrial flutter/atrial fibrillation; previous DCCV
  - TIA vs. migraine
  - Bilateral CTS, status post-CTR x2
  - Lumbar spinal stenosis
  - BPH
  - OA
- Meds
  - Metoprolol 50 mg BID
  - Apixaban 5 mg BID
  - Furosemide 20 mg daily
  - Pantoprazole
- NYHA 3
- HR 62, BP 118/72
- JVP 8 cm ASA, mild edema

Investigations

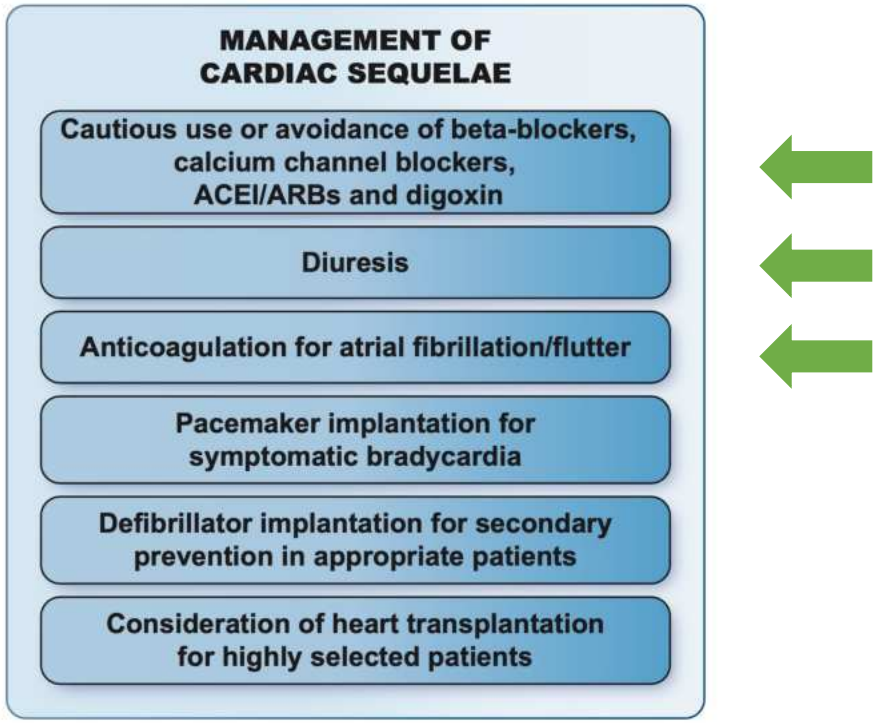
- Echo: normal LV size, thick walls (septum 16 mm), LVEF 50%. GLS -11% with ASP. Normal RV size and function, increased RVWT. Moderate TR, moderate AS.
- PYP: grade 3
- SPEP/UPEP/IFE/SFLC normal
- NT-proBNP 4000, TnT 43
- GFR 52
- Genetic testing: no mutation in *TTR*



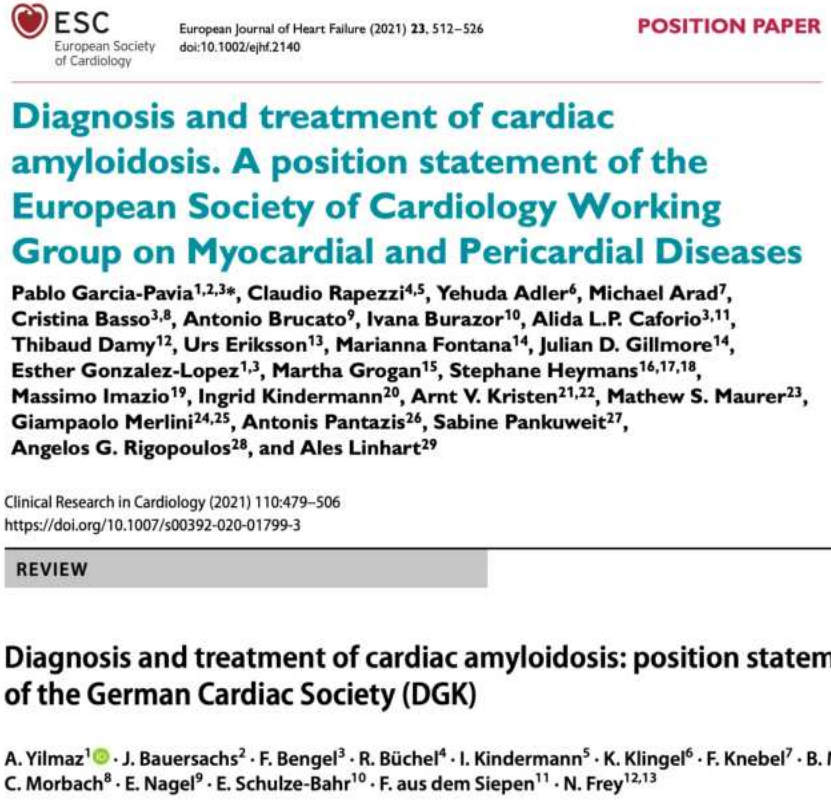
So, he has ATTRwt… Now what?



How can we optimize his supportive management?



Other Scientific Societies have opinions, too



ESC European Society of Cardiology

European Journal of Heart Failure (2021) 23, 512–526
doi:10.1002/ejhf.2140

POSITION PAPER

Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

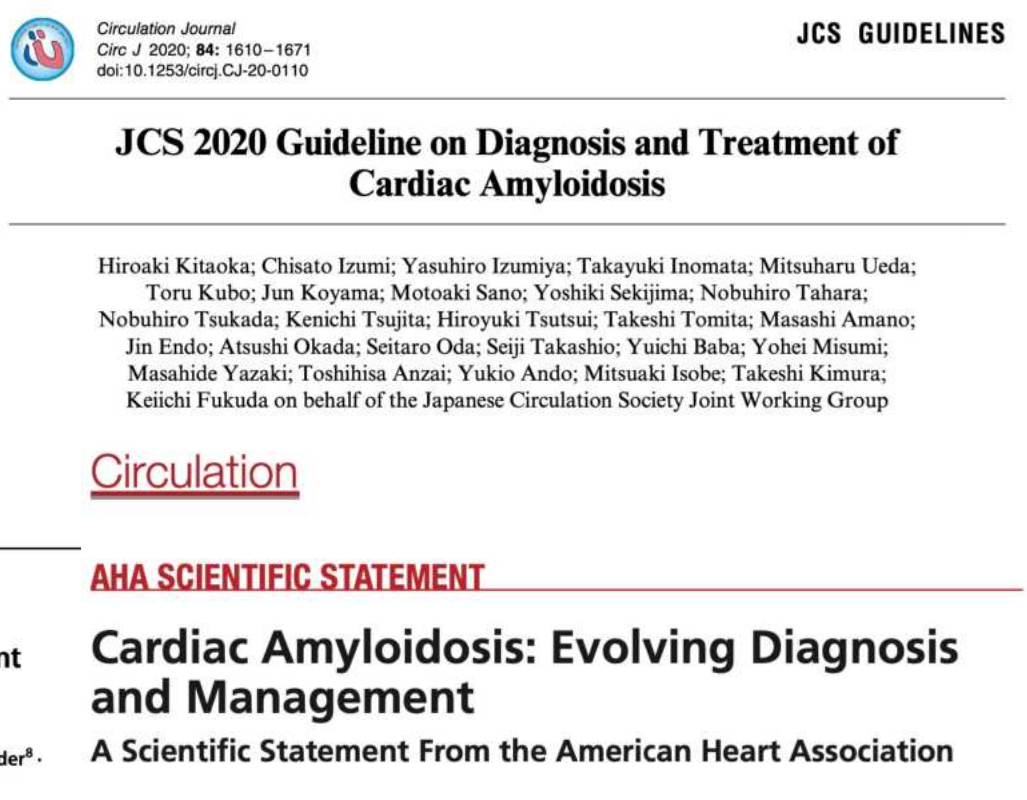
Pablo Garcia-Pavia[1,2,3]*, Claudio Rapezzi[4,5], Yehuda Adler[6], Michael Arad[7], Cristina Basso[3,8], Antonio Brucato[9], Ivana Burazor[10], Alida L.P. Caforio[3,11], Thibaud Damy[12], Urs Eriksson[13], Marianna Fontana[14], Julian D. Gillmore[14], Esther Gonzalez-Lopez[1,3], Martha Grogan[15], Stephane Heymans[16,17,18], Massimo Imazio[19], Ingrid Kindermann[20], Arnt V. Kristen[21,22], Mathew S. Maurer[23], Giampaolo Merlini[24,25], Antonis Pantazis[26], Sabine Pankuweit[27], Angelos G. Rigopoulos[28], and Ales Linhart[29]

Clinical Research in Cardiology (2021) 110:479–506
https://doi.org/10.1007/s00392-020-01799-3

REVIEW

Diagnosis and treatment of cardiac amyloidosis: position statement of the German Cardiac Society (DGK)

A. Yilmaz[1] · J. Bauersachs[2] · F. Bengel[3] · R. Büchel[4] · I. Kindermann[5] · K. Klingel[6] · F. Knebel[7] · B. Meder[8] · C. Morbach[8] · E. Nagel[9] · E. Schulze-Bahr[10] · F. aus dem Siepen[11] · N. Frey[12,13]



Circulation Journal
Circ J 2020; 84: 1610–1671
doi:10.1253/circj.CJ-20-0110

JCS GUIDELINES

JCS 2020 Guideline on Diagnosis and Treatment of Cardiac Amyloidosis

Hiroaki Kitaoka; Chisato Izumi; Yasuhiro Izumiya; Takayuki Inomata; Mitsuharu Ueda; Toru Kubo; Jun Koyama; Motoaki Sano; Yoshiki Sekijima; Nobuhiro Tahara; Nobuhiro Tsukada; Kenichi Tsujita; Hiroyuki Tsutsui; Takeshi Tomita; Masashi Amano; Jin Endo; Atsushi Okada; Seitaro Oda; Seiji Takashio; Yuichi Baba; Yohei Misumi; Masahide Yazaki; Toshihisa Anzai; Yukio Ando; Mitsuaki Isobe; Takeshi Kimura; Keiichi Fukuda on behalf of the Japanese Circulation Society Joint Working Group

Circulation

AHA SCIENTIFIC STATEMENT

Cardiac Amyloidosis: Evolving Diagnosis and Management

A Scientific Statement From the American Heart Association

Canada vs. The World

- Comparison of five Scientific Society documents
- General agreement on diuresis
- General agreement on avoiding ACE/ARB, BB, digoxin, CCB
- General agreement on anticoagulation in AF

Rapezzi C, et al. J Am Coll Cardiol. 2022;79(13):1288–1303.

TABLE 3 Drug Therapies for HF and AF

Drug	ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
HF setting					
Loop or thiazide diuretics	Recommended[a]	Recommended[a]	Recommended[a]	Recommended, but avoid underfilling and worsening renal function from restrictive physiology[c]	Recommended[a]
Nitrates or carperitide (AHF)	No recommendation	No recommendation	No recommendation	No recommendation	Might be considered[a]
Catecholamines, PDE inhibitor (AHF)	No recommendation	No recommendation	No recommendation	No recommendation	Might be considered[a]
Beta-blockers	Not recommended, deprescribe (should be avoided)[c]	Avoid or very cautious use[c]	Avoid or very cautious use[c]	No data for benefit; may not be tolerated given fixed stroke volume (should be avoided)[c]	Tolerated dosing might be considered[a]
ACE inhibitor/ARB	Not recommended (should be avoided)[c]	Avoid or very cautious use[c]	Avoid or very cautious use[c]	No data for benefit; may exacerbate amyloid-related hypotension from autonomic dysfunction (should be avoided)[c]	Tolerated dosing might be considered[a]
Sacubitril/valsartan	No recommendation	No recommendation	No recommendation	No data for benefit; may exacerbate amyloid-related hypotension from autonomic dysfunction (should be avoided)[c]	No recommendation
MRA	No recommendation	No recommendation	Recommended[a]	Might be considered in conjunction with loop diuretics if adequate blood pressure and renal function[a]	Tolerated dosing might be considered[a]
AF/flutter/tachycardia setting					
Digoxin	Might be considered[b]	Avoid or very cautious use[c]	Avoid or very cautious use[c]	Might be considered; use cautiously[b]	Not recommended (should be avoided)[c]
Amiodarone	Might be considered (first choice)[a]	No recommendation	Might be considered (first choice)[a]	Might be considered (first choice)[a]	No recommendation
Beta-blockers	Not recommended (should be avoided)[c]	Avoid or very cautious use[c]	Avoid or very cautious use[c]	Might be considered[a]	Case-by-case decision (may be considered)[a]
Non-DHP CCB: ATTR-CA, preserved LV function	No recommendation	Avoid or very cautious use[c]	Avoid or very cautious use[c]	Avoid whenever possible[c]	Case-by-case decision (may be considered)[a]
Non-DHP CCB: ATTR-CA, reduced LV function					Not recommended (should be avoided)[c]
Non-DHP CCB: AL-CA				Not recommended (should be avoided)[c]	Not recommended (should be avoided)[c]
Anticoagulation regardless of CHA_2DS_2-VASc score?	Yes (recommended)[a]	No recommendation	Yes (recommended)[a]	Yes (recommended)[a]	No recommendation
Anticoagulation in SR?	Might be considered[a]	No recommendation	No recommendation	Might be considered[a]	No recommendation

Back to Mr. F

- Metoprolol reduced to 25 BID, HR 89
- Lasix increased to 40 BID, spironolactone 12.5 mg daily added
- He feels better!
- GFR stable, NT-proBNP 2300

- Metoprolol stopped, average HR on Holter now 115 bpm
- What should we do now?

Catheter ablation, device therapies, and heart transplantation

- Very little evidence, sparse recommendations of AF ablation

- General agreement on secondary prevention ICDs
- General agreement that benefit is unclear in primary prevention ICDs
- General agreement that PPM is reasonable per standard indication; CRT in selected patients

Rapezzi C, et al. J Am Coll Cardiol. 2022;79(13):1288–1303.

