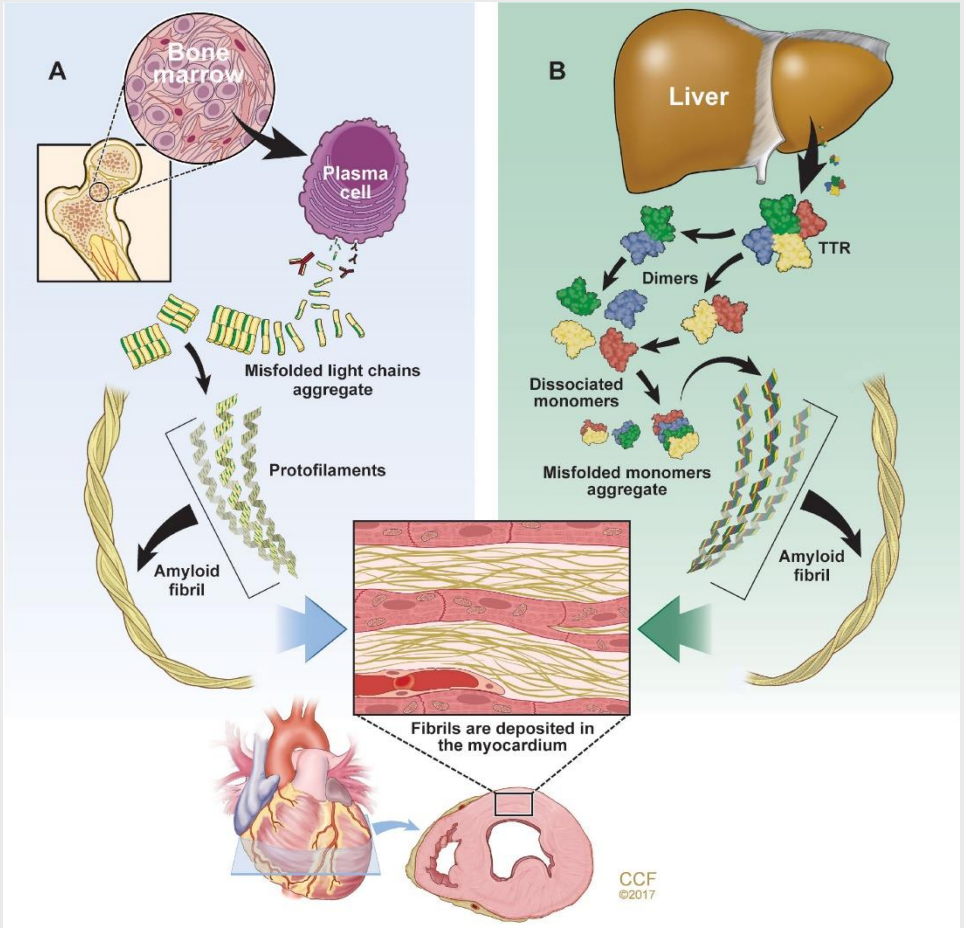
Kardiale Amyloidose

Ätiologien der kardialen Amyloidosen

Donnelly JP et al Cleve Clin J Med 2017



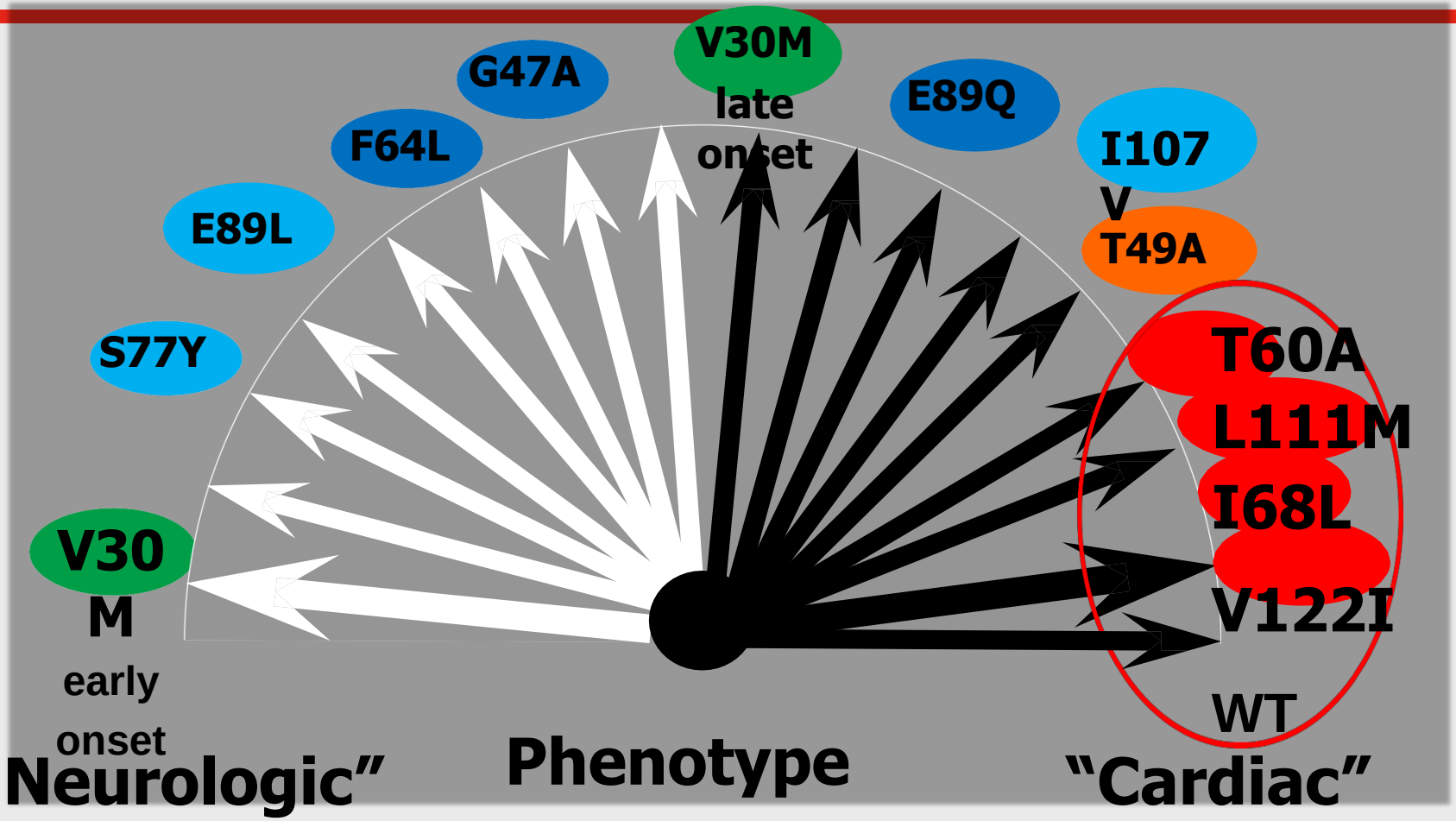
Klassifizierung der Amyloidosen

1. Ando Y et al., *Arch Neurol* 2005;62:1057–1062. 2. Merlini G et al., *J Intern Med* 2004;255:159–178.
3. Falk R et al., *N Engl J Med* 1997;337:898–909. 4. Sekijima Y et al. *Curr Pharm Des* 2008;14:3219–3230.

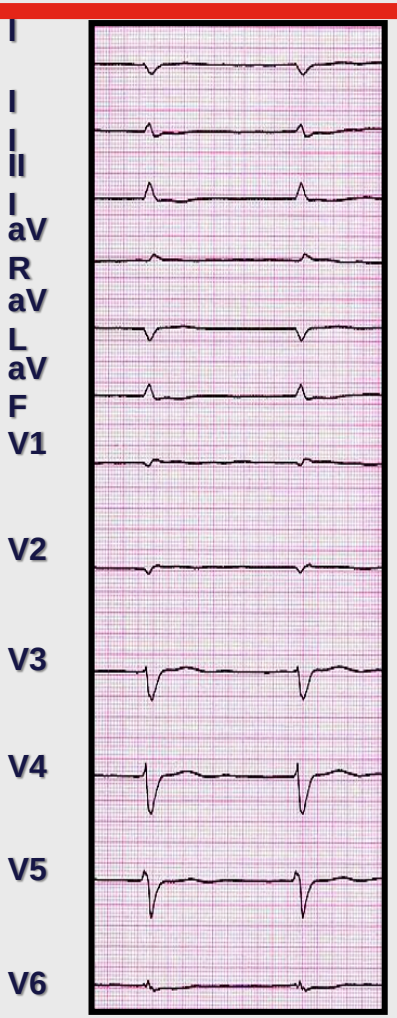
TYPE OF AMYLOID	PRECURSOR PROTEIN	MAJOR ORGANS INVOLVED	COMMENT
AL	Immunoglobulin light chain	Heart, kidney, liver, nerves, skin, bowel	Rapidly Progressive. Related to multiple myeloma
TTRm	Variant transthyretin	Nerve Heart	Autosomal dominant with variable penetrance. High gene prevalence in African Americans
TTRwt	Wild-type TTR	**Heart**	Slowly progressive. Rapidly increasing prevalence. Disease of men.
Isolated atrial amyloidosis	ANP	Atrium	Little clinical significance

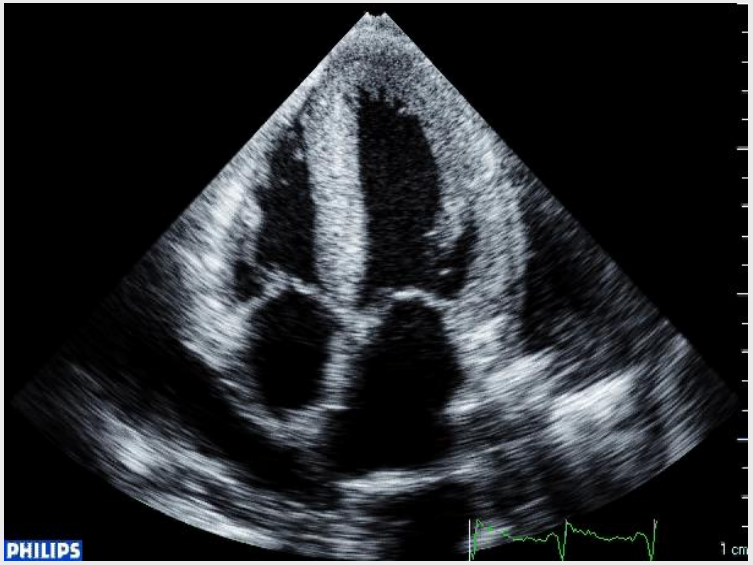
Genotyp-Phenotyp Korrelation bei ATTR

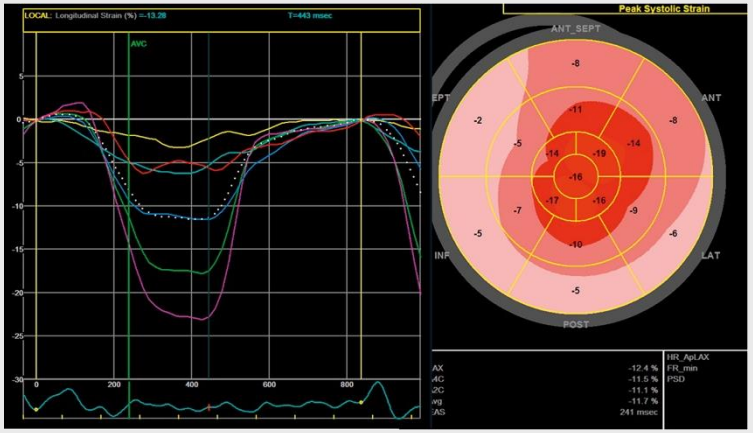
Rapezzi (THAOS database) Rapezzi EHJ 2013



