Εφαρμογή των νεώτερων κατευθυντήριων οδηγιών στην καρδιακή ανεπάρκεια σε αρρώστους με αμυλοείδωση

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Disclosures

- Chair or Committee Member of trials sponsored by Bayer, Novartis, Vifor, Servier
- Research Grants: European Union
- Associate Editor: European Heart Journal, Int J Cardiol
- Past President, Heart Failure Association

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

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2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration With the International Society for Heart and Lung Transplantation

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Circulation / JACC / JCF 2016

Classes of Recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness /efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/ effective, and in some cases may be harmful.

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

ESC

Clinician Update: Cardiac Amyloidosis
Circulation 2011

- A 55-year-old woman, very physically active, noted a gradual decrease in exercise tolerance over a period of 3 to 4 months to the extent that she had to rest briefly after climbing a single flight of stairs.
- She had consulted a dermatologist 6 months earlier because of recurrent, small bruises of her eyelids, but no cause had been found.
- An ECG suggested an old myocardial infarction and a cardiology consultation described symmetrical left ventricular hypertrophy on the echocardiogram with normal left ventricular ejection fraction, normally functioning valves, and mild right ventricular hypertrophy.

Rodney Falk: From the Cardiac Amyloidosis Program, Brigham and Women's Hospital and Harvard Vanguard Medical Associates, Boston, MA,.

New Classification and Diagnosis

New Classification!

- **Heart failure with preserved, mid-range and reduced EF**

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

*it is only in patients with **HFrEF** that therapies have been shown to reduce both morbidity and mortality*

www.escardio.org/guidelines

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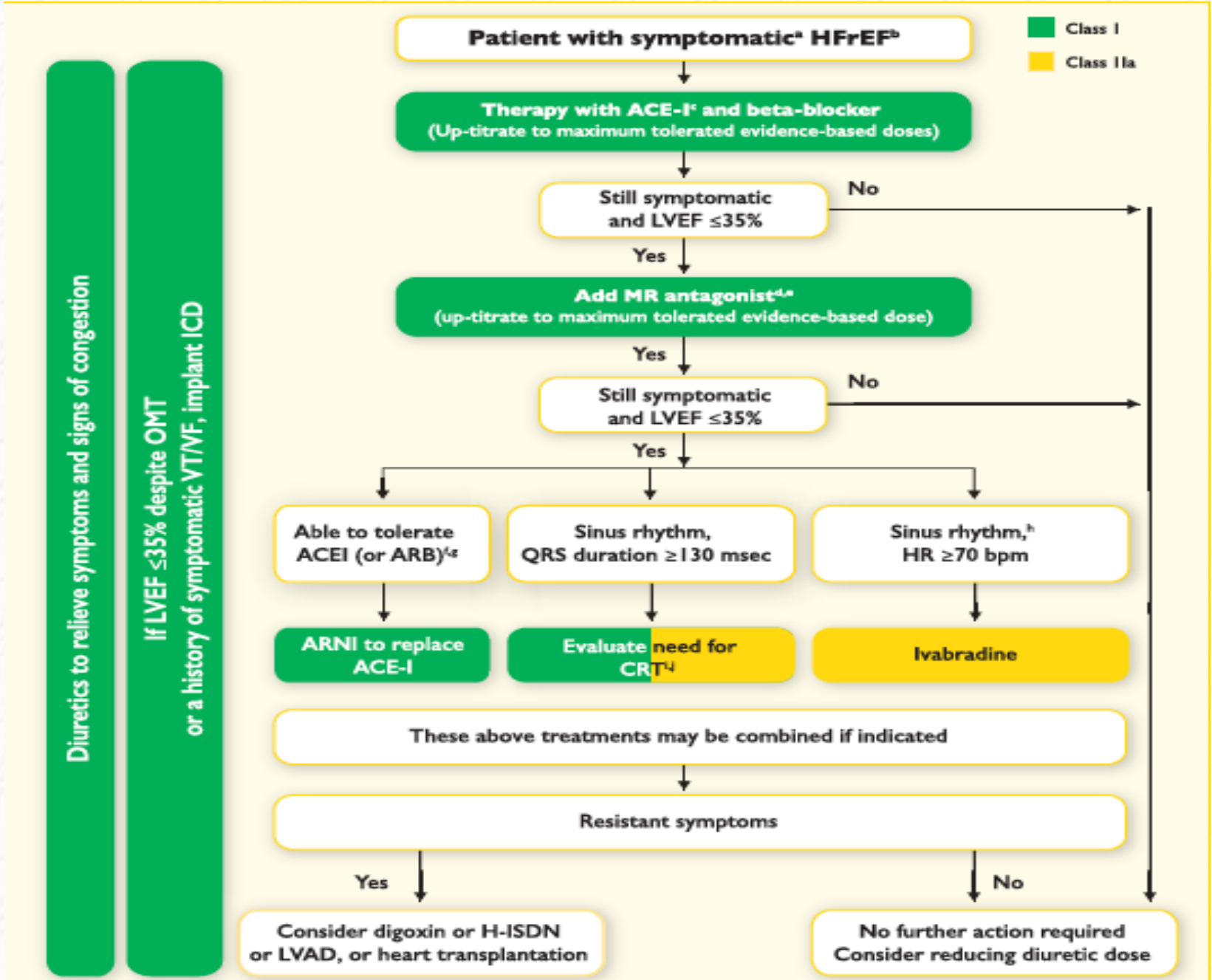
ESC Heart Failure Guidelines: HFPEF

Manage HF co-morbidities in all heart failure patients.

In HFpEF, this is the only evidence based treatment approach.