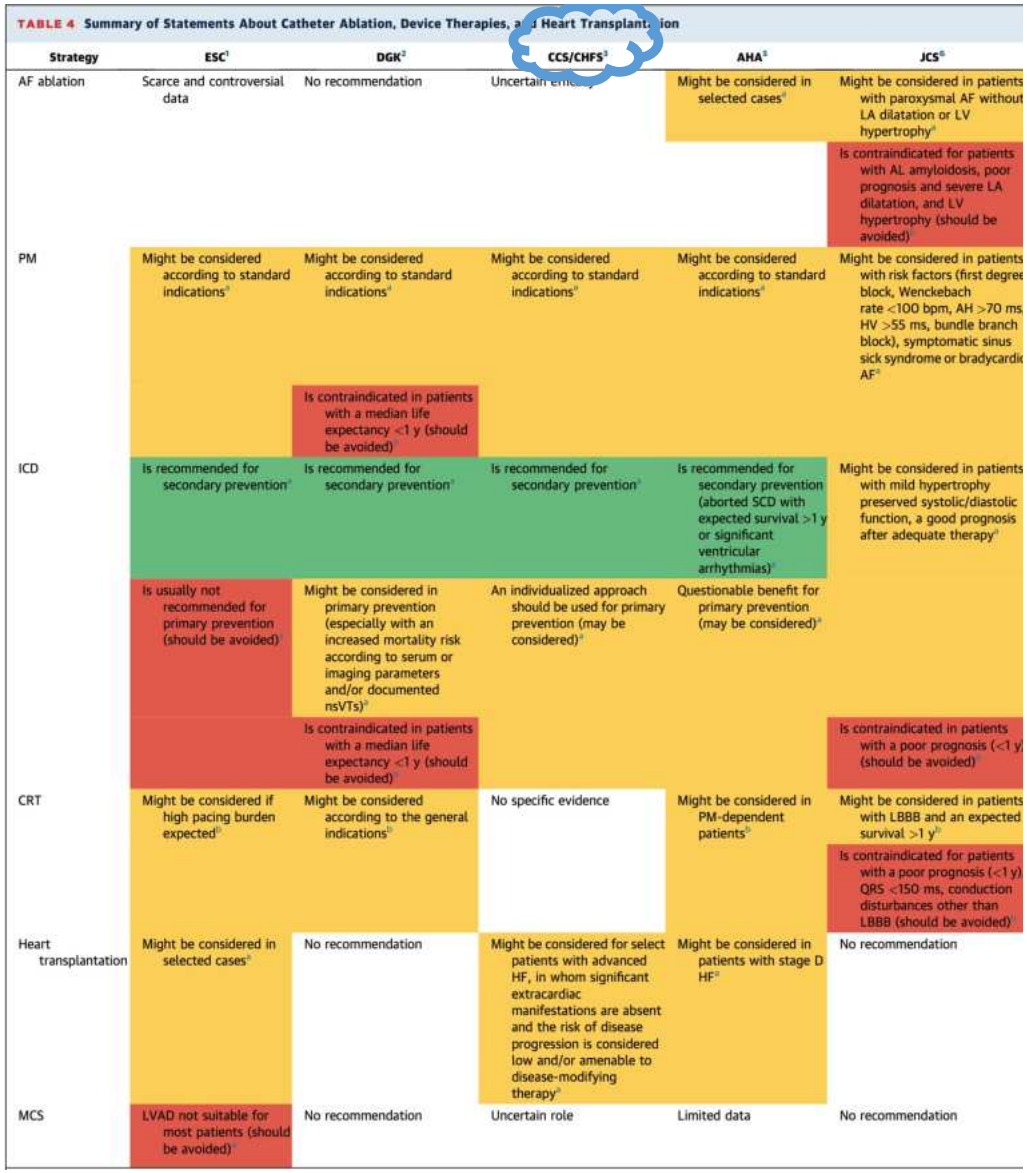
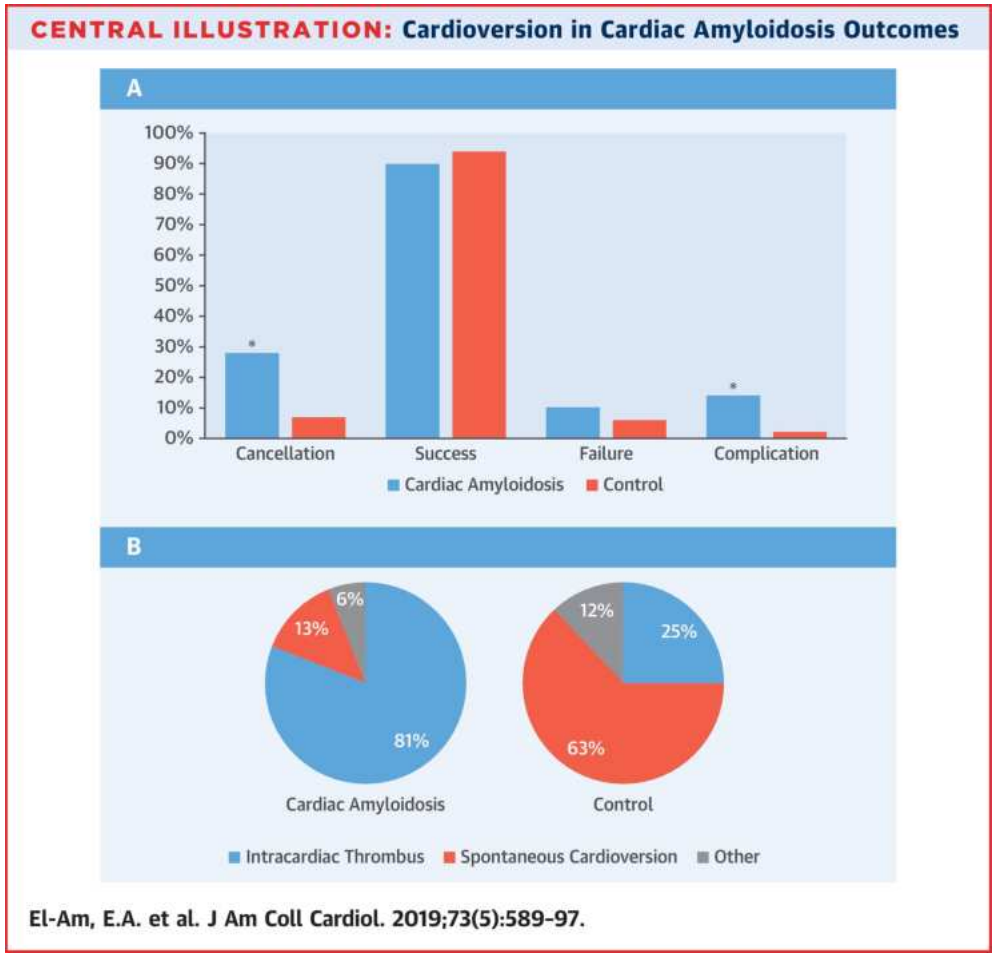


TABLE 4 Summary of Statements About Catheter Ablation, Device Therapies, and Heart Transplantation

Strategy	ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
AF ablation	Scarce and controversial data	No recommendation	Uncertain effect	Might be considered in selected cases[a]	Might be considered in patients with paroxysmal AF without LA dilatation or LV hypertrophy[a]
					Is contraindicated for patients with AL amyloidosis, poor prognosis and severe LA dilatation, and LV hypertrophy (should be avoided)[c]
PM	Might be considered according to standard indications[b]	Might be considered according to standard indications[d]	Might be considered according to standard indications[e]	Might be considered according to standard indications[d]	Might be considered in patients with risk factors (first degree block, Wenckebach rate <100 bpm, AH >70 ms, HV >55 ms, bundle branch block), symptomatic sinus sick syndrome or bradycardic AF[e]
		Is contraindicated in patients with a median life expectancy <1 y (should be avoided)[c]			
ICD	Is recommended for secondary prevention[c]	Is recommended for secondary prevention[c]	Is recommended for secondary prevention[c]	Is recommended for secondary prevention (aborted SCD with expected survival >1 y or significant ventricular arrhythmias)[c]	Might be considered in patients with mild hypertrophy preserved systolic/diastolic function, a good prognosis after adequate therapy[a]
	Is usually not recommended for primary prevention (should be avoided)[c]	Might be considered in primary prevention (especially with an increased mortality risk according to serum or imaging parameters and/or documented nsVTs)[a]	An individualized approach should be used for primary prevention (may be considered)[a]	Questionable benefit for primary prevention (may be considered)[a]	
		Is contraindicated in patients with a median life expectancy <1 y (should be avoided)[c]			Is contraindicated in patients with a poor prognosis (<1 y (should be avoided)[c]
CRT	Might be considered if high pacing burden expected[b]	Might be considered according to the general indications[b]	No specific evidence	Might be considered in PM-dependent patients[b]	Might be considered in patients with LBBB and an expected survival >1 y[b]
					Is contraindicated for patients with a poor prognosis (<1 y), QRS <150 ms, conduction disturbances other than LBBB (should be avoided)[c]
Heart transplantation	Might be considered in selected cases[b]	No recommendation	Might be considered for select patients with advanced HF, in whom significant extracardiac manifestations are absent and the risk of disease progression is considered low and/or amenable to disease-modifying therapy[b]	Might be considered in patients with stage D HF[b]	No recommendation
MCS	LVAD not suitable for most patients (should be avoided)[c]	No recommendation	Uncertain role	Limited data	No recommendation

Anticoagulation in AF and cardiac amyloidosis

- Of 13 cardiac amyloidosis patients with DCCV cancelled due to thrombus on TEE:
  - 2 had AF <48 hrs
  - 4 had INR >2 for >3 weeks



Back to Mr. F

- He is loaded with oral amiodarone followed by 100 mg daily maintenance
- HR improved to 80
- TEE-guided cardioversion successful
- Continues on apixaban
- NYHA 2

What about the other parallel track?

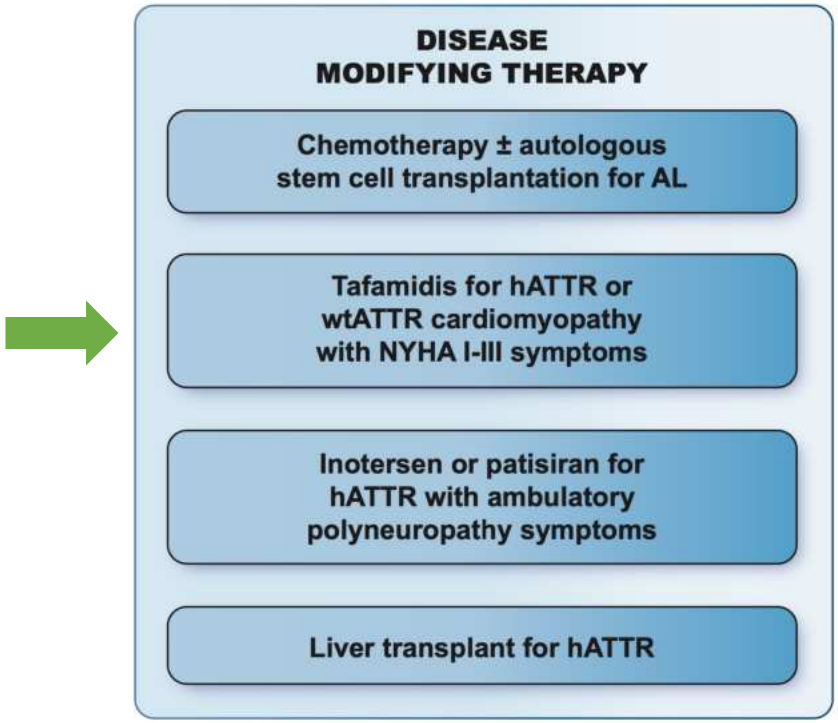


TABLE 5 Recommendations About Disease-Modifying Drugs for ATTRv or ATTRwt Amyloidosis

Rapezzi C, et al. J Am Coll Cardiol. 2022;79(13):1288–1303.

Drug	ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
Tafamidis	ATTRwt-CA or ATTRv-CA (recommended)[a] ATTRv-CA + PN (stage 1) (recommended) ATTRv PN (stage 1) (recommended)[b]	ATTRwt-CA or ATTRv-CA (recommended)[a]	Recommended for patients with ATTR-CA and NYHA functional class I-III symptoms[a]	Patients with predominantly cardiac disease from ATTRv or ATTRwt, NYHA functional class I to III symptoms (recommended)[a]	• ATTRwt-CA with NYHA functional class I-II symptoms (recommended) • ATTRwt-CA with NYHA functional class III symptoms (recommended) • ATTRv-PN and CA with NYHA functional class I-II symptoms (recommended) • ATTRv-PN and CA with NYHA functional class III symptoms (recommended)[b]
Notes	ESC HF guidelines recommendations: • ATTRwt-CA with NYHA functional class I-II symptoms (Class I, LOE B) • ATTRwt-CA with NYHA functional class I-II symptoms (Class I, LOE B) Reasonable expected survival	ATTR-ACT inclusion and exclusion criteria should be met Case-by-case decision is needed when NYHA functional class III symptoms	ATTR-ACT inclusion (NT-proBNP >600 ng/L) and exclusion criteria (NYHA functional class IV, severe functional disability, 6MWD <100 m) should be considered when determining eligibility for treatment The expected benefit is greater in patients with NYHA functional class I-II symptoms	Benefit of tafamidis not observed in patients with NYHA functional class IV, severe aortic stenosis, or eGFR <25 mL/min/1.73 m^2	Need for histological documentation of ATTR amyloid deposits in the heart or peripheral tissue Tafamidis doses: 20 mg PN, 80 mg CA
Patisiran	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv with ambulatory PN (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]
	ATTRv PN (stage 1-2) + CA (recommended)[b]	No sufficient data about ATTRv PN (stage 1-2) + CA	No sufficient data about ATTRv PN + CA	–	No sufficient data about ATTRv PN + CA
Inotersen	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv with ambulatory PN (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	Not approved in Japan

Disease modifying therapy for Mr. F?

- Does he meet criteria for tafamidis?
  - ATTR-CM with septum >12 mm
  - ATTRwt or ATTRv
  - NYHA I-III
- What if he had ATTRv, V122I mutation, minimal polyneuropathy symptoms?
- What if he had ATTRv, T60A mutation, symptomatic but ambulatory polyneuropathy?