Eine Blickdiagnose

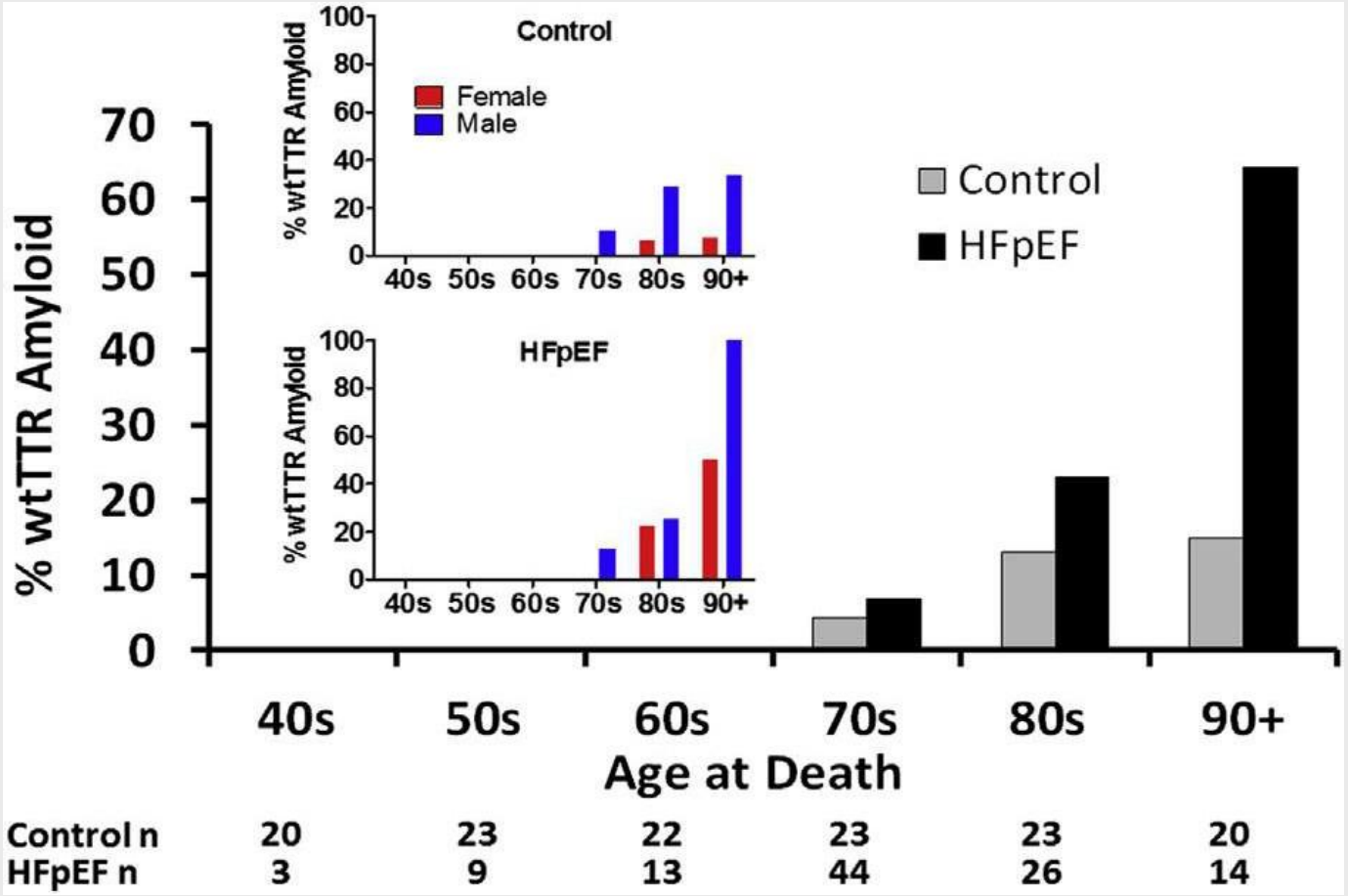






30% der Männer im Alter mit HFpEF haben eine wtATTR

Esther González-López et al. Eur Heart J 2015;36:2585-2594



Einfacher Diagnose Score zur Differentialdiagnose der LVH
Kardiale Amyloidose vs nicht Amyloidose

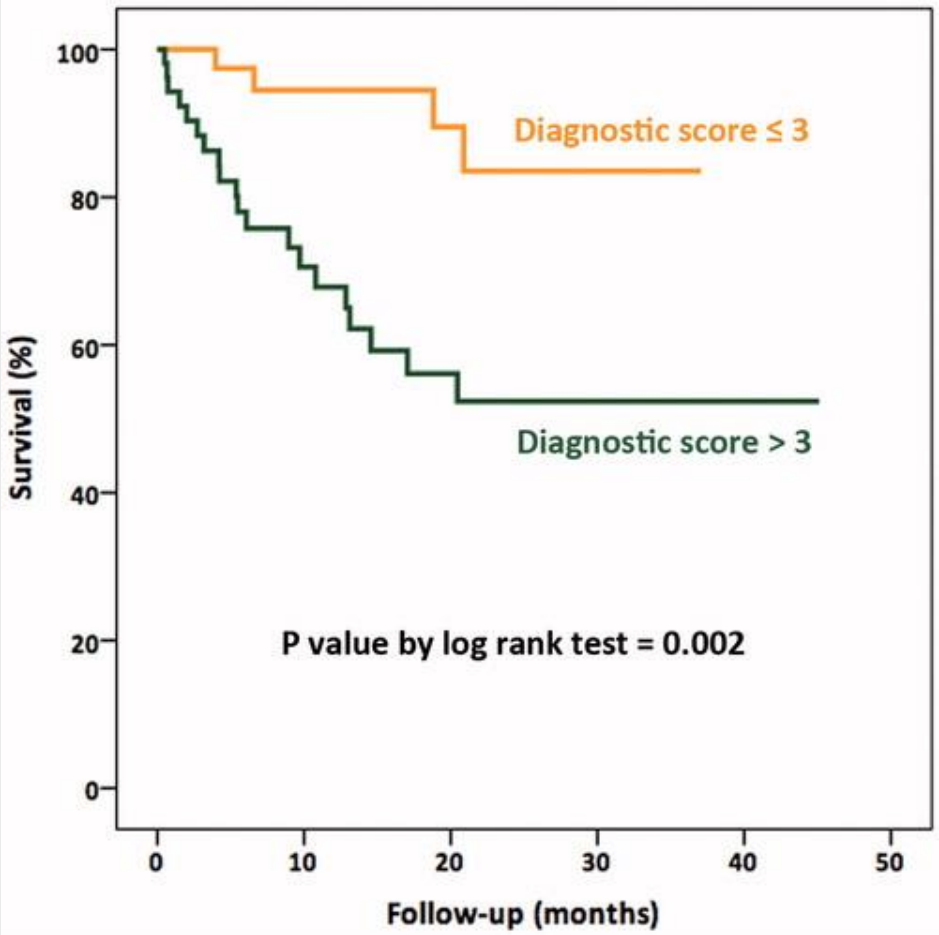
Cariou et al Amyloid 2017

7 Kriterien

EKG Veränderungen:	**Sokolov < 12mV, PR > 200ms**
Echoveränderungen:	**LVH > 12mm, E/Ea > 10, Strain < -12%,**
	Summe basaler Strain > -47%)
Blutdruck Werten :	**RR< 120mmHg**