Treatment Algorithm

Available online on Eur J Heart Fail

We are HFA

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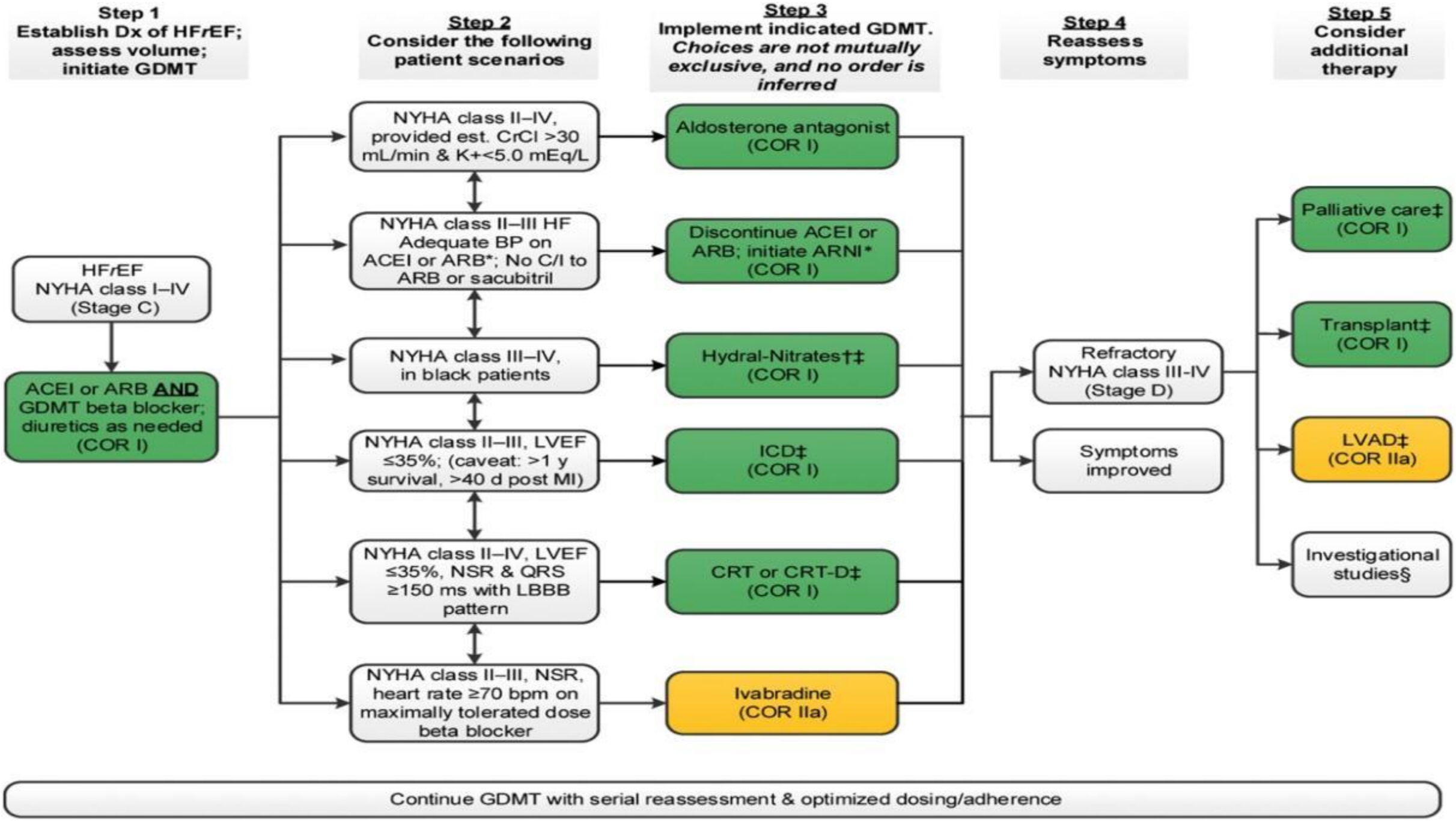

Step 1
Establish Dx of HFrEF; assess volume; initiate GDMT
Step 2
Consider the following patient scenarios
Step 3
Implement indicated GDMT. Choices are not mutually exclusive, and no order is inferred
Step 4
Reassess symptoms
Step 5
Consider additional therapy
HFrEF
NYHA class I–IV
(Stage C)
ACEI or ARB AND GDMT beta blocker; diuretics as needed
(COR I)
NYHA class II–IV, provided est. CrCl >30 mL/min & K+<5.0 mEq/L
Aldosterone antagonist
(COR I)
NYHA class II–III HF Adequate BP on ACEI or ARB*; No C/I to ARB or sacubitril
Discontinue ACEI or ARB; initiate ARNI*
(COR I)
NYHA class III–IV, in black patients
Hydral-Nitrates†‡
(COR I)
NYHA class II–III, LVEF ≤35%; (caveat: >1 y survival, >40 d post MI)
ICD‡
(COR I)
NYHA class II–IV, LVEF ≤35%, NSR & QRS ≥150 ms with LBBB pattern
CRT or CRT-D‡
(COR I)
NYHA class II–III, NSR, heart rate ≥70 bpm on maximally tolerated dose beta blocker
Ivabradine
(COR IIa)
Refractory NYHA class III-IV
(Stage D)
Symptoms improved
Palliative care‡
(COR I)
Transplant‡
(COR I)
LVAD‡
(COR IIa)
Investigational studies§
Continue GDMT with serial reassessment & optimized dosing/adherence

Treatment of cardiac amyloidosis

- **Non-amyloid specific therapies**
  - Diuretics
  - Neurohormonal modulators (BB, ACEI, MRA)-?
  - Cardiac devices (ICD, CRT)?
  - VAD?
  - Heart transplantation
- **Amyloid-specific therapies**
  - AL-amyloidosis: chemotherapy, autologous stem cell transplantation, immunomodulators, proteasome inhibitors
  - TTR amyloidosis: diflunisal, RNA interference approaches, tafamidis

Gertz, M. A. et al. Nat. Rev. Cardiol 2015
Omar K. Siddiqi, et al. Trends in Cardiovasc Med 2018

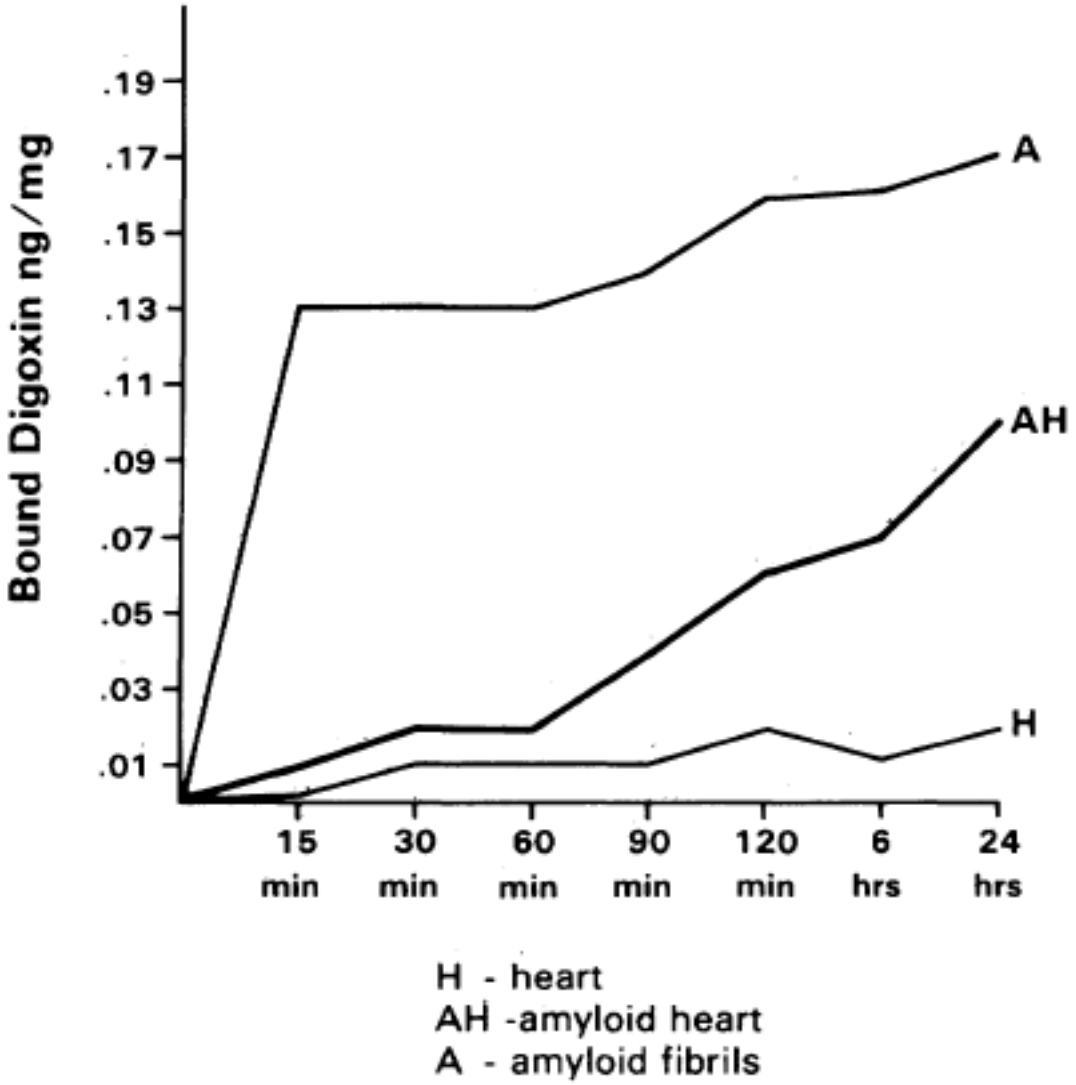
Pharmacologic management of cardiac-related symptoms