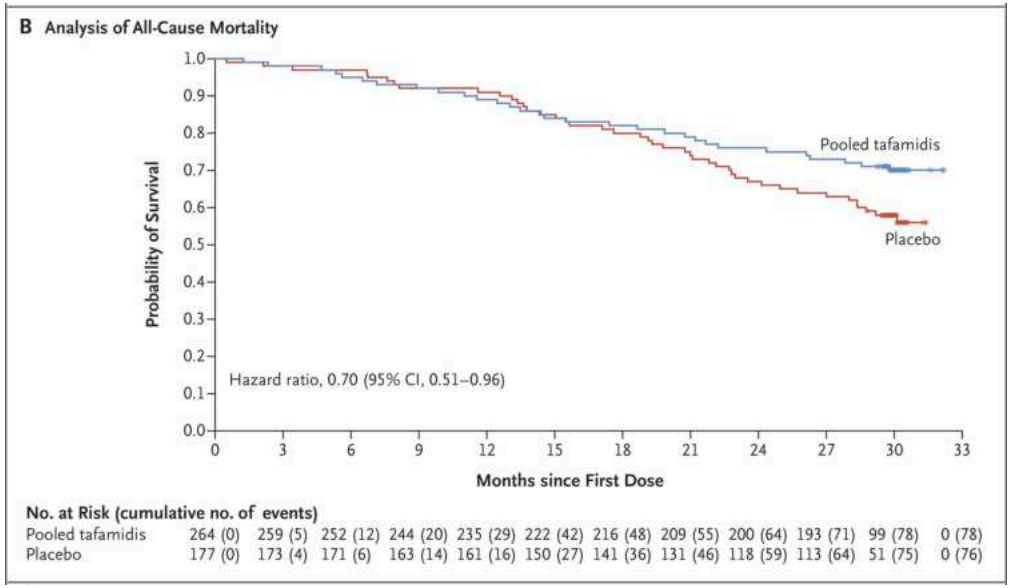
ATTR-ACT: Primary Analysis and Components

A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30
				no. (%)	*per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

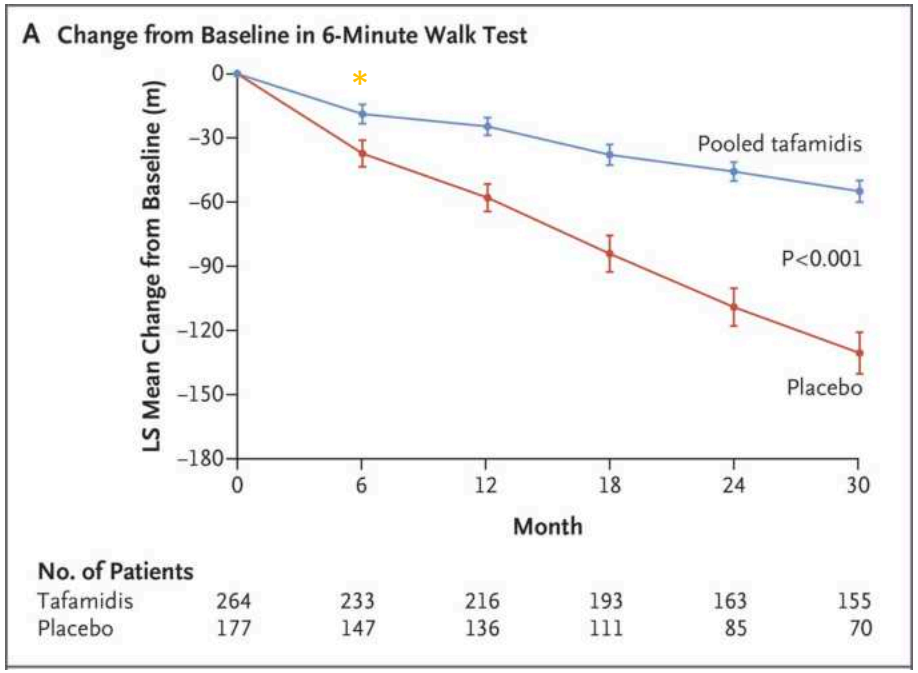
C Frequency of Cardiovascular-Related Hospitalizations

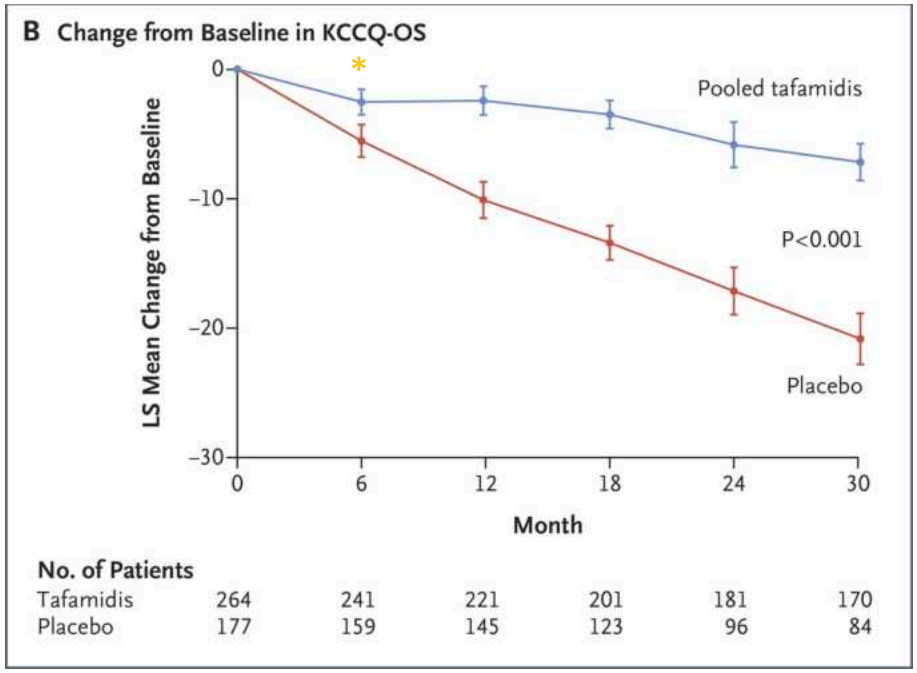
	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	



Maurer MS et al. N Engl J Med 2018;379:1007-1016

ATTR-ACT: Key Secondary End Points

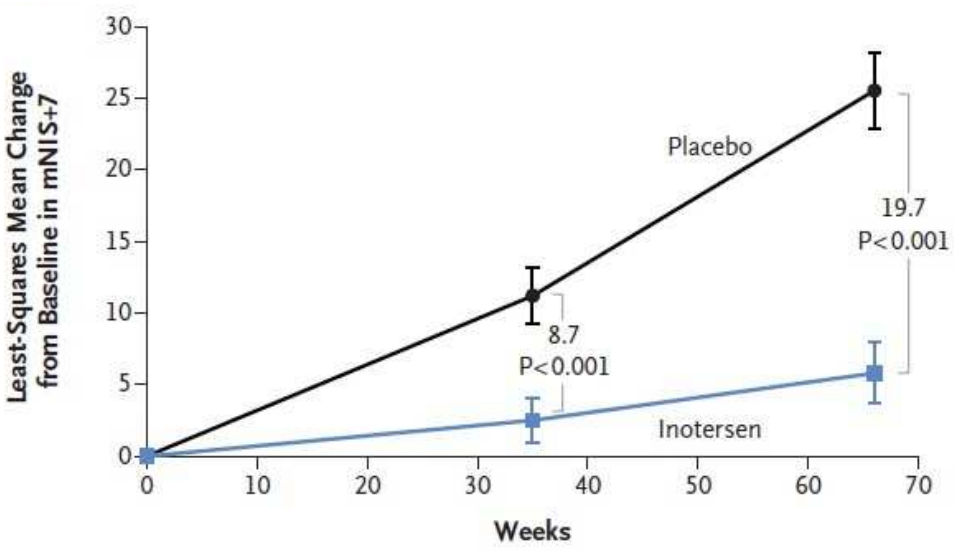




Maurer MS et al. N Engl J Med 2018;379:1007-1016

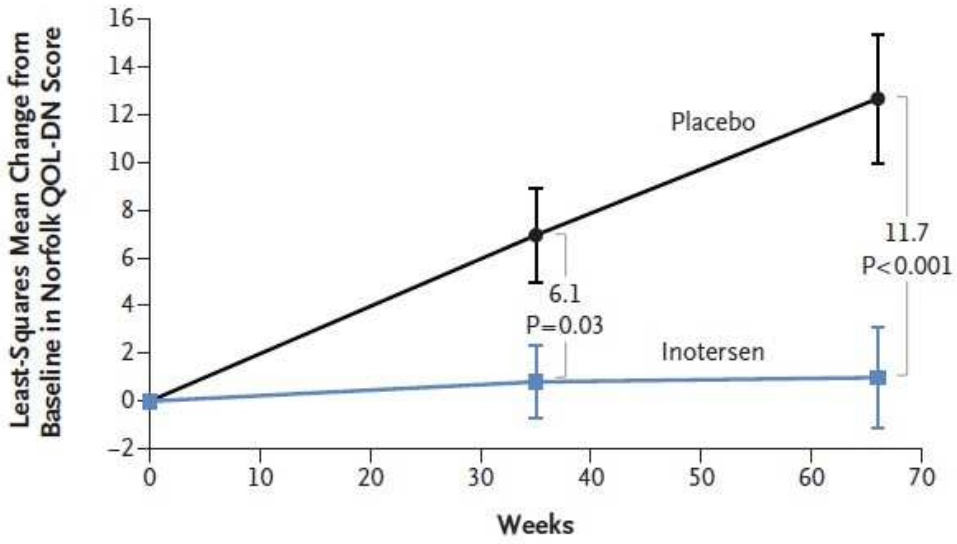
Inotersen: Change From Baseline in mNIS+7 and Norfolk QOL-DN Score Over 15 Months

mNIS+7



The higher the score, the poorer the function.

Norfolk QOL-DN

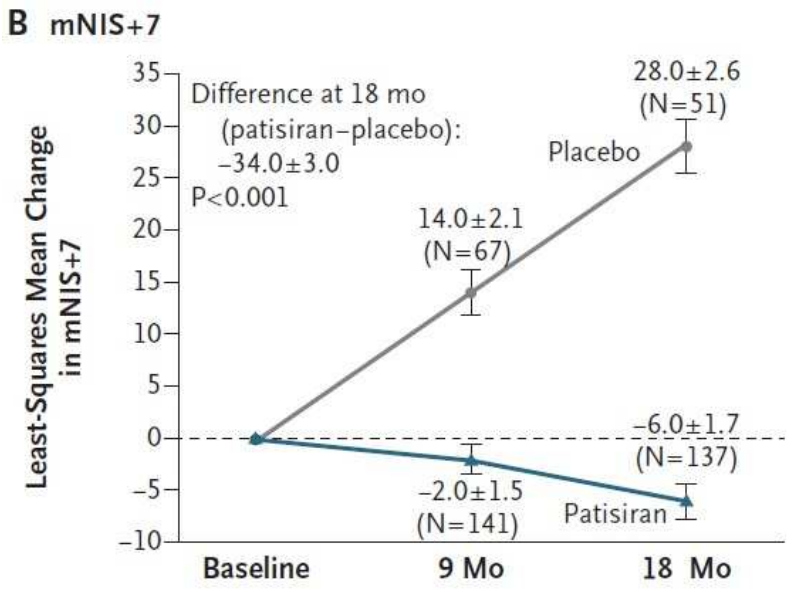


The higher the score, the poorer the QoL.
A decrease in score indicates an improvement in QoL.

mNIS+7, modified Neuropathy Impairment Score+7; QoL, quality of life; QOL-DN, Norfolk Quality of Life – Diabetic Neuropathy.
Adapted from Benson MD et al. N Engl J Med 2018;379(1):22-31.

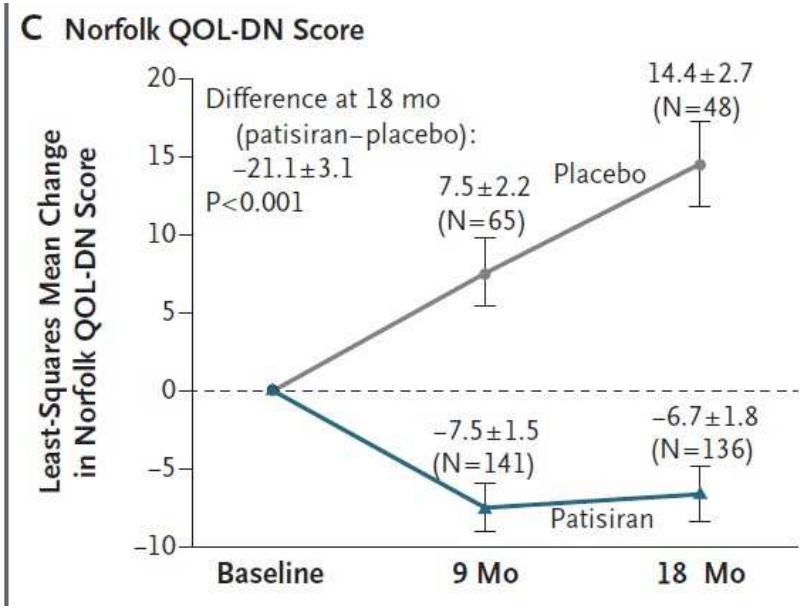
Patisiran: Change From Baseline in mNIS+7 and Norfolk QOL-DN Score Over 18 Months

mNIS+7



The higher the score, the poorer the function.
A decrease in score indicates an improvement in function.

Norfolk QOL-DN



The higher the score, the poorer the QoL.
A decrease in score indicates an improvement in QoL.

mo, months; mNIS+7, modified Neuropathy Impairment Score+7; QoL, quality o life; QOL-DN, Norfolk Quality of Life – Diabetic Neuropathy.
Adapted from Adam D et al. N Engl J Med 2018;379(1):11-21.