Einfacher Diagnose Score zur Differentialdiagnose der LVH
Kardiale Amyloidose vs nicht Amyloidose

Cariou et al Amyloid 2017



RED FLAGS bei kardialen Amyloidosen

Donnelly JP et al Cleve Clin J Med 2017

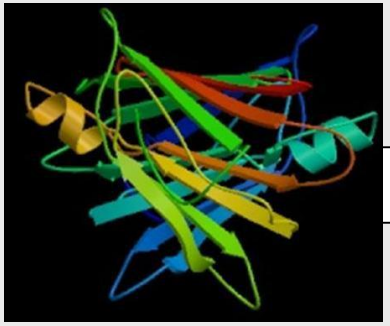
TABLE 1
Symptoms that raise suspicion of cardiac amyloidosis

Red Flags for Cardiac Amyloidosis	
Echocardiography: ▪ Low voltage on ECG and thickening of the septum/posterior wall > 1.2 cm ▪ Thickening of right ventricle free wall, valves	
Intolerance to beta-blockers or ACE inhibitors	
Low normal blood pressure in patients with a previous history of hypertension	
History of bilateral carpal tunnel syndrome, often requiring surgery	
AL	**ATTR**
HFpEF + nephrotic syndrome	White male age ≥ 60 with HFpEF + history of carpal tunnel syndrome and/or spinal stenosis
Macroglossia and/or periorbital purpura	African American age ≥ 60 with HFpEF without a history of hypertension
Orthostatic hypotension	New diagnosis of hypertrophic cardiomyopathy in an elderly patient
Peripheral neuropathy	New diagnosis of low flow, low gradient aortic stenosis in an elderly patient
MGUS	Family history of ATTRm amyloidosis

ACE = angiotensin-converting enzyme; AL = immunoglobulin light chain amyloidosis; ATTR = transthyretin amyloidosis; ECG = electrocardiogram; ATTRm = hereditary mutant variant ATTR; HFpEF = heart failure with preserved ejection fraction ("diastolic heart failure"); MGUS = monclonal gammopathy of undetermined significance

"Senile Systemic Amyloidosis"
(wt TTR-related Amyloidosis)

100%

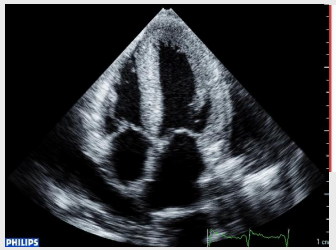


wild-type ATTR

35%

Diagnosealgorythmus bei kardialen Amyloidosen

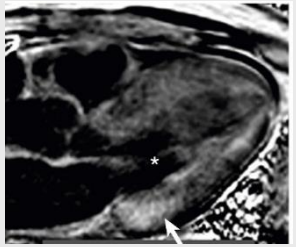
Falk et al JACC 2016 und Donnelly JP et al Cleve Clin J Med 2017



Echocardiogram or MRI suggestive of cardiac amyloidosis

↓

Clinical and laboratory evaluation including:
NTproBNP, troponin T, SPEP, serum immunofixation and free light chain assay



Prognose Vergleich der ATTRs

Gillmore JD et al EHJ 2017

Stadium I:

NT-pro-BNP ≤ 3.000 ng/l und eGFR ≤ 40 ml/min

Stadium II:

NT-pro-BNP > 3.000 ng/l und eGFR < 45 ml/min

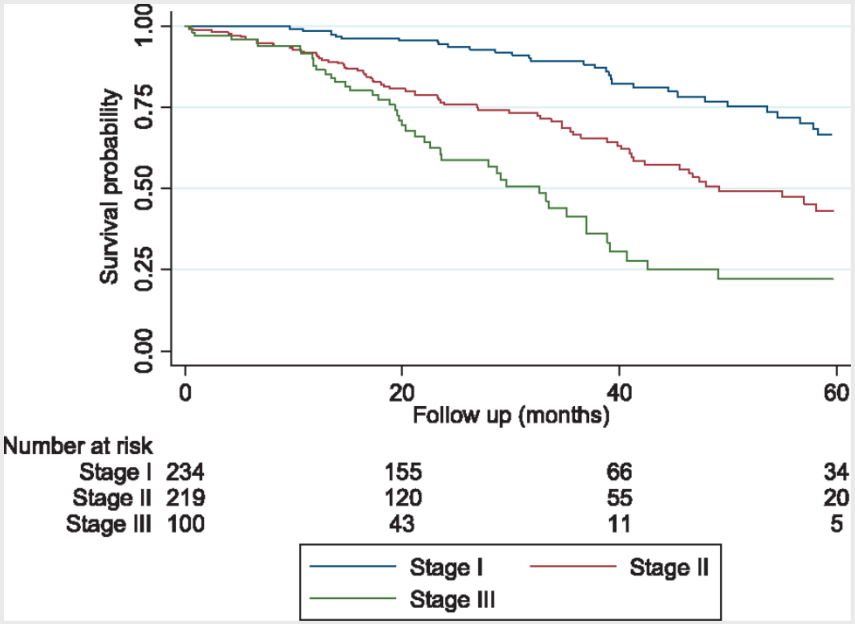
Stadium III:

alle Patienten, die nicht in Stadium I und II vertreten sind.