- **No evidence base for HF specific pharmacologic therapies in cardiac amyloidosis**
- Diuretics:
  - Mainstay of treatment for the cardiac-related symptoms
  - Combination of loop diuretics and potassium-sparing diuretics to maintain adequate volume and potassium balance
  - Avoid overdiuresis that promote hypotension
- ACE inhibitors/angiotensin II inhibitors:
  - Use with caution
  - Even low doses are often poorly tolerated, resulting in profound hypotension, possibly by exposing a subclinical autonomic neuropathy.
- b-blockers:
  - No survival data available in cardiac amyloidosis patients.
  - Limited use due to refractory heart failure or severe hypotension
- Digoxin
  - Not recommended owing to a higher risk of digoxin toxicity, as the drug binds avidly to amyloid fibrils

Gertz, M. A. et al. Nat. Rev. Cardiol. 2015;12:91–102

Digoxin sensitivity in amyloid cardiomyopathy

Circulation 1985



Digoxin uptake by non amyloidotic heart homogenate (H), an (AH) homogenate and isolated amyloid fibrils (A)

Atrial arrhythmias in cardiac amyloidosis

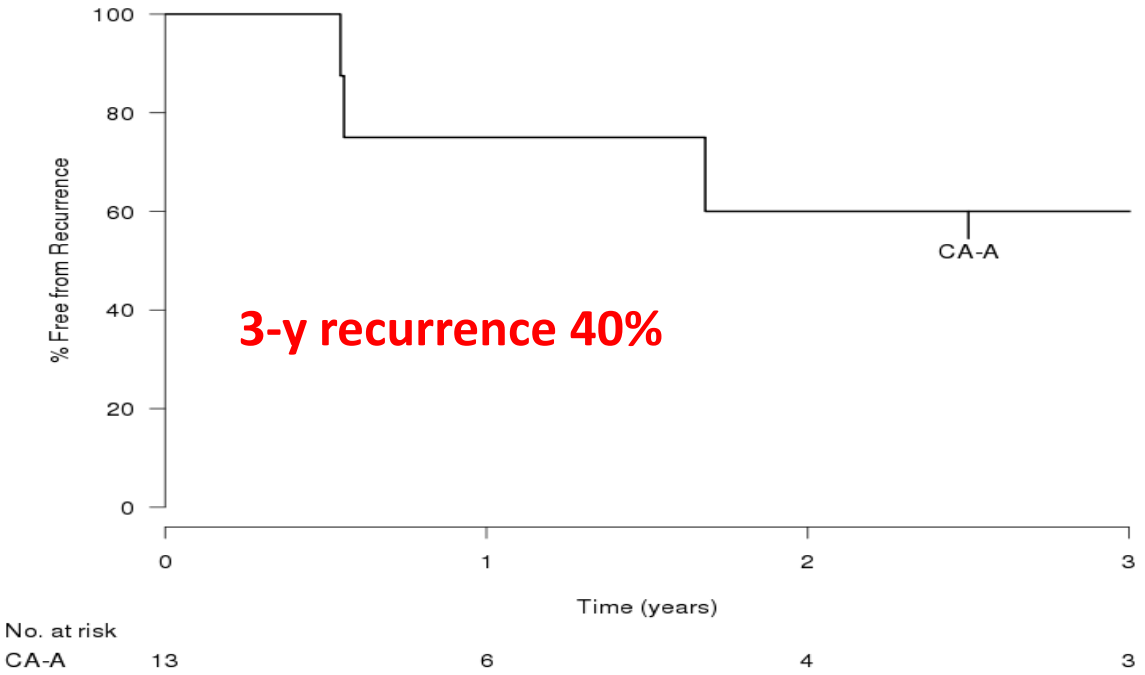
- Poorly tolerated, frequently necessitating cardioversion and/or antiarrhythmic therapy

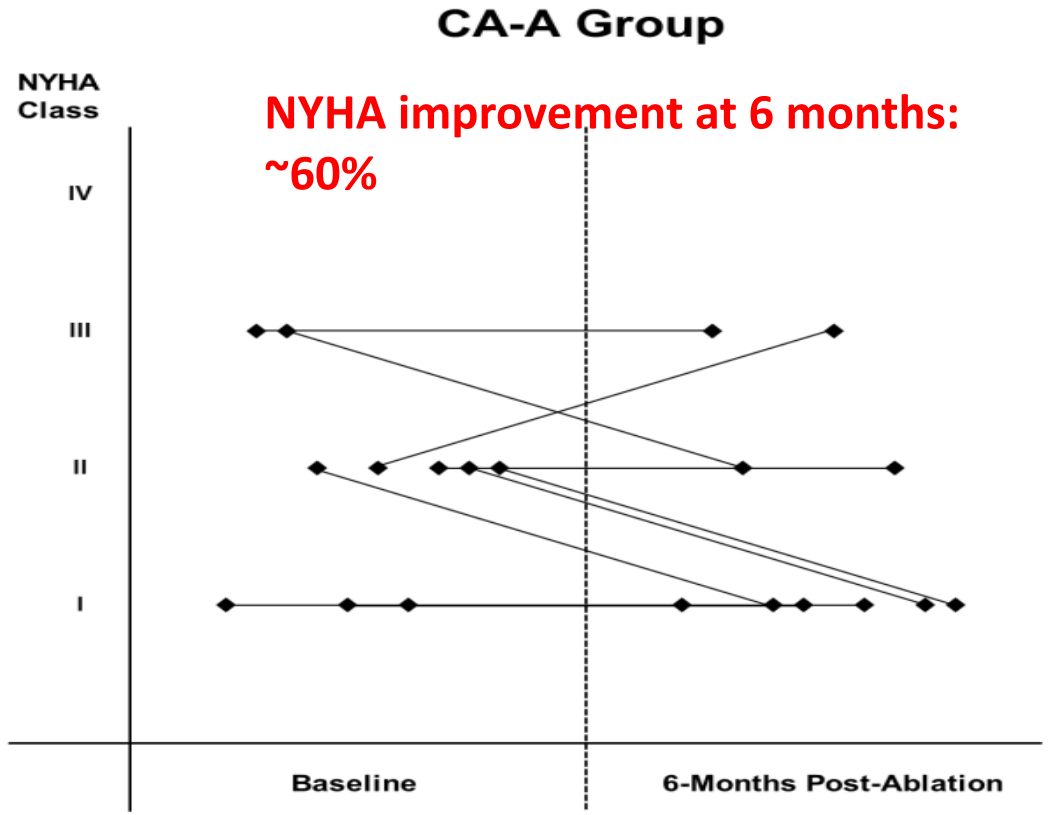
- Rhythm control options limited; amiodarone most commonly used and relatively well tolerated

Siddiqi OK, Ruberg FL. Trends Cardiovasc Med. 2018;28(1):10-21.