Follow-up protocols

No evidence, no agreement

TABLE 6 Proposed Follow-Up Protocols for Patients With Cardiac Amyloidosis

ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
AL-CA Every month (during initial hematological treatment): • Complete blood count, basic biochemistry, NT-proBNP, and troponin • Serum-free light-chain quantification • Clinical evaluation by hematology • Evaluation by cardiology if clinically indicated Every 3-4 mo (after completing initial hematological treatment): • Complete blood count, basic biochemistry, NT-proBNP and troponin • Serum-free light-chain quantification • Clinical evaluation by hematology Every 6 mo: • ECG • Echocardiography/CMR • Evaluation by cardiology Every 12 mo: • 24-h Holter ECG ATTR-CA Every 6 mo: • ECG • Blood tests including NT-proBNP and troponin • Neurological evaluation (if ATTRv) • 6MWD (optional) • KCCQ (optional) Every 12 mo: • Echocardiography/CMR • 24-h Holter ECG • Ophthalmological evaluation (if ATTRv)	AL-CA During specific drug therapy Every 3 mo (or after every 2 further therapy cycles): • NT-proBNP • Troponin T or I Every 6 mo: • Resting ECG + Holter ECG • Transthoracic echocardiography including strain measurements • If available: CMR including LGE and T1 mapping After remission or in stable condition without specific therapy Every 6 mo: • Resting ECG • NT-proBNP • Troponin T or I • Transthoracic echocardiography including strain measurements Every 12 mo: • Holter ECG • Additional CMR including LGE and T1 mapping in case of suspected disease progression due to serum biomarkers and/or echocardiographic findings ATTR-CA During specific drug therapy Every 3-6 mo: • NT-proBNP • Troponin T or I Every 12 mo: • Resting ECG + Holter ECG • Transthoracic echocardiography including strain measurements • If available: CMR including LGE and T1 mapping After remission or in stable condition without specific therapy Every 6 mo: • Resting ECG • NT-proBNP • Troponin T or I • Transthoracic echocardiography including strain measurements Every 12 mo: • Holter ECG Every 12-24 mo: • Additional CMR including LGE and T1 mapping in case of suspected disease progression due to serum biomarkers and/or echocardiographic findings	• Serial imaging with echocardiography or CMR in addition to measuring BNP/NT-proBNP • Echo or CMR repeated every 6-48 mo or when the clinical picture deteriorates • Integration of imaging and laboratory findings indicated • No role for bone scintigraphy to monitor the response to treatment	– (no accepted definition of progression or response to therapy)	–

Conclusions

- A lack of evidence in many areas of cardiac amyloidosis management leads to recommendations that are often driven by expert opinion or small studies, leading to some inconsistency between Scientific Society documents.
- There is general consensus in international guidelines that conventional HF and AF medications should be used cautiously or not at all; atrial fibrillation should be anticoagulated regardless of CHADS; disease-modifying therapy appropriate in ATTR patients with mild-moderate symptoms.
- Follow-up protocols have been described but are largely based on expert opinion. Further research is needed to understand how best to follow progression of disease and response to therapy.

Cardiac Sarcoidosis: Different Faces of a Case

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Conflict of Interest Disclosures

- **Grants/research support**: Novartis, Abbott
- **Consulting fees**: Novartis, Servier, Boehringer Ingelheim-Lilly, Bayer
- **Speaker fees**: Novartis, Servier

Sarcoidosis: Quick Facts

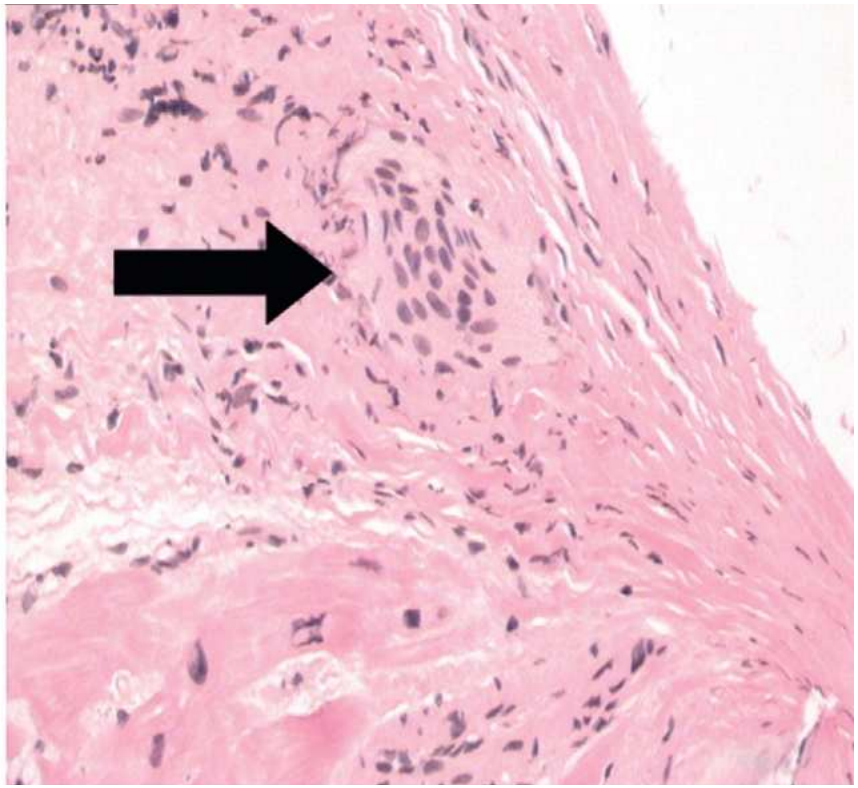
Multisystem inflammatory disease
- Non-caseating granulomas in various tissues

Unknown etiology
- Immune dysregulation following antigen exposure
- Environmental and genetic modifiers

90% of cases involve lungs/lymph nodes

~25% will have cardiac involvement (often silent)

~5% will have clinically manifest cardiac sarcoid



Birnie et al, J Am Coll Cardiol 2016

Cardiac Sarcoidosis (CS): Quick Facts

Active inflammatory phase

- Potentially responsive to immunosuppression

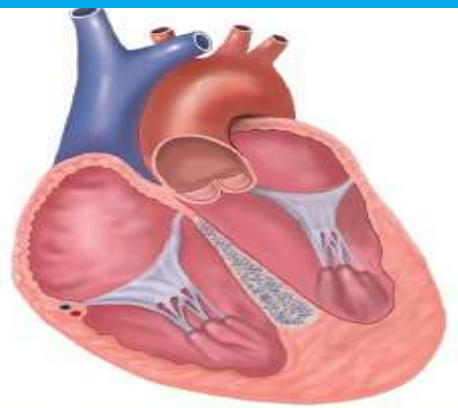
Chronic fibrosis phase

- Less likely amenable to immunosuppression therapy

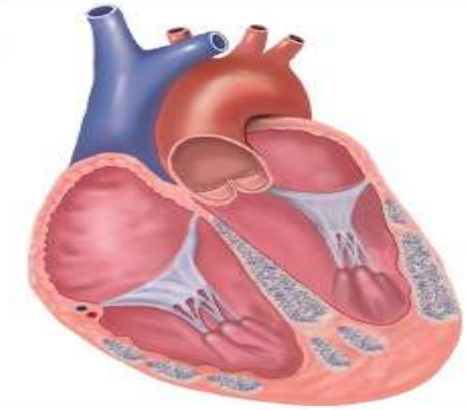
- Predilection for septum (common initially)
- May become extensive with multifocal patchy disease; mid-wall and epicardial involvement +/- RV involvement is typical
- Cardinal manifestations:

1) AV block and conduction defects
2) VT
3) LV dysfunction and heart failure

Usual indications for treatment



Large area of septal involvement, often clinically manifest as heart block

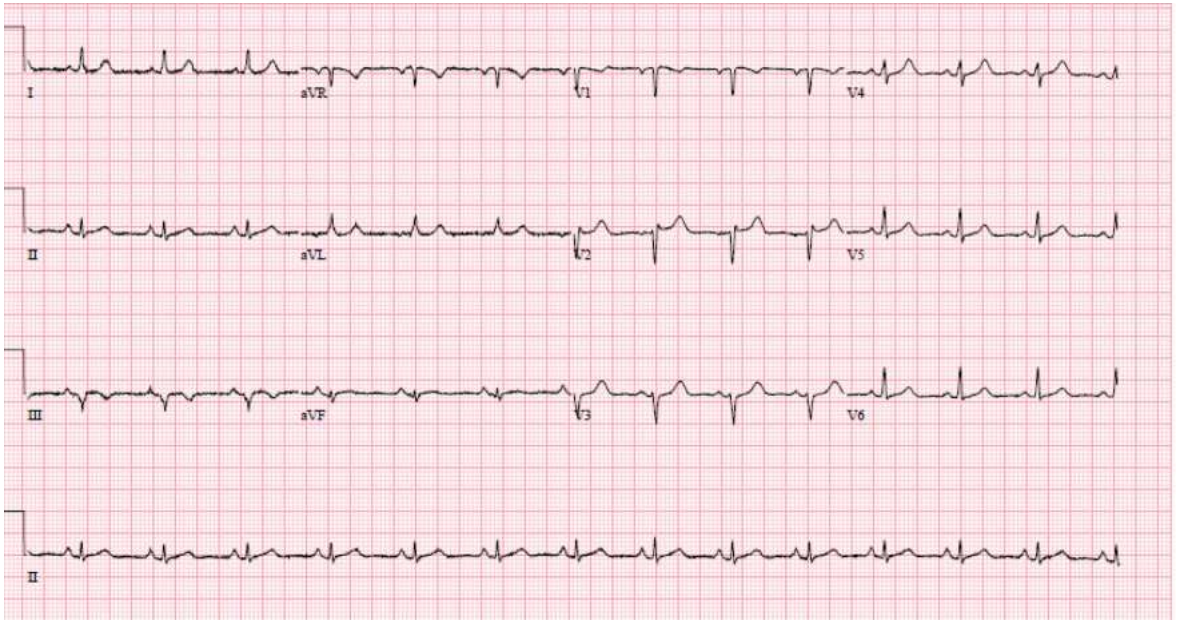


Extensive areas of LV and RV involvement, often clinically manifest as heart failure +/- heart block +/- VT

Birnie et al, J Am Coll Cardiol 2016
Lemay et al, Can J Cardiol Open 2021

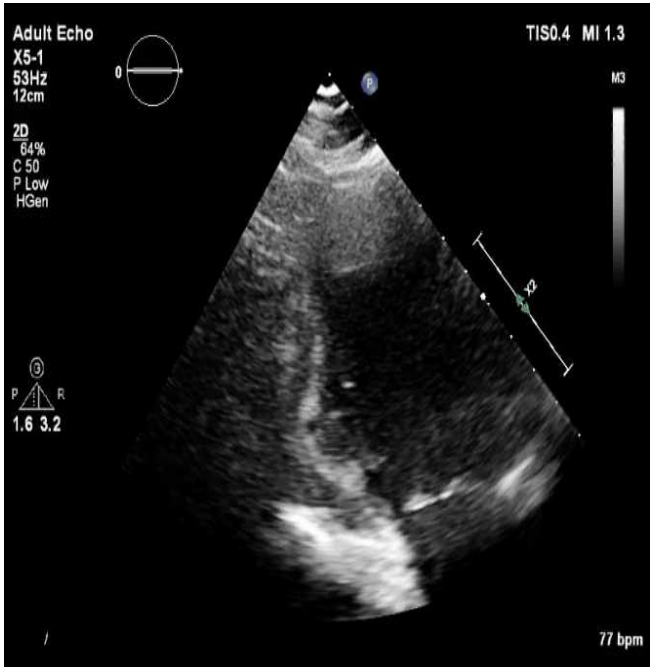
Case

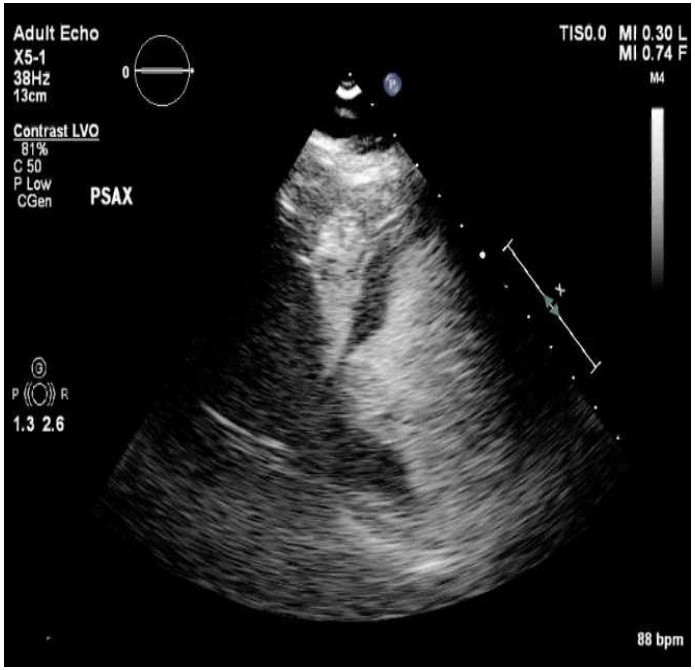
- 53 year old admitted for recurrent chest pain, low grade troponin rise
- Prior episode ’myo-pericarditis’ 6 months ago
  - Normal coronaries, preserved LVEF
  - Resolved with colchicine/NSAIDs
- Recurrent pleuritic chest pain similar to prior episode
- Hemodynamically stable, no arrhythmias



Echo

Overall preserved LVEF with inferior hypokinesis, basal infero-lateral dyskinesis





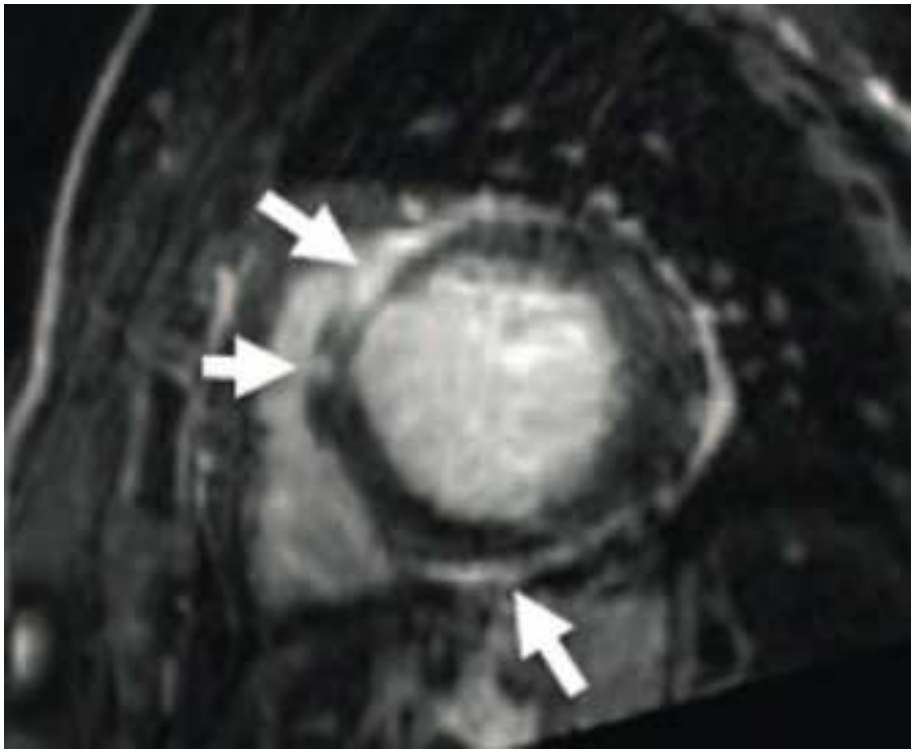
Should we now consider MRI? PET scan? Biopsy?