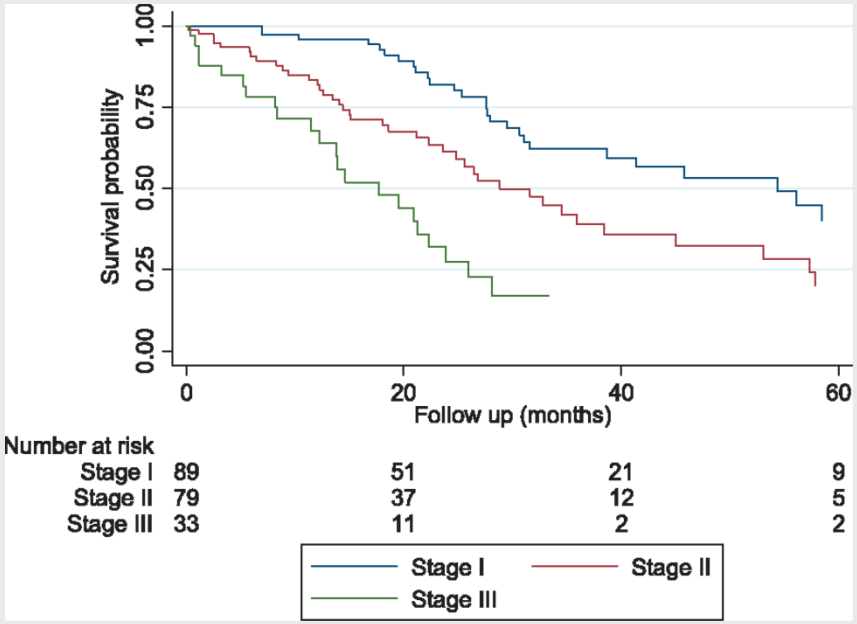
Prognose Vergleich der ATTRs

Gillmore JD et al EHJ 2017

Wild Typ

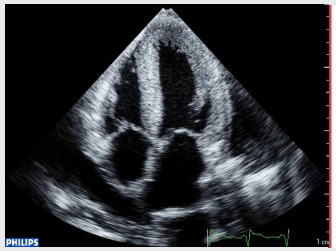


V122I Typ



Diagnosealgorythmus bei kardialen Amyloidosen

Falk et al JACC 2016 und Donnelly JP et al Cleve Clin J Med 2017



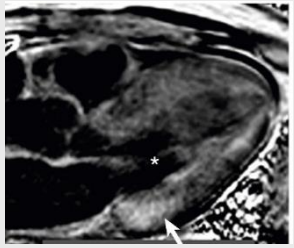
Echocardiogram or MRI suggestive of cardiac amyloidosis

↓

Clinical and laboratory evaluation including:
NTproBNP, troponin T, SPEP, serum immunofixation and free light chain assay

↓

Is plasma-cell dyscrasia present?*



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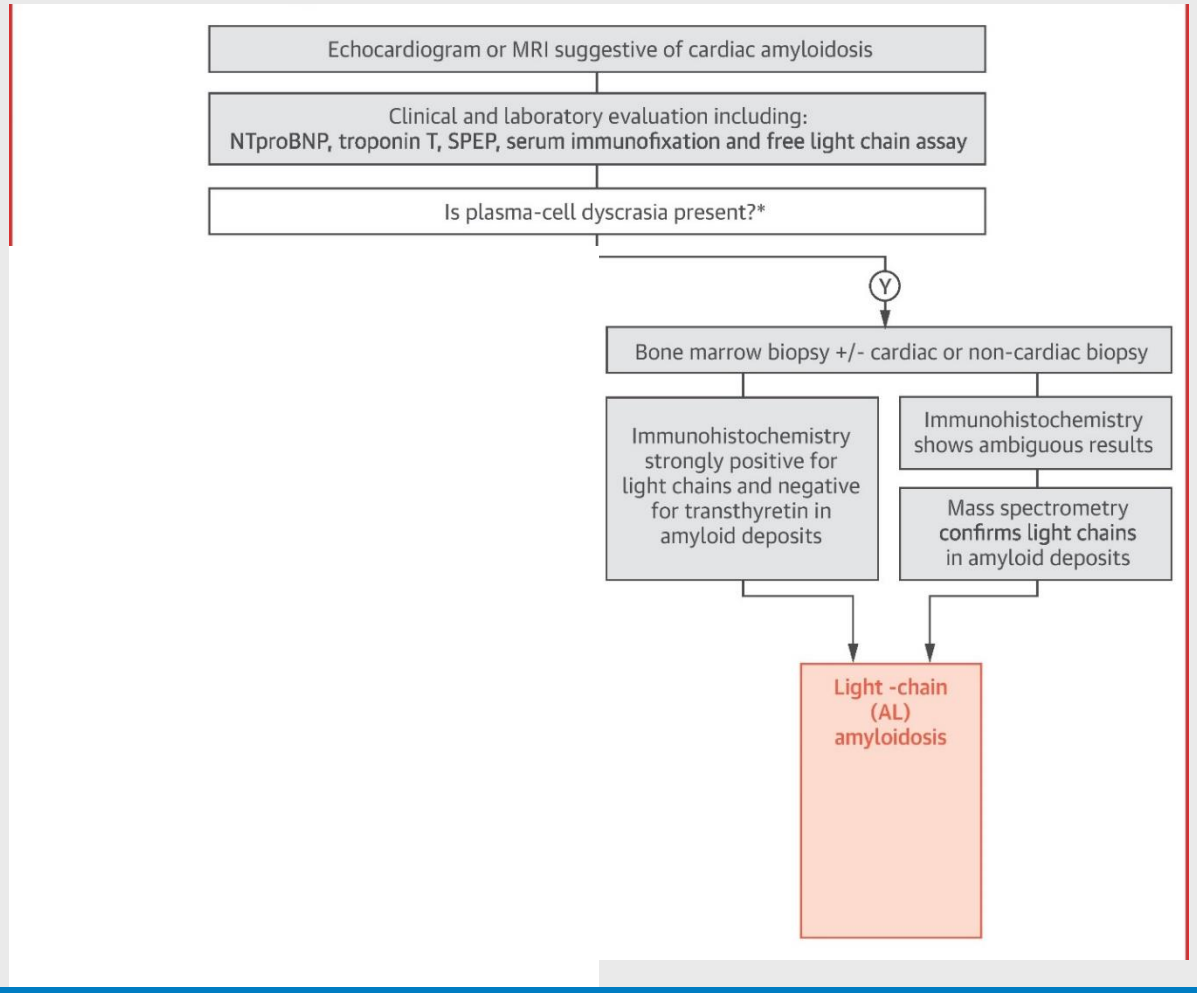