Catheter ablation of atrial arrhythmias in cardiac amyloidosis

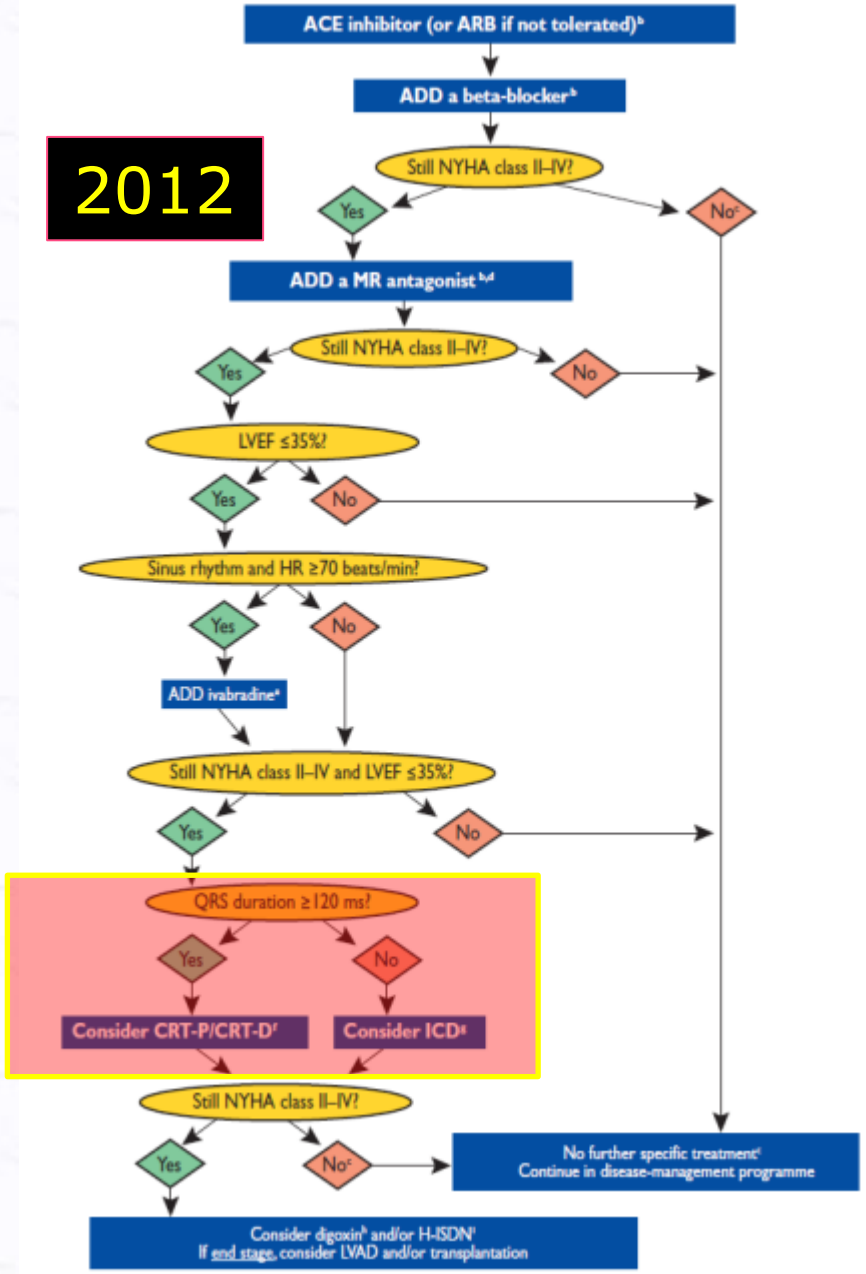
Mayo Clinic,
N= **27 patients** (7 AL, 17 TTRw, 2 TTRm)





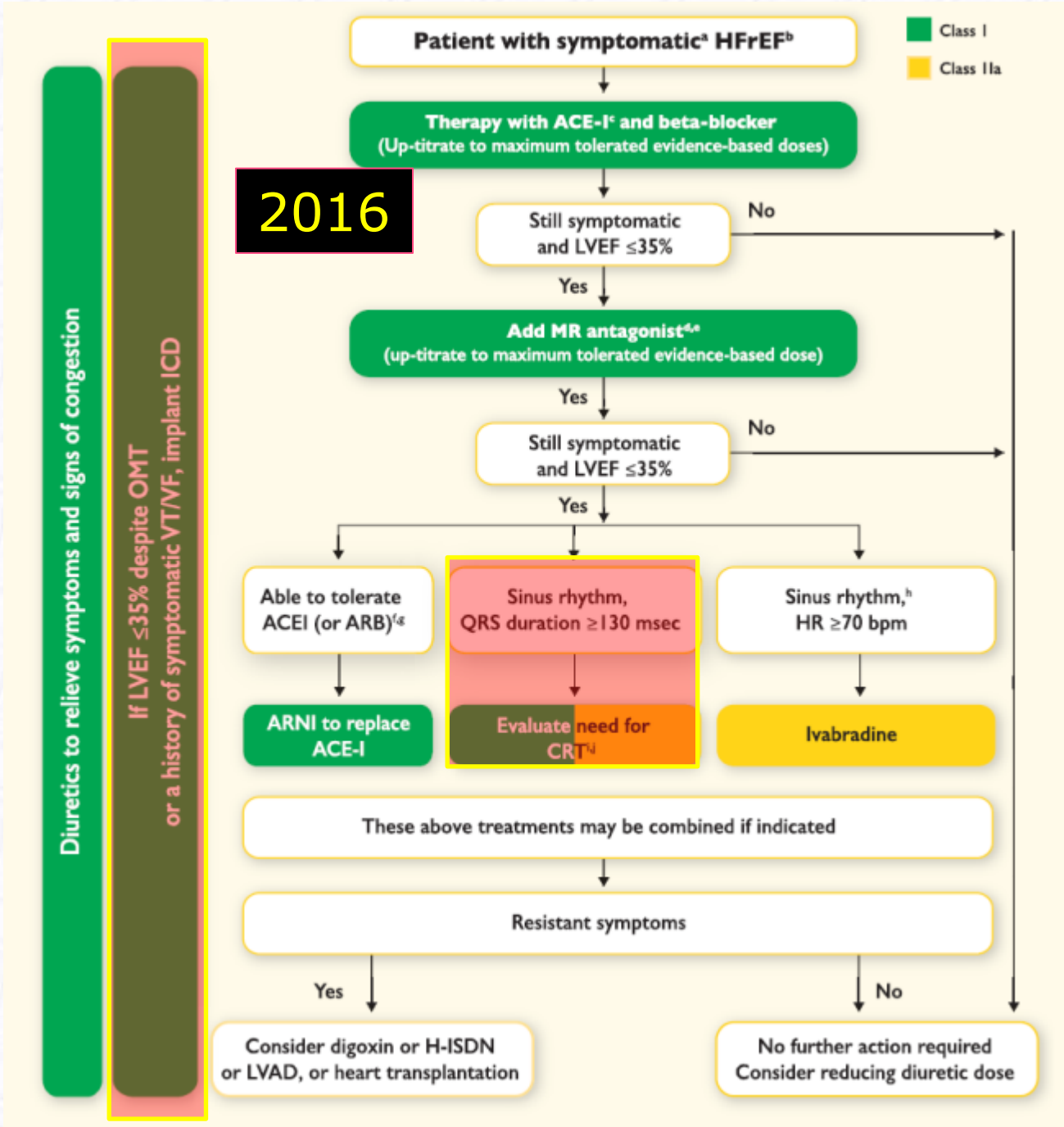
Tan, N et al. J Cardiovasc Electrophysiol 2016

2012



www.escardio.org/guidelines

2016



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Ventricular arrhythmias and SCD

- Prevalence of sudden cardiac death: 25%
- Complex ventricular arrhythmias: ~50%
- Pulseless electrical activity probably the dominant cause of SCD.
- Primary prevention of SCD with ICDs:
  - Small case series
  - Inconsistent results
  - Probably more effective in the current/future era of development of effective amyloid-specific therapies