Cardiac MRI

Our patient:

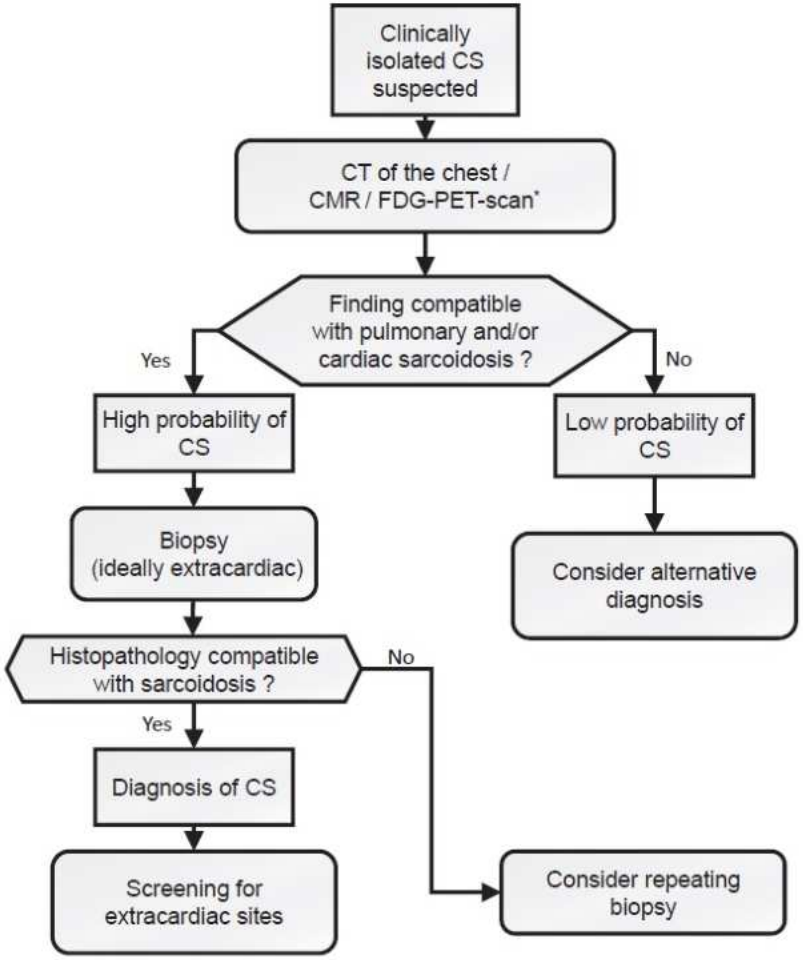
- Mildly impaired LV systolic function with dyskinesis of basal inferior septum; EF 50%
- Thinning of segments in base-mid inferior septum, inferior wall
- Mod-severe intensity LGE mid wall at base-mid anterior wall, anterior-apical septum, inferior wall, pericardium
- T2 weighted hyperintensity suggests edema

Image of typical sarcoid involvement of basal septum



Birnie et al, J Am Coll Cardiol 2020

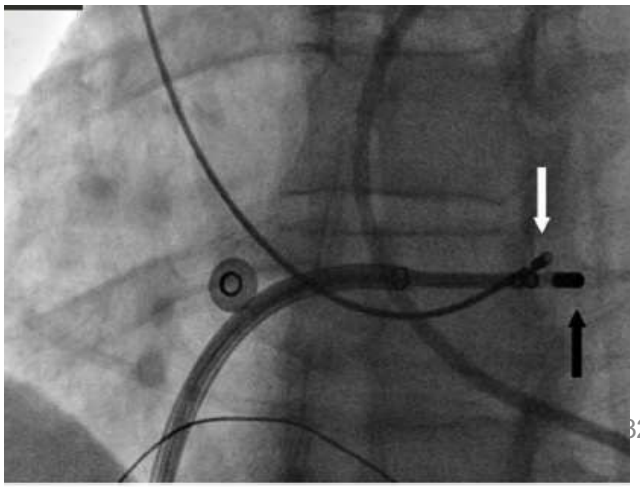
Should we biopsy now?



Lemay et al, Can J Cardiol Open 2021

Challenges with endomyocardial biopsy

- Limited sensitivity (25% most series)
- Patchy nature of CS
- Non-trivial risk of harm
- Techniques to increase biopsy yield have been suggested but not widely available or applicable



Biopsies were performed

Endomyocardial biopsy

- Complicated by perforation and tamponade that resolved with drainage
- Sufficient 6 fragment sample
- No evidence of granulomatous disease or myocarditis!

Endobronchial lymph node biopsy

- CT thorax demonstrated large paratracheal lymph notes
- EBUS guided LN sampling
- No evidence of granulomatous disease!

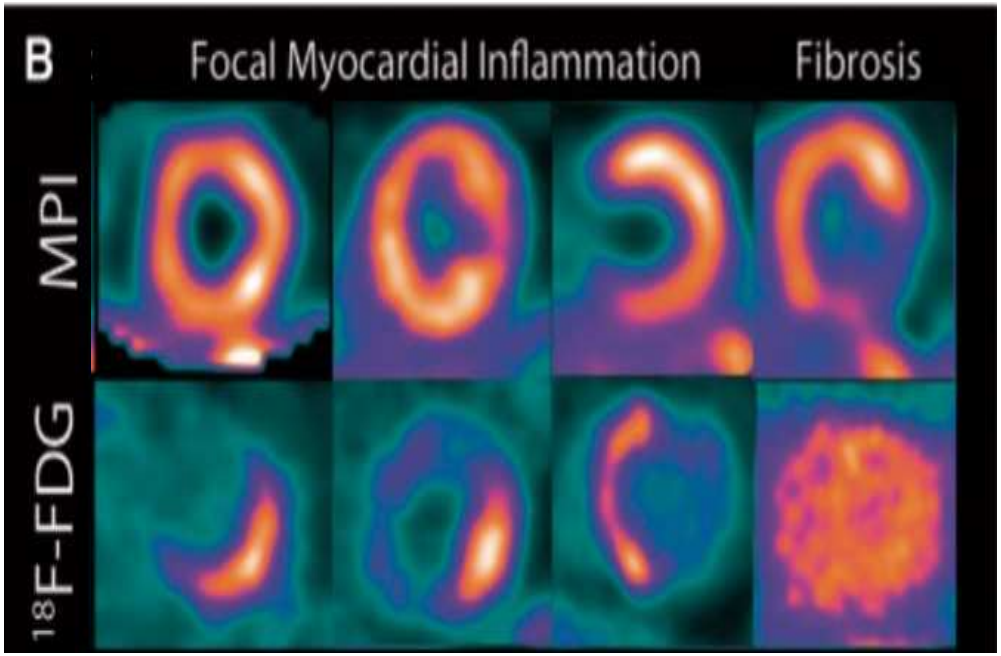
PET Scan… Eventually

Examples: Highly suggestive of inflammation

Patient Pet Report

FDG Imaging:
"Inflammation visualized…multiple areas of FDG especially in basal anterior wall, septum, inferior wall. These match with areas of hypoperfusion...."

Conclusion:
There is evidence suggestive of acute cardiac inflammation.
Acute cardiac inflammation consistent with myocarditis or sarcoid



Slart et al, Eur Heart J – Cardiovasc Imag 2017

So, does she have CS?

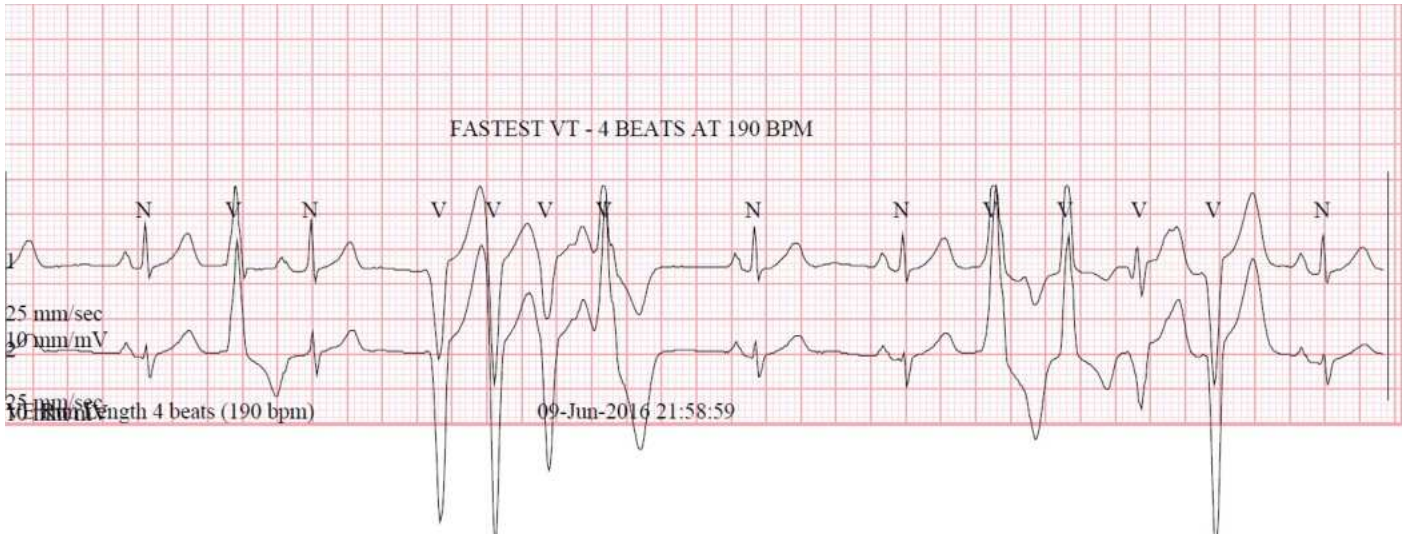
Heart Rhythm Society Guidelines	Japanese Circulation Society
Definite CS: Histologic confirmation from cardiac biopsy	**Possible CS:** **Nuclear study suggesting cardiac inflammation plus:** **3 major criteria**
Probable CS: Histologic confirmation of extracardiac sarcoid plus one of: LV dysfunction Significant AV block PET/CMR evidence	Major Criteria include: AV block LV segmental aneurysms LVEF <50% Typical LGE on CMR

Gilotra et al, J Cardiac Fail, 2022

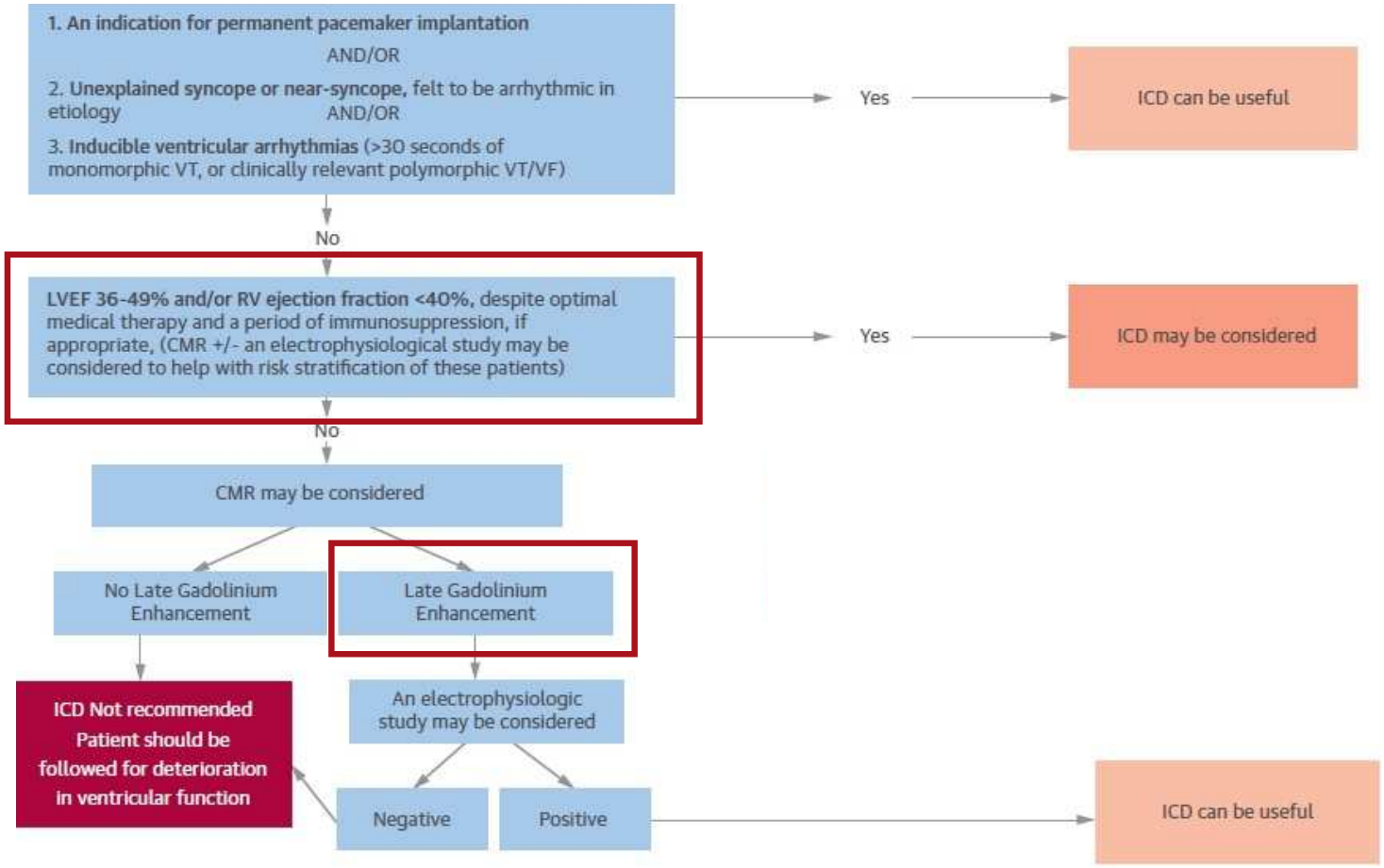
Clinical Course

- Discharged on low dose ACEi and prednisone 40 mg/d for presumed CS with active inflammation