Therapieoptionen bei kardialen Amyloidosen

Donnelly JP et al Cleve Clin J Med 2017

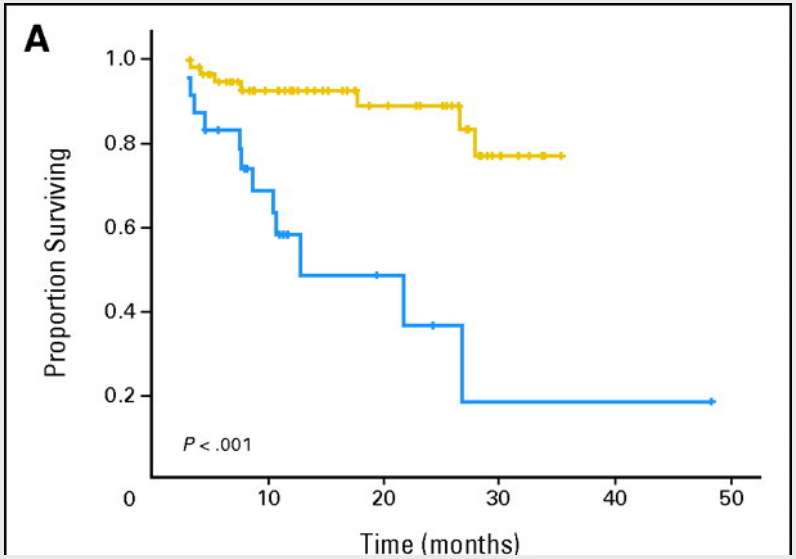
TABLE 2
Amyloid-specific pharmacotherapies

AL		
Anti-plasma cell therapies	*Alkylating agents*	Melphalan
		Cyclophosphamide
	Proteasome inhibitors	Bortezomib
		Ixazomib
	Immunomodulators	Pomalidomide
	Anti-CD38 monoclonal antibody	Daratumumab
Anti-amyloid antibody	NEOD001	