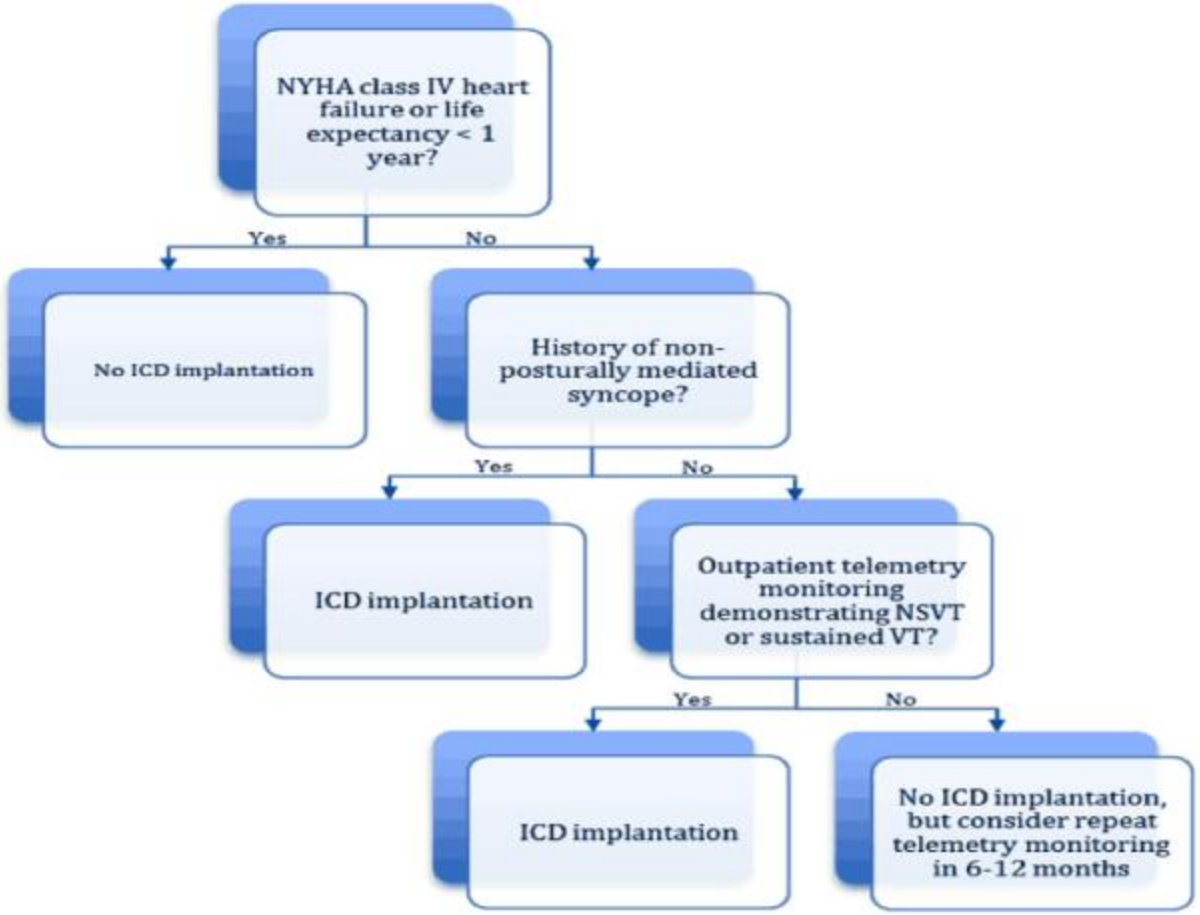
Morie A. Gertz, Angela Dispenzieri and Taimur Sher. Nat Rev Cardiol 2014

Recommendations for implantable cardioverter-defibrillator in patients with heart failure

Recommendations	Class [a]	Level [b]
Secondary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mor[illegible]ve recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status.	I	A
Primary prevention An ICD is recommended to reduce the risk of sudden death and all-caus[illegible] Class II–III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good functional status, and they have:		
• IHD (unless they have had an MI in the prior 40 days – see below).	I	A
• DCM.	I	B
ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis.	III	A
ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a ventricular assist device, or cardiac transplantation.	III	C
Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's needs and clinical status may have changed.	IIa	B
A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device.	IIb	C

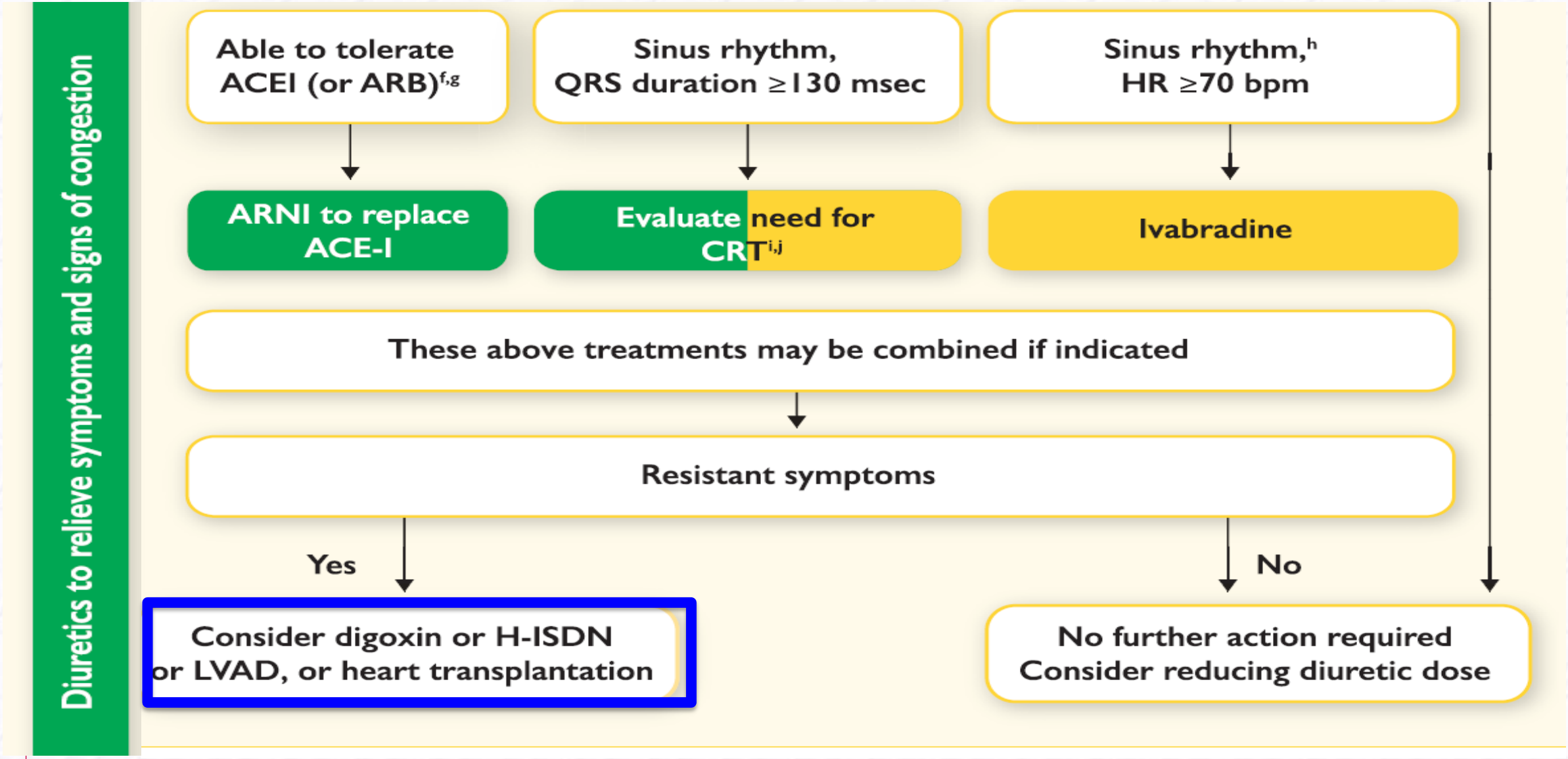
Suggested algorithm for patient selection for ICD implantation for primary SCD prevention