- 2 months later
  - Readmitted with palpitations and Holter evidence of high burden PVCs (21%) and 40 runs NSVT
  - Repeat echo showed drop in LVEF to 40-45%



Time for an ICD? HRS Guidelines for Cardiac Sarcoidosis

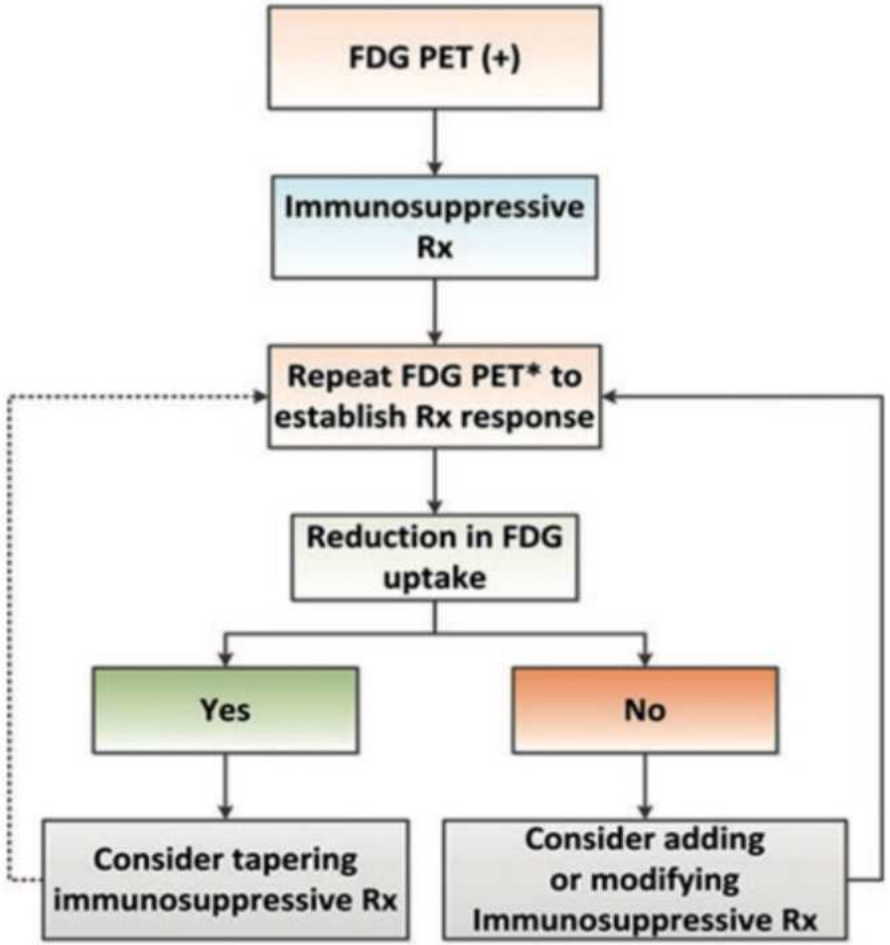


Birnie et al Heart Rhythm 2014

Back to the case

- Single chamber ICD implanted
- Over next 3 months:
  - Prednisone continued and weaned down to 10mg/d
  - Methotrexate added
- PET scan repeated
  - Persistent burden of inflammation … essentially unchanged
- Continued on prednisone and methotrexate
- Clinical and echo findings unchanged for 2 years

Proposed monitoring of response to therapy



Every 3-6 months

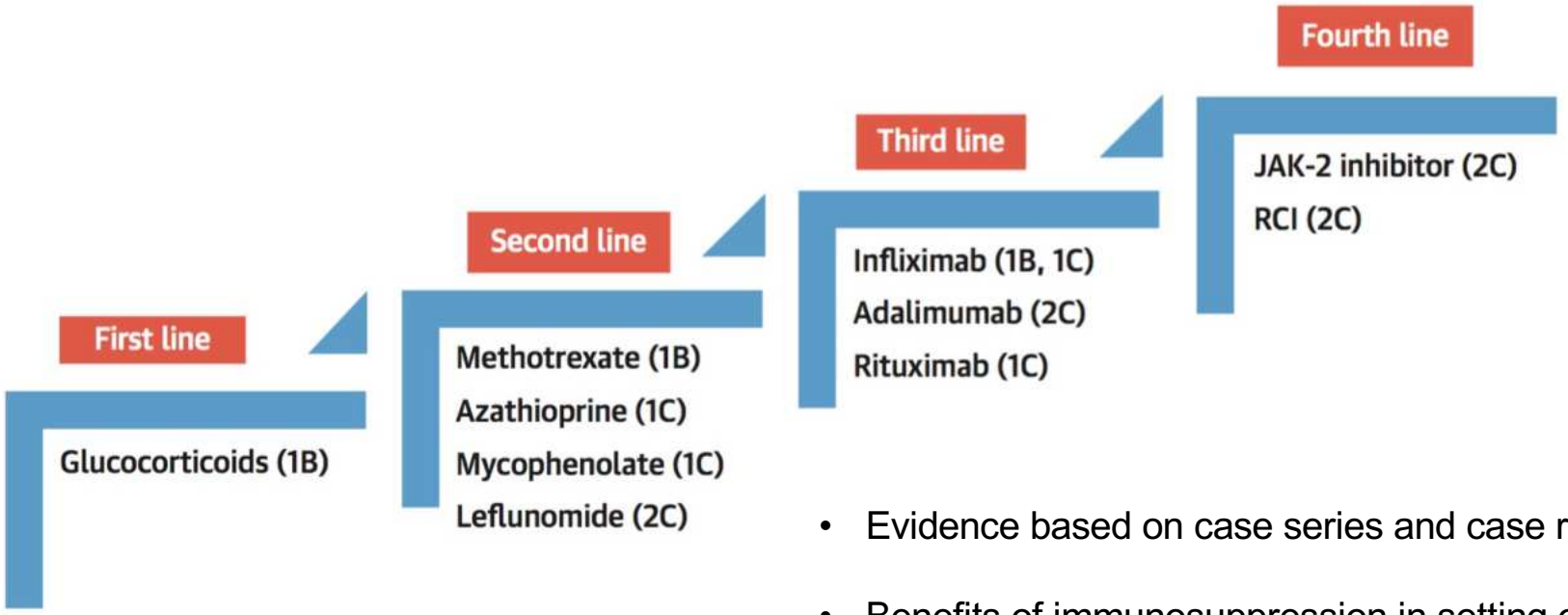
Every 3-6 months

Slart et al, Eur Heart J – Cardiovasc Imag 2017

More trouble

- Serial PET scans showed progressively increased inflammation
- Methotrexate changed to leflunominde >>> mycophenolate; poorly tolerated
- Admitted with VT storm and settled on amiodarone in addition to bisoprolol
  - LVEF 35%
  - On max tolerated MRA/b blocker/ACEi
  - Pulsed with solumedrol, started back on methotrexate

What to consider next: Contemporary approach to immunosuppression



- Evidence based on case series and case reports only
- Benefits of immunosuppression in setting of severe LV dysfunction (EF <30-35%) very uncertain
- RCTs of corticosteroids and biologic agents underway

Trivieri et al, J Am Coll Cardiol 2020

Epilogue

- Underwent successful VT ablation
  - Low dose amiodarone
  - No further VT/VF episodes
- Declined work up for LVAD or transplant
- Started receiving infliximab q 4 weeks through rheumatology clinic (2019)
- LVEF stable at 40%; no heart failure
- PET scans annually – No FDG uptake (as of April 2022)
  - Off prednisone
  - Weekly methotrexate

Summary: Cardiac Sarcoidosis

- Should be suspected based on a constellation of electrical and echo findings
  - Wall motion abnormalities, aneurysms
  - AV block, bundle branch block, VT/VF
- Diagnosis usually requires multimodal advanced imaging
  - Location and pattern of myocardial involvement
  - Active inflammation vs scar
- Active inflammation should prompt immunosuppressive treatment
- Aggressive management of LV dysfunction and rhythm should be pursued
- Multimodal imaging often required for assessing response to therapy; clinical course is highly variable

Peripartum Cardiomyopathy

Robert McKelvie MD PhD FRCPC
Profession of Medicine
Division of Cardiology
Western University

Disclosures

- Nothing related to this presentation

Case: Ms. P

June 23, 2021:

- 23 yo woman presenting with worsening SOB over the 7 days prior to ER presentation; orthopnea – 0 PND; 0 ankle swelling; 0 other symptoms – previously well
- PHx: 4 live births all C-section, 2015, 2016, 2019, 2021; anxiety/ depression
- SHx: Smoking since 16 (about 7 pack yrs) – FHx: nothing relevant
- Meds: ferrous fumarate, Ventolin inhaler prn, sertraline
- O/E: BP 129/94; P 101; O_2 Sat 97% RA; RR 18; T 36.8

Chest – slight basal crackles bilaterally; JVP 6cm ASA; S,S_2 N $0S_3$ $0S_4$; 0 edema

Investigations: ECG: Sinus 101 bpm T wave inversion poor R wave progression V_{1-4}

Troponin 118, Cr 77, Na 140, K 3.7, Hgb 126, Lac 3 mmol/l

Echo: LVEF 20%, RV moderately dilated; 0 clot, moderate MR + TR

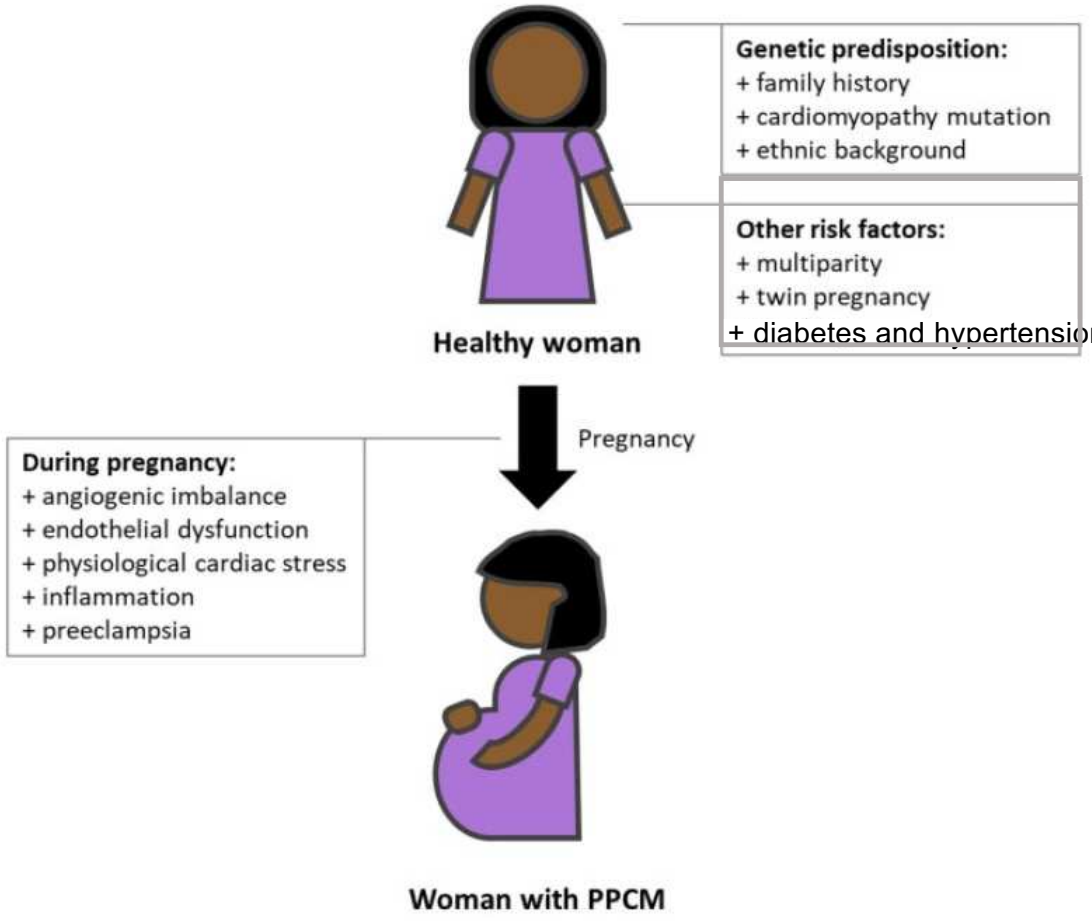
CXR: Cardiac enlargement only

A: Peripartum Cardiomyopathy

Definition of Peripartum Cardiomyopathy

- Heart failure secondary to left ventricular systolic dysfunction with LVEF <45%
- Occurrence towards the end of pregnancy or in the months following delivery (mostly in the month following delivery)
- No other identifiable cause of heart failure