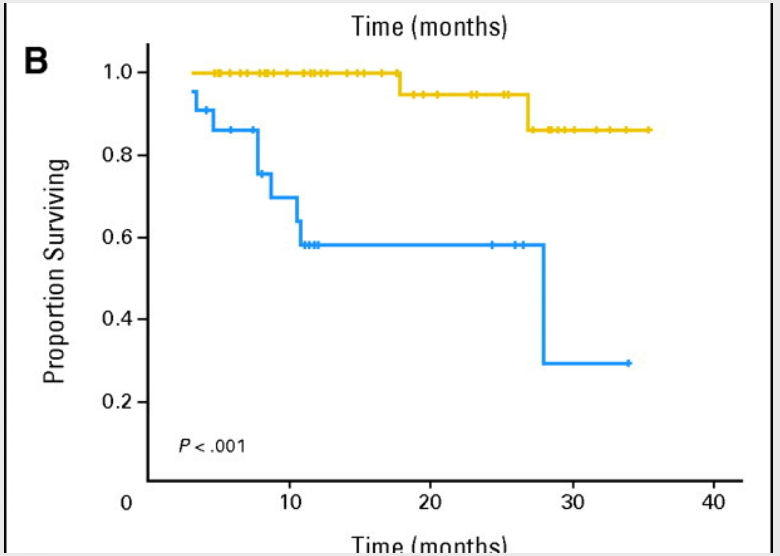
Chemotherapie mit Bortezomib bei AL

Kastritis et al J Clin Oncol 2010

Hämatologische Response



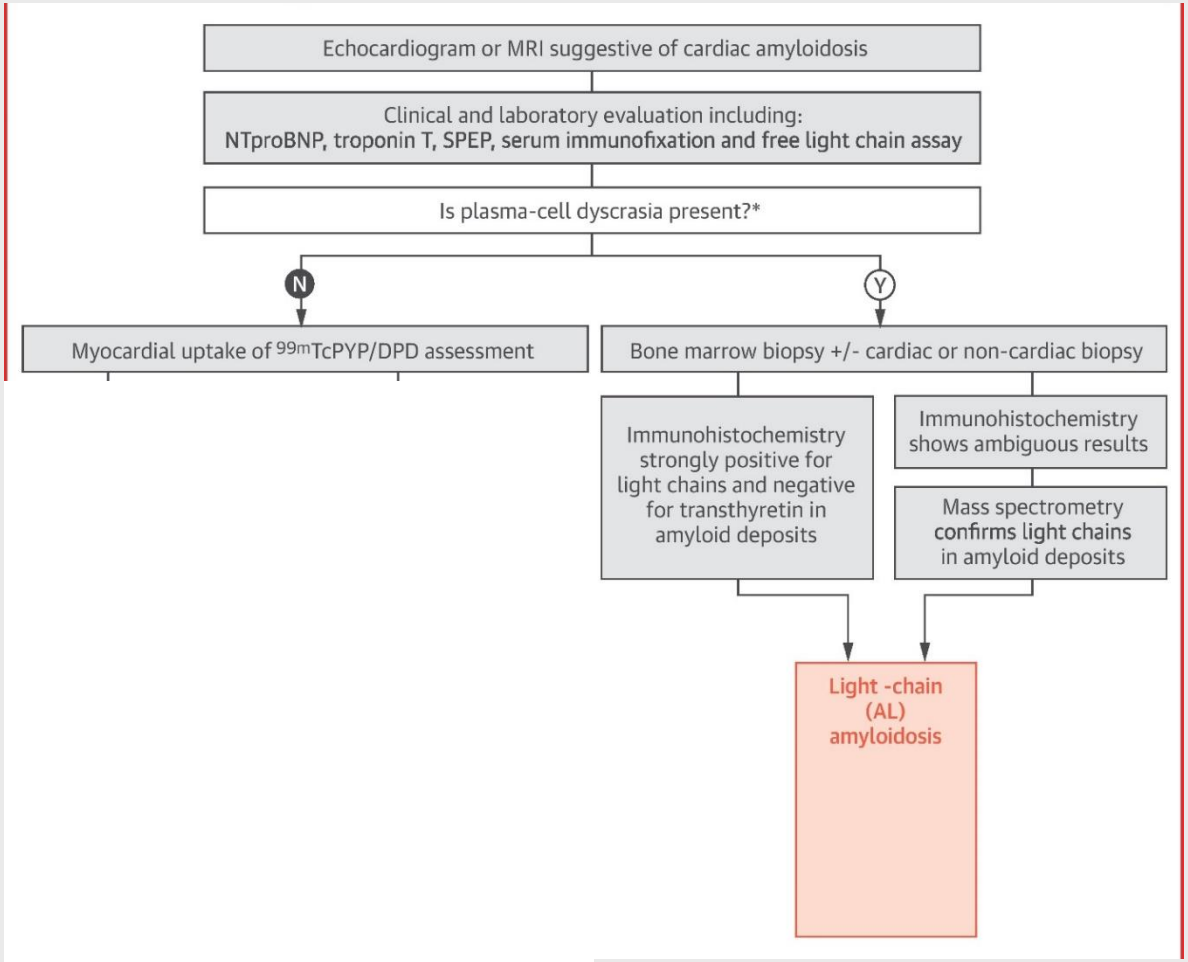
Kardiale* Response



*** BNP Abfall**

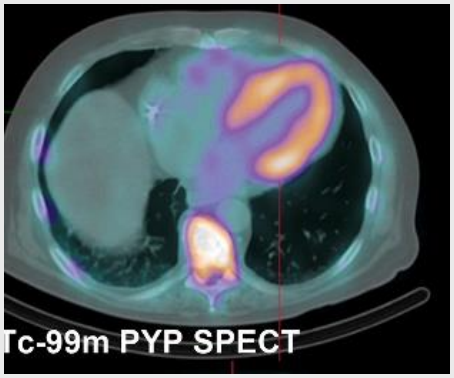
Diagnosealgorythmus bei kardialen Amyloidosen