Stanford Amyloid Center's ICD implantation criteria for cardiac amyloidosis



Varr BC, et al. Heart Rhythm 2014

Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction

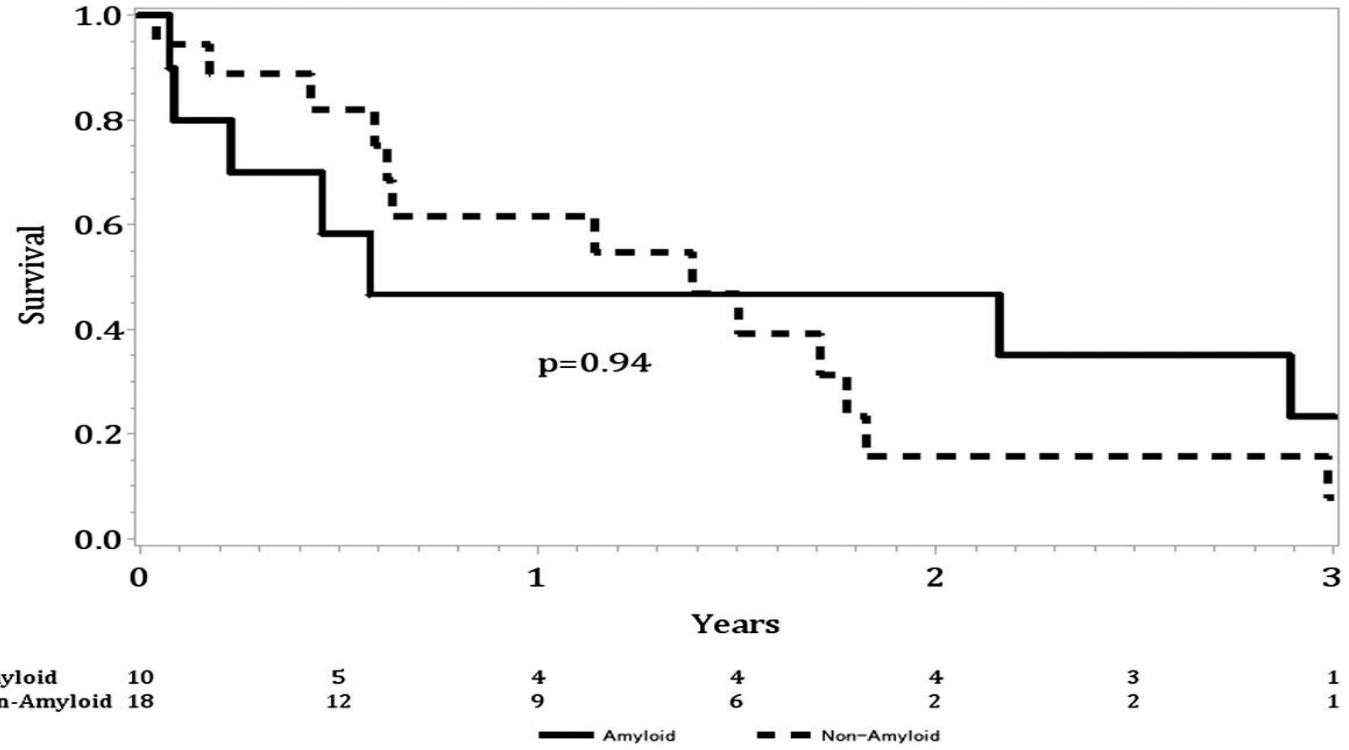


Ventricular assist devices

Mayo Clinic,
N= 28 patients with restrictive CM: 10 cardiac amyloidosis
(1 AL, 6 TTRw, 3 TTRm)
DT/BTT 4/5

Mean survival post-VAD 536 days
In-hospital death 2/9

Complications:
GI bleeding (3/9)
RV failure (2/9)



"Firm conclusions cannot be drawn from our investigation, but the present observations suggest LVAD implantation is technically feasible for patients with severe heart failure due to advanced cardiac amyloidosis"

Swiecicki, PL, J Heart Lung Transplant 2013;32:563–568

Heart transplantation in cardiac amyloidosis

- Isolated HTx
  - In selected patients with AL cardiac amyloidosis, followed by autologous stem cell transplantation
  - In highly selected wild-type senile amyloidosis (however, frequently old patients, ineligible for HTx)
- Combined HLTx
  - In selected younger patients with familial TTR cardiac amyloidosis

Heart transplantation in cardiac amyloidosis: ISHLT guidelines

Recommendations: 2.2.1 Selected patients with HF due to AL amyloidosis who are not candidates for disease-specific therapies due to cardiovascular compromise may be considered for HT in experienced centers with established collaborations between cardiovascular and hematology teams. Autologous stem cells transplantation (ASCT) should be planned as soon as clinically feasible after recovery from HT (Class IIA, Level of Evidence: B).

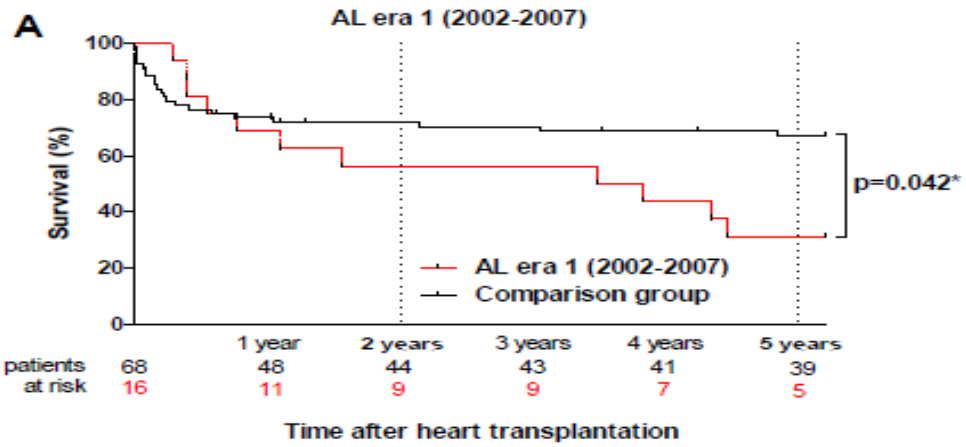
2.2.2 Patients with transthyretin related (TTR) amyloidosis involving the heart may be considered for HT. Familial TTR cardiac amyloidosis patients should be considered for combined heart and liver transplantation in experienced centers with established collaboration between cardiology, hepatology, and neurology teams (Class IIA, Level of Evidence: B).