Predisposing Factors

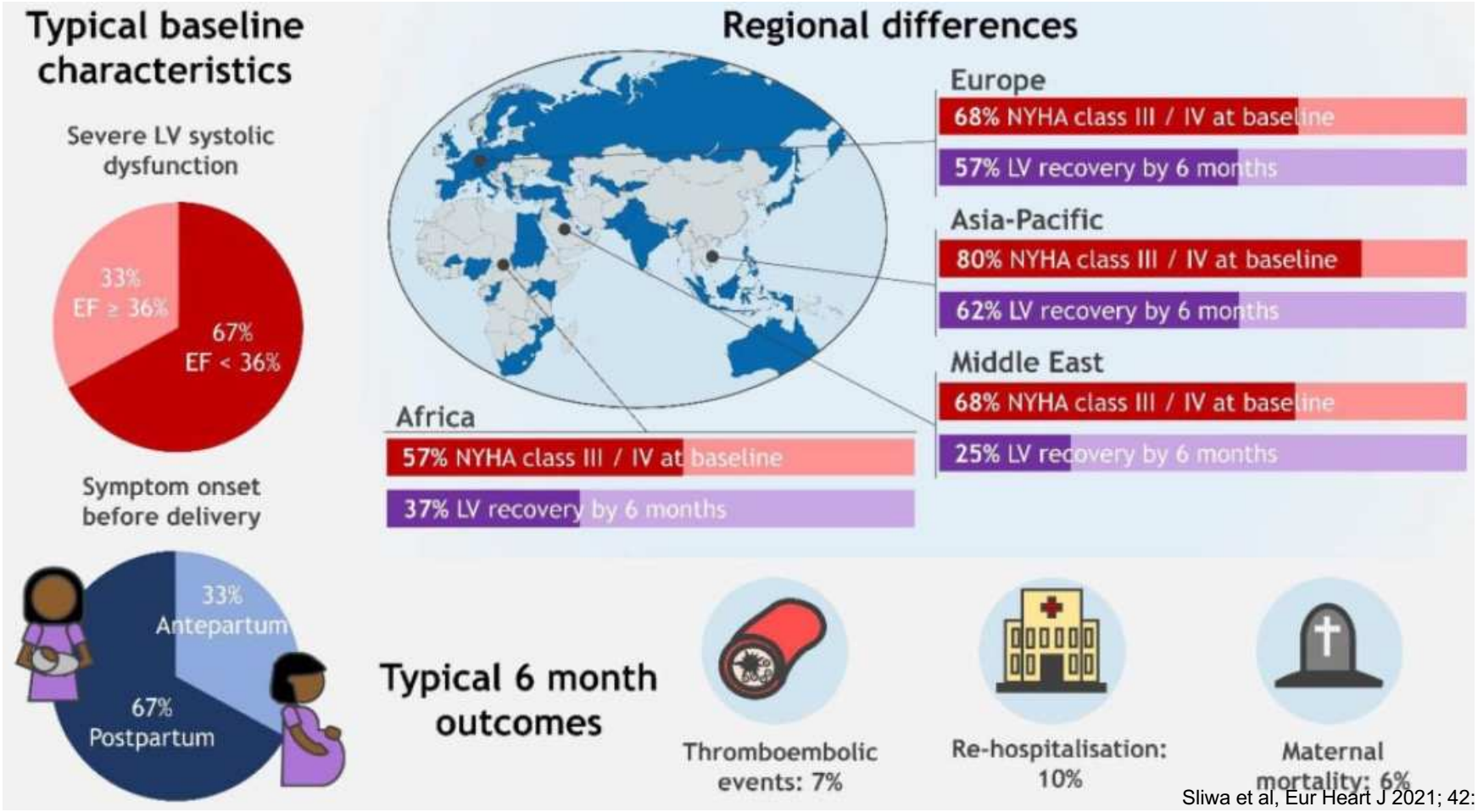


Sliwa et al, European Heart Journal 2021; 42: 3094-3102

Incidence of PPCM

- Incidence differ widely depending on ethnic/ racial and regional background of the woman
- 1:100 pregnancies Nigeria and 1:299 in Haiti
- 1:1,500 pregnancies in Germany to 1:10,000 pregnancies Denmark
- 1:20,000 in Japanese cohort
- 1:1,000 – 1:4,000 pregnancies in USA
- Many cases may be unrecognized thus the true incidence is unknown

Clinical Characteristics of Patients from 49 Countries: EURObservational Research Program (EORP)



Sliwa et al, Eur Heart J 2021; 42: 3094-3102

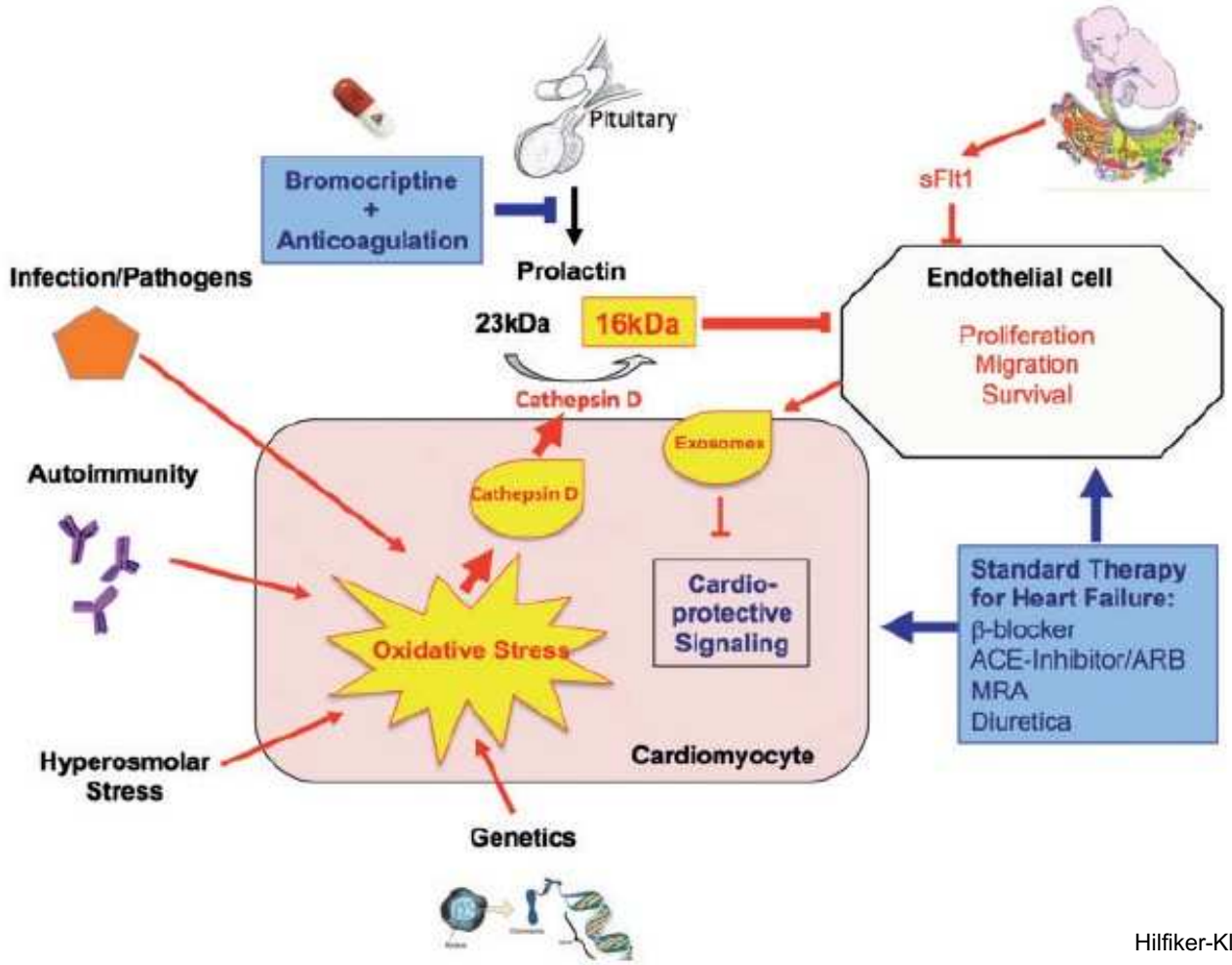
Case continued

- Patient appeared clinically well but there was concern about hypoperfusion because of the elevated HR and Lac of 3mmol/L
- Started on milrinone for a brief period
- Heart cath demonstrated normal coronary arteries with severely depressed global LV function
- Stabilized and improved in hospital with diuresis along with initiation of GDMT
- discharged on June 28, 2021 to be followed up in HFC

Discharged Medications:

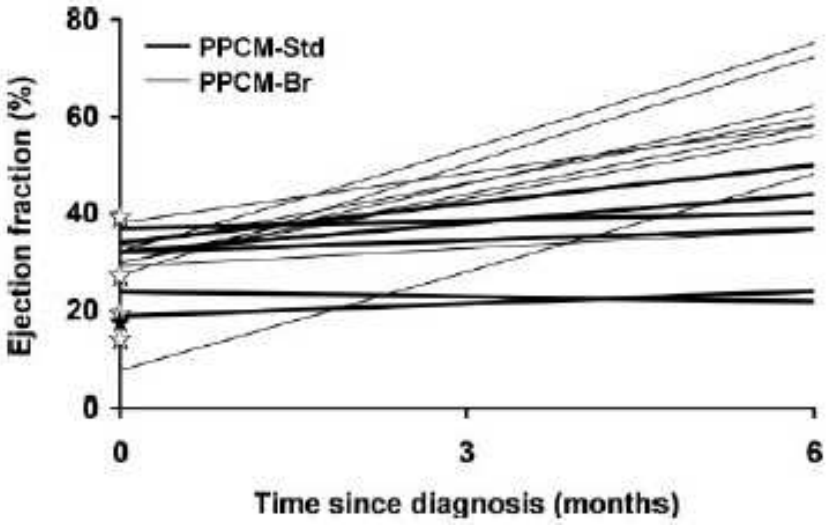
- Lasix 40mg OD, bisoprolol 2.5mg OD, bromocriptine 2.5mg bid for 2 weeks then bromocriptine 2.5mg OD for 6 weeks, eplerenone 25mg OD, entresto 24/26mg bid, rivaroxaban 20mg OD, Ventolin inhaler prn, ferrous fumarate 300mg OD, sertraline 50mg OD
- Told not to breast feed because of medical therapy

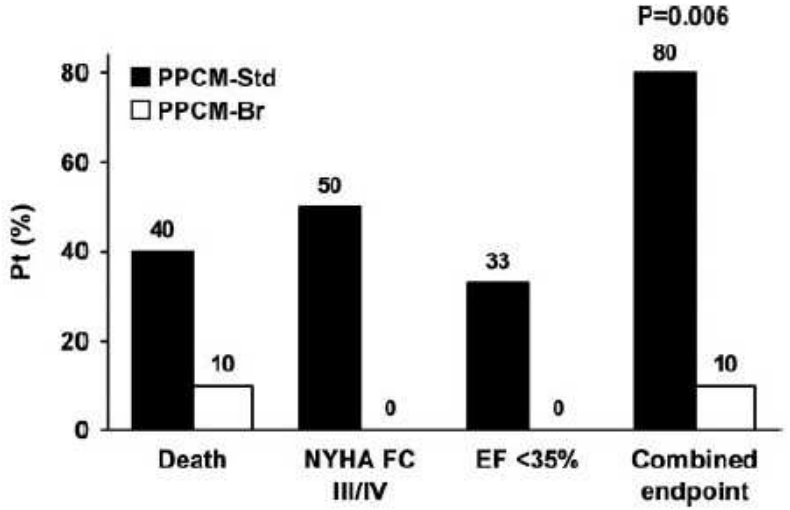
Rationale for bromocriptine



Hilfiker-Kleiner et al, Eur Heart J 2017; 38:2671-2

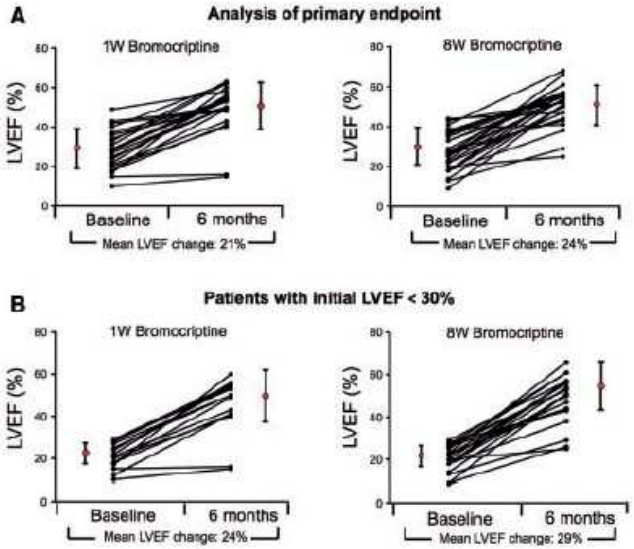
Bromocriptine in Acute Severe PPCM: A Proof-of-Concept Pilot Study