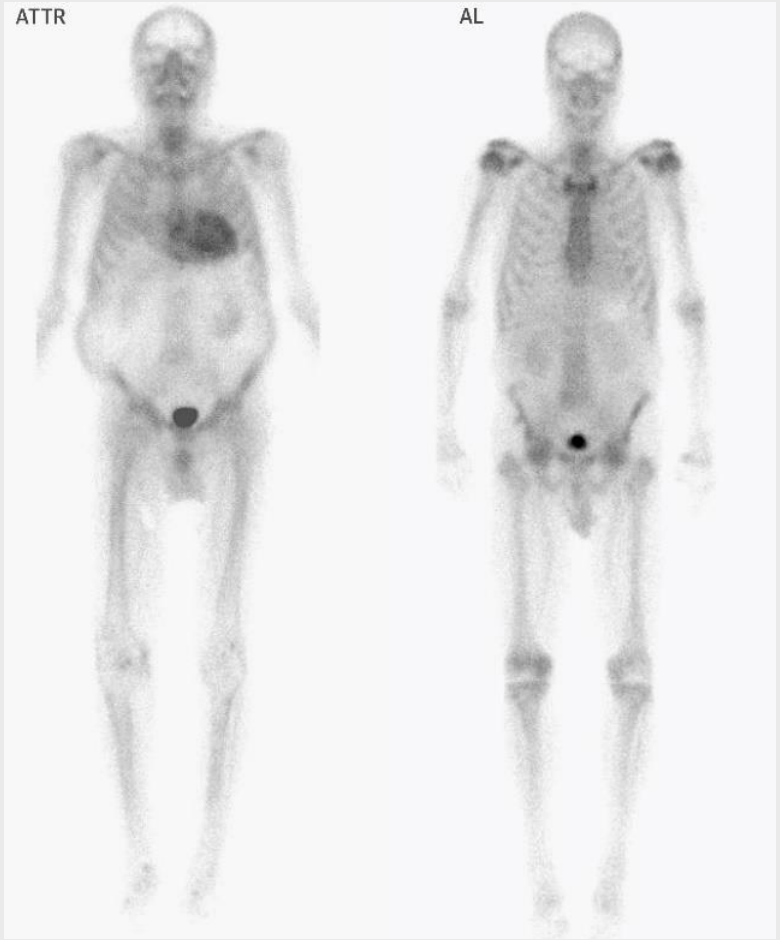
Falk et al JACC 2016 und Donnelly JP et al Cleve Clin J Med 2017

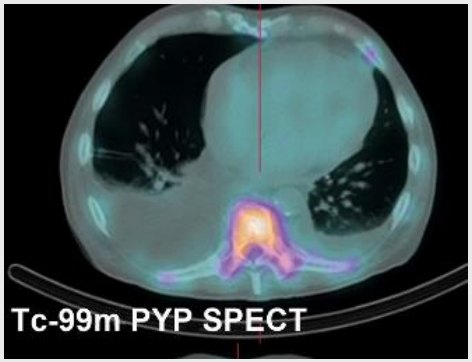


TcDPD Sintigraphie

Donnelly JP et al Cleve Clin J Med 2017







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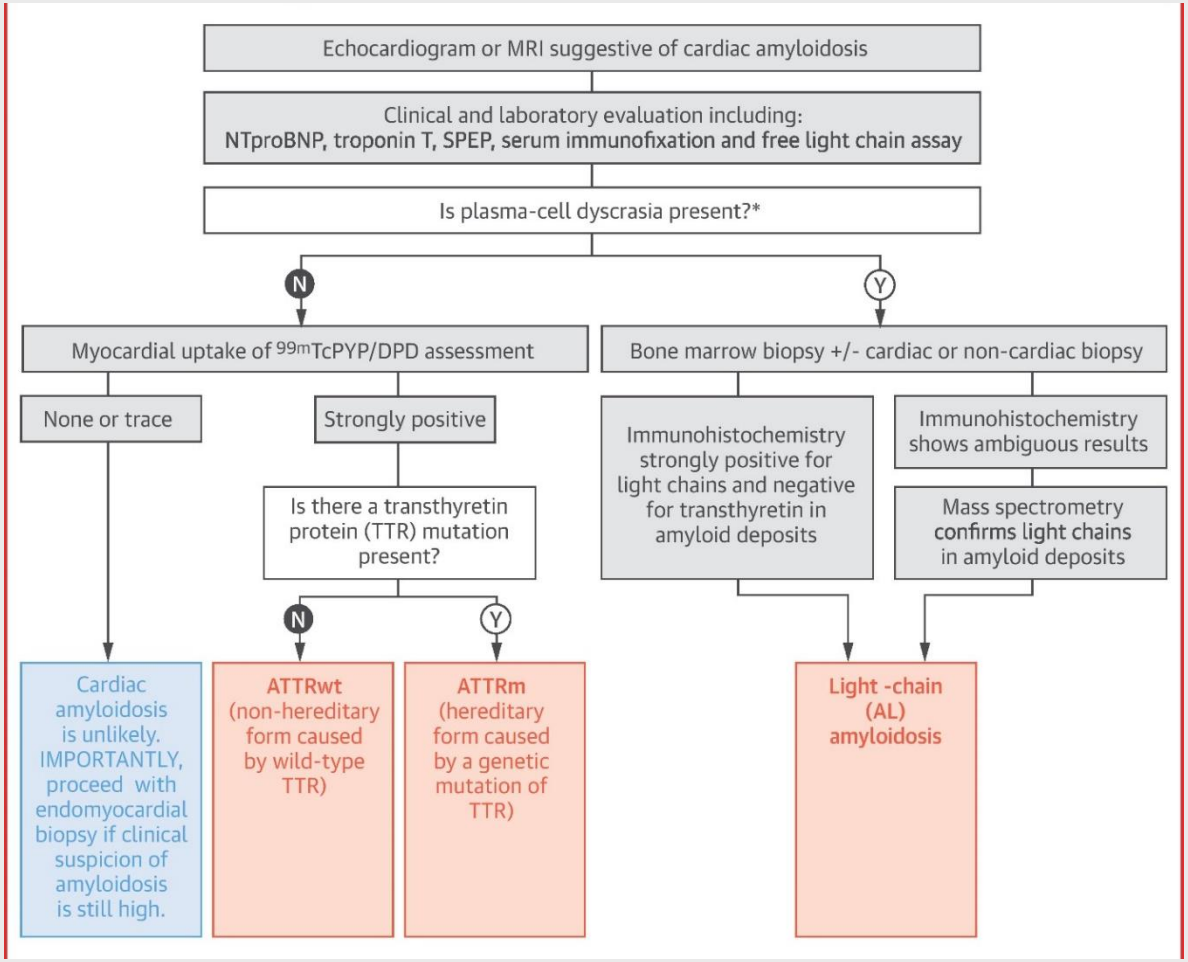