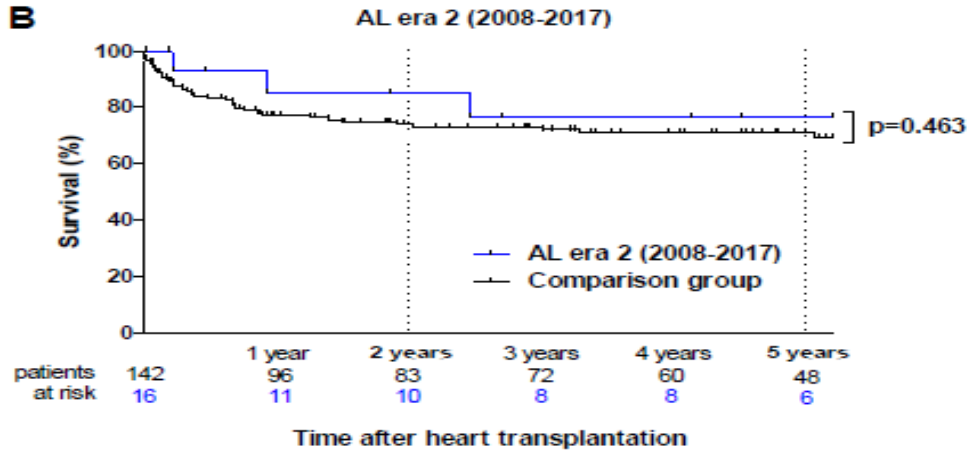
2.2.3 Amyloid involvement of extracardiac organs must be carefully evaluated when considering AL amyloid patients for sequential HT/ASCT (AL patients) or TTR amyloid patients for HT or combined HT with liver transplantation. Severe extracardiac amyloid organ dysfunction should be considered a contraindication to proceeding with HT (Class IIA, Level of Evidence: B).

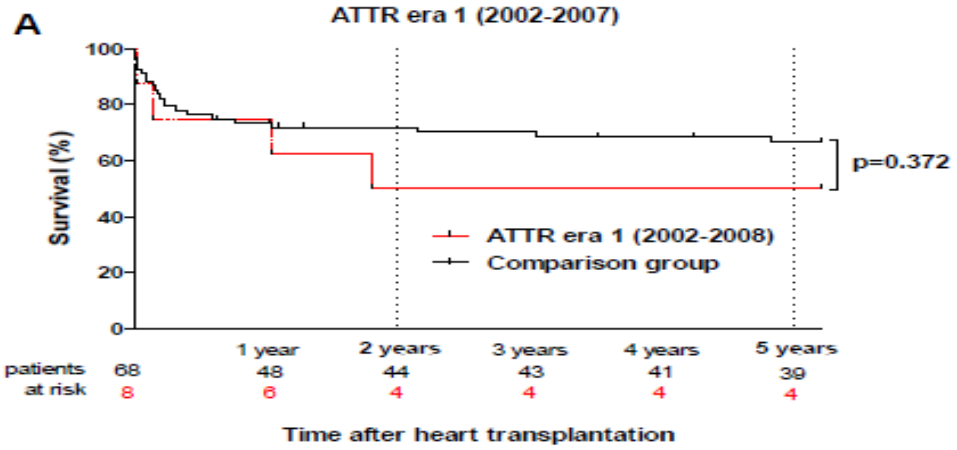
Mehra M, et al. J Heart Lung Transplant 2016

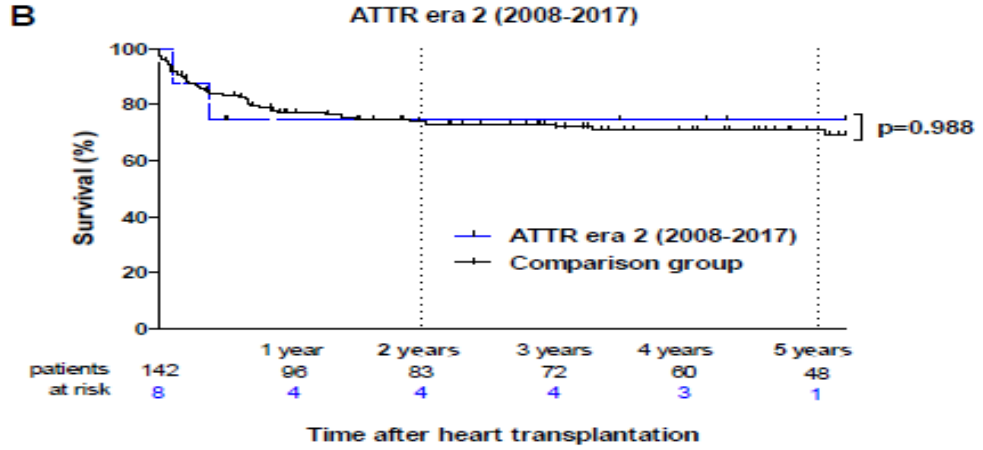
Temporal trends in outcomes after HTX for cardiac amyloidosis