Sliwa et al, Circulation 2010; 121:1465-1473

Bromocriptine for the treatment of PPCM: a multicentre randomized study



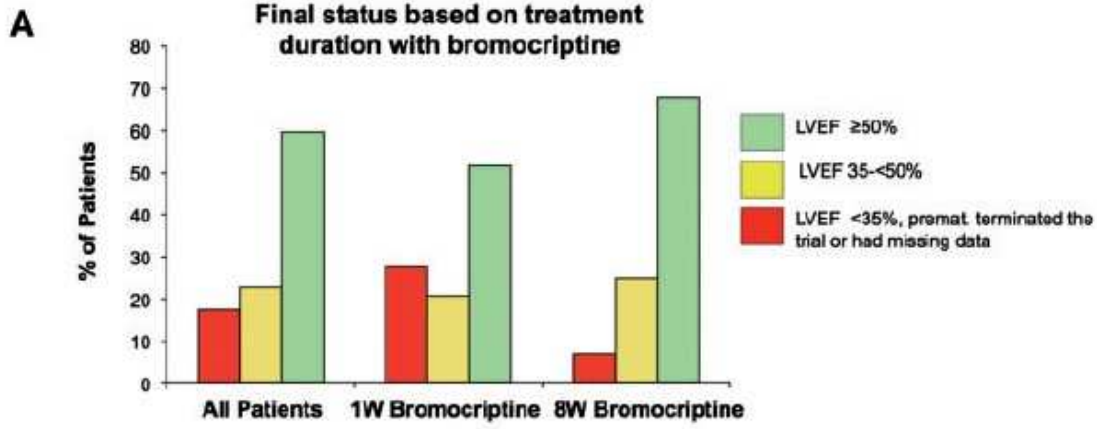


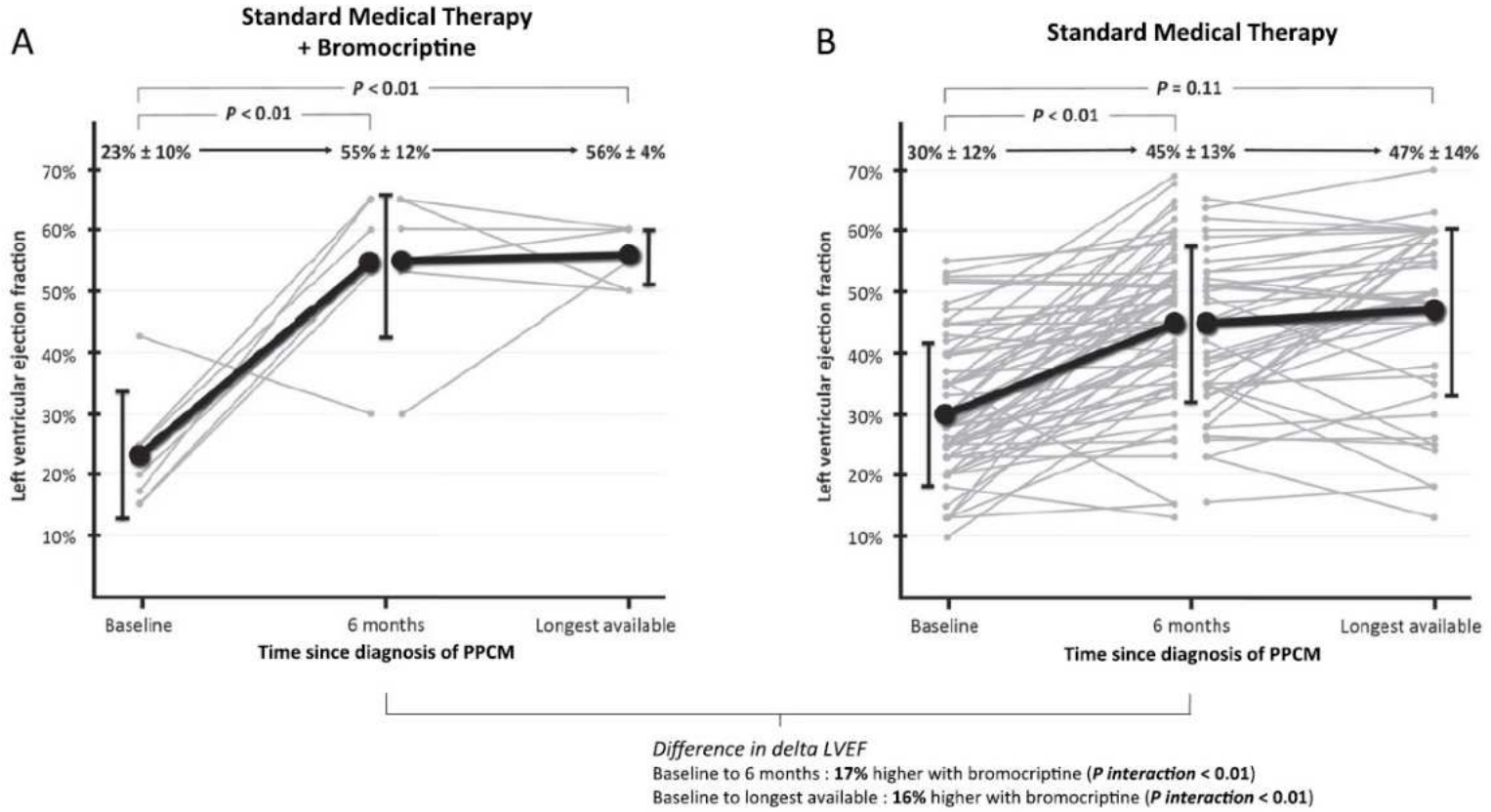
Table 4 Effect of treatment on outcome in peripartum cardiomyopathy patients with left ventricular ejection fraction <30% in the bromocriptine study (treated either with 1W or 8W bromocriptine) compared with the IPAC study without bromocriptine treatment[19]

Follow-up characteristics	1W bromocriptine baseline LVEF <30% (*n* = 18)	8W bromocriptine baseline LVEF <30% (*n* = 19)	1W and 8W bromocriptine baseline LVEF <30% (*n* = 37)	IPAC study placebo baseline LVEF <30% (*n* = 27)
LVEF <35%	0% (0/18)	5% (1/19)	3% (1/37)	37%
LVEF 35–49%	22% (6/18)	37% (7/19)	35% (13/37)	26%
Full recovery, LVEF ≥50	67% (12/18)	58% (11/19)	62% (23/37)	37%
LVAD and HTX	0% (0/18)	0% (0/19)	0% (0/37)	19% (5/27)
Death	0% (0/18)	0% (0/19)	0% (0/37)	15% (4/27)

LVEF was analysed by echocardiography in the core labs of both studies. Follow-up in the IPAC study was 12 months, follow-up in our study was at 6–36 months.
LVEF, left ventricular ejection fraction; LVAD, left ventricular assist device; HTX, heart transplantation.

Hilfiker-Kleiner et al, European Heart J 2017; 38:2671-2679

The Effect of bromocriptine on LV Functional Recovery in PPCM: Insights from BRO-HF Retrospective Cohort Study



Tremblay-Gravel et al ESC Heart Failure 2019; 6:27-36

Ongoing Studies of Bromocriptine to treat PPCM

- Bromocriptine in the treatment of PPCM (BRO-HF)
  - Montreal Heart Institute
  - Bromocriptine 2.5mg bid for 2 weeks then 2.5mg OD for 42 days
  - n= 80 LV systolic dysfunction, reduced LVEF
  - Primary outcome: Composite CV death, aborted sudden death, heart transplant mechanical circulatory support or hospitalization for CV causes
  - Finishes January 2023 started January 2017

- Impact of bromocriptine on clinical outcomes for PPCM (REBIRTH)
  - NIH - USA
  - Bromocriptine 2.5mg bid for 2 weeks then 2.5mg OD for 6 weeks
  - n= 200 LVEF <35%
  - n= 50 observational cohort excluded due to breast feeding
  - Primary outcome: LVEF at 6 months
  - Secondary outcome:
    - survival free from major event (LVAD on heart transplant)
    - Survival free from HF hospitalization
  - Start /March 2022; finishes August 2026

What do Guidelines Recommend for Bromocriptine

CCS HF Guidelines 2017

We recommend that bromocriptine not be used routinely for PPCM (Strong Recommendation; Low-Quality Evidence)

Values and Preferences

Adequately powered and appropriately designed RCTs have not been completed. The safety of bromocriptine is not well established

AHA/ACC/HFSA HF Guidelines 2022

If bromocriptine is used for postpartum women with severe acute HF caused by PPCM and LVEF <35% it should be accompanied by at least prophylactic-dosed anticoagulation because of the potential association with thromboembolic events. However, the efficacy and safety of bromocriptine for PPCM treatment currently remains uncertain and further randomized placebo-controlled trials are required to define the role of this therapy, particularly in the setting of contemporary HF GDMT and cardiogenic shock management

ESC HF Guidelines 2021

Bromocriptine may be considered for treatment of PPCM. Untoward effects of treatment, including deep vein thrombosis and cessation of lactation, must be considered if it is initiated. It should be accompanied by prophylactic (or therapeutic) anticoagulation.

Heart Failure Medications: Indications and Safety in Pregnancy and During Lactation

SGLT2i, e.g., dapagliflozin and empagliflozin not known to be safe during pregnancy or lactation

MEDICATION	DURING PREGNANCY	POTENTIAL ADVERSE EFFECTS	INDICATIONS	DURING LACTATION
HEART FAILURE MEDICATIONS				
Loop diuretics	Yes	Caution for hypovolemia or hypotension that may lead to decreased placental perfusion	For signs and symptoms of congestion and fluid overload.	Yes, but over-diuresis can lead to decreased milk production.
Beta blockers (metoprolol tartrate used most commonly)	Yes	IUGR; fetal bradycardia and hypoglycemia	For standard treatment of HF; consider treatment of women with subsequent pregnancy.	Yes
Hydralazine/nitrates	Yes	Caution with hypotension	Use for afterload reduction during pregnancy (instead of ACE-I/ARB) when needed.	Yes, but ACE-I/ARB typically chosen post-partum
Digoxin	Yes	No associated congenital defects	Can be used with symptomatic heart failure and/or systolic dysfunction during pregnancy, or afterwards per guidelines.	Yes
ACE-I/ARB	No	Anuria, oligohydramnios, fetal limb contractures, craniofacial deformation, pulmonary atresia, fetal hypocalvaria, intra uterine growth restriction, prematurity, patent ductus arteriosus, stillbirth, neonatal hypotension and death	Cannot use during pregnancy. After delivery, should be used as part of guideline-directed medical therapy for afterload reduction and LV remodeling.	Enalapril and captopril can be used
Aldosterone receptor antagonists	No	Spironolactone has been associated with antiadrenergic activity, feminization of male rat fetuses and permanent changes in reproductive tract in both sexes	As per guideline-directed medical therapy for heart failure.	Spironolactone can be used
Sacubitril-valsartan	No	Same as ACE-I/ARB	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk
Ivabradine	Scant data in humans; would avoid due to concerns in animal studies	Scant data in humans, animal data suggest risk	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk
ANTICOAGULANTS				
Low molecular weight heparin	Yes	Caution at time of delivery and with neuraxial anesthesia; does not cross placenta; consider the need for monitoring anti-Xa levels	For prevention and treatment of thromboembolic complications during pregnancy and as bridge to warfarin postpartum.	Yes
Warfarin	Avoid	Warfarin embryopathy and fetopathy	For prevention and treatment of thromboembolic complications postpartum.	Yes

Legend:

Data or experience to support use
Caution with using this medication
Data is limited or inconclusive

Safety of medications need to be considered during pregnancy and lactation. ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; HF = heart failure; IUGR = intra-uterine growth restriction; LV = left ventricular; SSP = subsequent pregnancy.

Davis et al J.Am College Cardiology 2(

Case Continued

HFC July 14, 2021:

Meds same on discharge; 0 SOBOE; 0 orthopnea; 0 PND; JVP 1cm ASA; 0 edema; lungs clear.HR 50 bpm BP 101/65 Hgb 132 Cr 71 K 4.0; echo LVEF 35-40%; no changes made

HFC August 16, 2021:

Bromocriptine stopped August 5. 0 symptoms BP 100/65 HR 57

JVP 1cm ASA; 0 edema; lungs clear

K 4.4 Cr 67; pocus IVC 1 cm, >50% collapse NYHA class 1; ↑Entresto 49/51 bid

HFC September 29, 2021:

Stable, ↑ Entresto 97/103 bid

HFC March 4, 2022:

Stable, Entresto 49/51mg bid other medications unchanged; NYHA class 1

March 4, 2022 echo LVEF 50-55% N RV

Discharged from HFC on current medications to follow up with cardiologist

Now what do we do?

- In presence of persistent cardiac dysfunction cardiac medications continue indefinitely
- After LV Recovery??
  - Rational to continue medical therapy is presence of subclinical LV dysfunction and anecdotal reports of late deterioration of LV function
  - Impaired LV global longitudinal and apical circumferential 2 dimensional strain reported in 29 women with recovered LVEF at least 12 months after acute PPCM (Goland etal, Cir HF 2016)
  - Reports of decreased contractile reserve on dobutamine stress echo with PPCM and recovered LVEF (Lampert etal am J Obstet Gynecol 1997)
  - TRED - HF - 44% DCM patients needed to restart medications within 6 months of stopping (Halliday etal, Lancet 2019)
- If stopped, should be weaned in a stepwise fashion with frequent clinical assessment and echo's every 3-6 months
- After discontinuation follow annually echo clinical assessment

Counselling and Management of Subsequent Pregnancies

Subsequent Pregnancy	Recovered (LVEF ≥50%)	Nonrecovered (LVEF <50%)
Preconception or First Visit	Preconception risk counseling and follow-up planning. Clinical and LVEF reassessment off renin-angiotensin blocking agents for 3 months. Baseline echocardiogram and BNP/NT-proBNP level.	Preconception risk counseling including discussion of alternative ways to build a family. If pregnant and not considering termination: Close follow-up planning, stop renin-angiotensin blocking agents and switch to hydralazine/isosorbide dinitrate. Baseline echocardiogram and BNP/NT-proBNP level.
Maternal Risks	~20% have a relapse Severe deterioration is rare Mortality unlikely Rate of subsequent recovery is high	Higher risk of relapse ~50% show further deterioration in LV dysfunction Increased morbidity and mortality Premature delivery and abortion more common
Medications	Continue beta blocker therapy (metoprolol tartrate preferred). Yield of starting prophylactic beta blocker therapy unclear. Diuretics and hydralazine/isosorbide dinitrate in case of clinical or LV functional deterioration.	Continue beta blocker therapy (metoprolol tartrate preferred). Hydralazine/Isosorbide dinitrate for hemodynamic and symptomatic improvement. Consider digoxin. Consider anticoagulation if severe LV dysfunction (LVEF <35%).
Follow-up	Close monitoring of symptoms during pregnancy and the postpartum period with repeat echocardiographic assessment of LV function and BNP/NT-proBNP level at the end of the 1st and 2nd trimesters, 1 month prior to delivery, after delivery prior to hospital discharge, 1 month postpartum, and at any time if symptoms develop.	
Labor and Delivery	Multidisciplinary team for planning; patient involved. Spontaneous vaginal delivery preferred unless fetal or maternal instability. Monitor for volume overload in the first 48 hours after delivery in cases of recurrent LV dysfunction.	Multidisciplinary team for planning; patient involved. Spontaneous vaginal delivery preferred unless fetal or maternal instability. Early delivery if further decrease in LV function and hemodynamic deterioration. Consider hemodynamic monitoring for optimization prior to delivery and monitoring during and after delivery. Monitor for volume overload in the first 48 hours after delivery.

Risks of a subsequent pregnancy differ based on the pre-conception recovery status. There is higher risk with nonrecovered myocardial function and pregnancy should be discouraged. Peripartum management options depend on the clinical status and myocardial function. ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; LV = left ventricular; LVEF = left ventricular ejection fraction; PPCM = peripartum cardiomyopathy.

Davis etal, J Am College Cardiol 2020; 75:207

Conclusions

- PPCM is a global disease, often associated with a delayed diagnosis lead to a significant morbidity/mortality
- Reported 1-year mortality ranges 5% to 25%
- Increasing awareness and better diagnostic tools PPCM moved from “rare” to “relatively frequent” pregnancy complication
- PPCM should be considered in any pregnant or postpartum woman with symptoms concerning for HF
- ↑ BNP followed by echo
- Treatment with medications tailored for pregnancy and lactation
- Limited studies suggest breast feeding safe
- Specialized multidisciplinary teams for acutely ill
- Women considering subsequent pregnancy should be counselled and monitored
- Long term follow up important, optimal duration of medical therapy unclear
- Role of bromocriptine remains unclear, further studies are required