AL, n=32; familial ATTR, n= 16







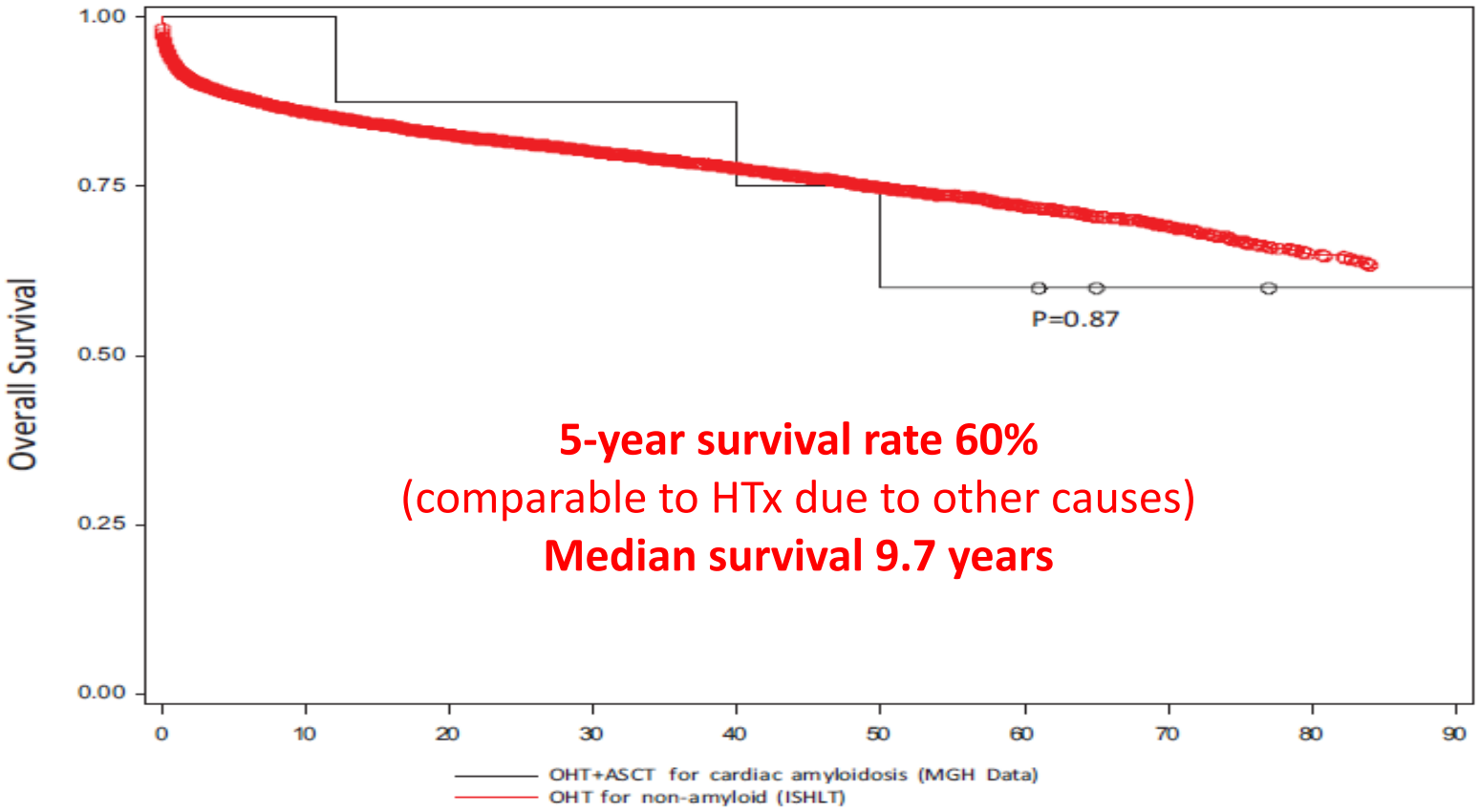


Kristen, AV et al. J Heart Lung Transplant 2017

Heart transplantation

- The majority with cardiac AL amyloidosis have significant noncardiac amyloidosis and are not suitable candidates for heart transplantation.
  - In one series, only 4 percent had clinically isolated cardiac disease
- Early cardiac transplantation did not address the underlying plasma cell dyscrasia, which later progressed in other organs and/or returned in the transplanted heart.
- Heart transplantation is followed by high–dose chemotherapy and autologous HCT within a 12-month period. Long-term follow-up data in these patients is not yet available, but several appear to have had good results

Heart transplantation+ASCT in AL cardiac amyloidosis



5-year survival rate 60%

(comparable to HTx due to other causes)

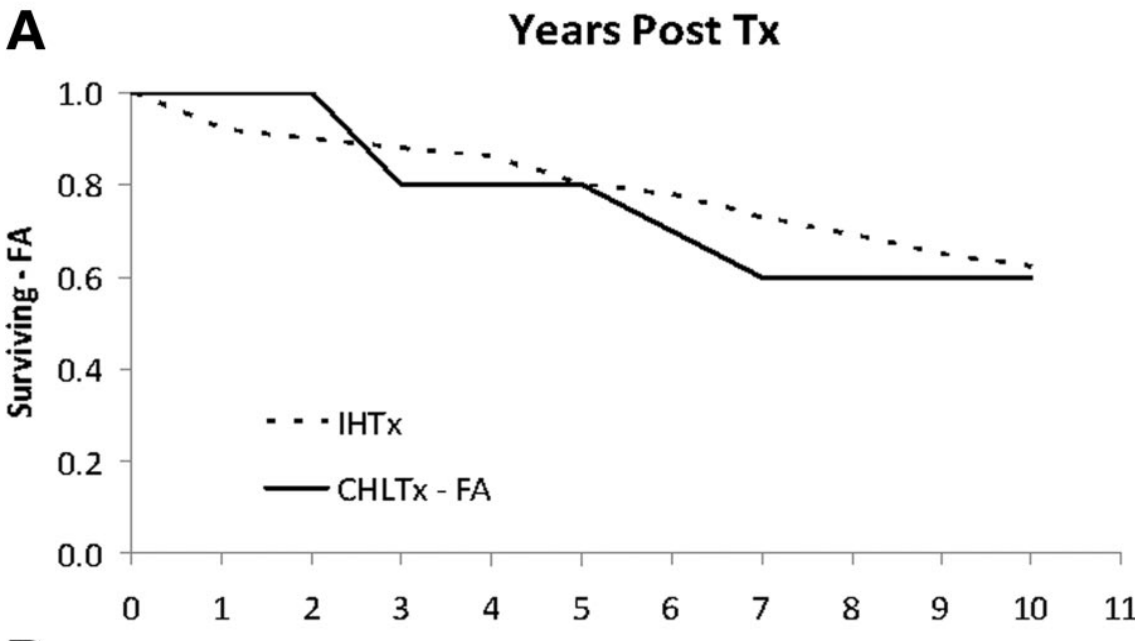
Median survival 9.7 years

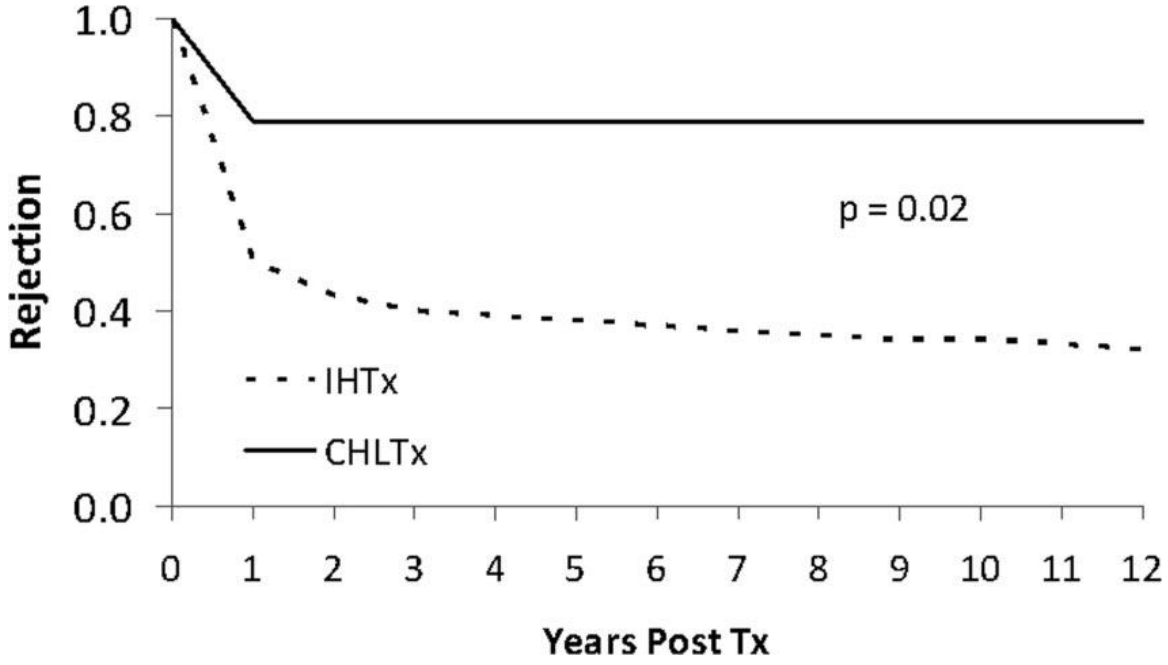
Bimalangshu R. Dey, et al. Tranplantation 2010

Combined Liver and Heart Tx in familial TTR cardiac amyloidosis

Similar survival rates after combined HLTx vs Isolated HTx

Less cardiac allograft rejection with combined HLTx vs Isolated HTx





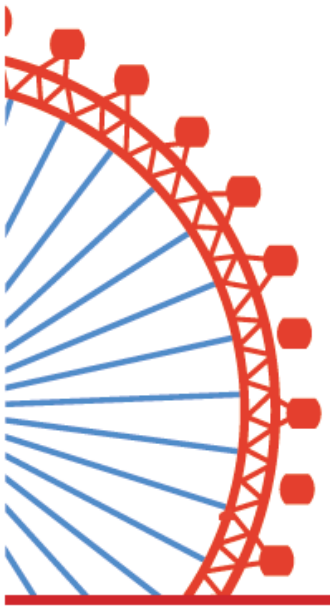
Raichlin, et al. Transplantation 2009

HEART FAILURE 2018

including the World Congress on Acute Heart Failure

VIENNA 26 -29MAY

HFA Heart Failure Association



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