Therapieoptionen bei kardialen Amyloidosen

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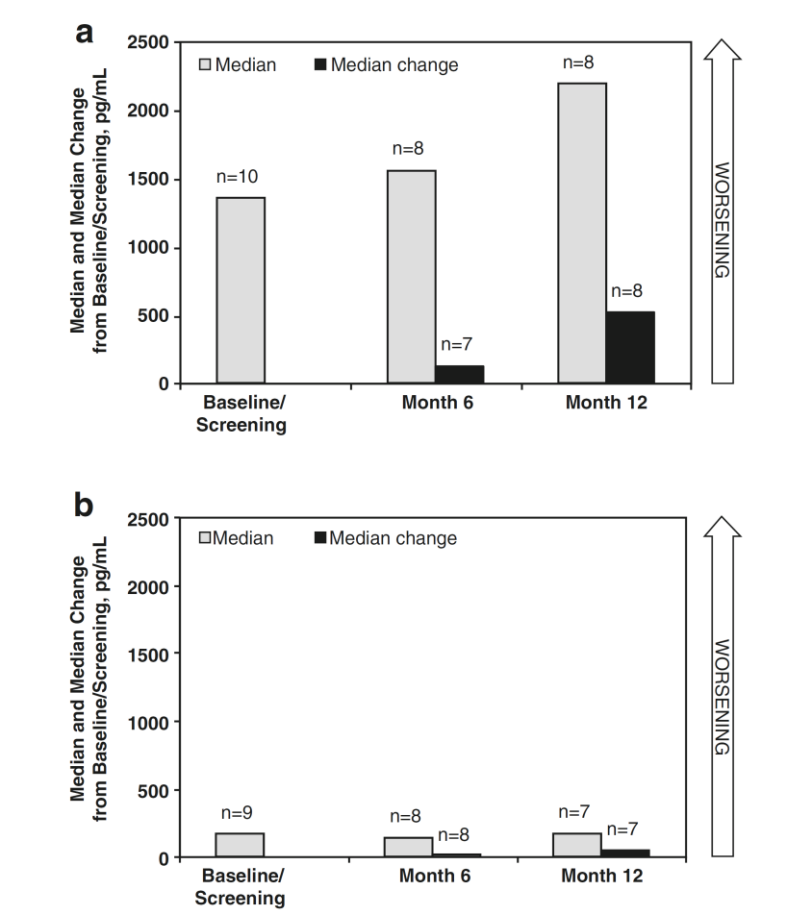
TABLE 2
Amyloid-specific pharmacotherapies

<table>
<tr><th colspan="3">AL</th><th colspan="3">ATTR</th></tr>
<tr><td rowspan="5">Anti-plasma cell therapies</td><td rowspan="2">Alkylating agents</td><td>Melphalan</td><td rowspan="2">TTR silencers</td><td>siRNA</td><td>Patisiran</td></tr>
<tr><td>Cyclophosphamide</td><td>ASO</td><td>Inotersen (IONIS-TTR$_{Rx}$)</td></tr>
<tr><td rowspan="2">Proteasome inhibitors</td><td>Bortezomib</td><td rowspan="4">TTR stabilizers</td><td colspan="2">Diflunisal</td></tr>
<tr><td>Ixazomib</td><td colspan="2">Tafamidis</td></tr>
<tr><td>Immunomodulators</td><td>Pomalidomide</td><td colspan="2">Tolcapone</td></tr>
<tr><td>Anti-CD38 monoclonal antibody</td><td>Daratumumab</td><td colspan="2">AG10</td></tr>
<tr><td rowspan="4">Anti-amyloid antibody</td><td colspan="2" rowspan="4">NEOD001</td><td rowspan="4">Fibril disruptors</td><td colspan="2">Doxycycline + TUDCA</td></tr>
<tr><td colspan="2">Green tea extract</td></tr>
<tr><td colspan="2">Curcumin</td></tr>
<tr><td>Anti-amyloid antibody</td><td>PRX004</td></tr>
<tr><td colspan="6">Ubiquitous Anti-Amyloid Fibril Antibody</td></tr>
<tr><td colspan="6">Monoclonal IgG1 anti-SAP antibody</td></tr>
</table>

AL = immunoglobulin (Ig) light chain amyloidosis; ASO = antisense oligonucleotide; ATTR = transthyretin amyloidosis; SAP = serum amyloid P component; siRNA = small interfering RNA; TTR = transthyretin protein; TUDCA = tauroursodeoxycholic acid

Reduktion der LVH und der BNP-Spiegel unter Tafamides

Merlini et al. J Cardiovasc Transl Res 2013

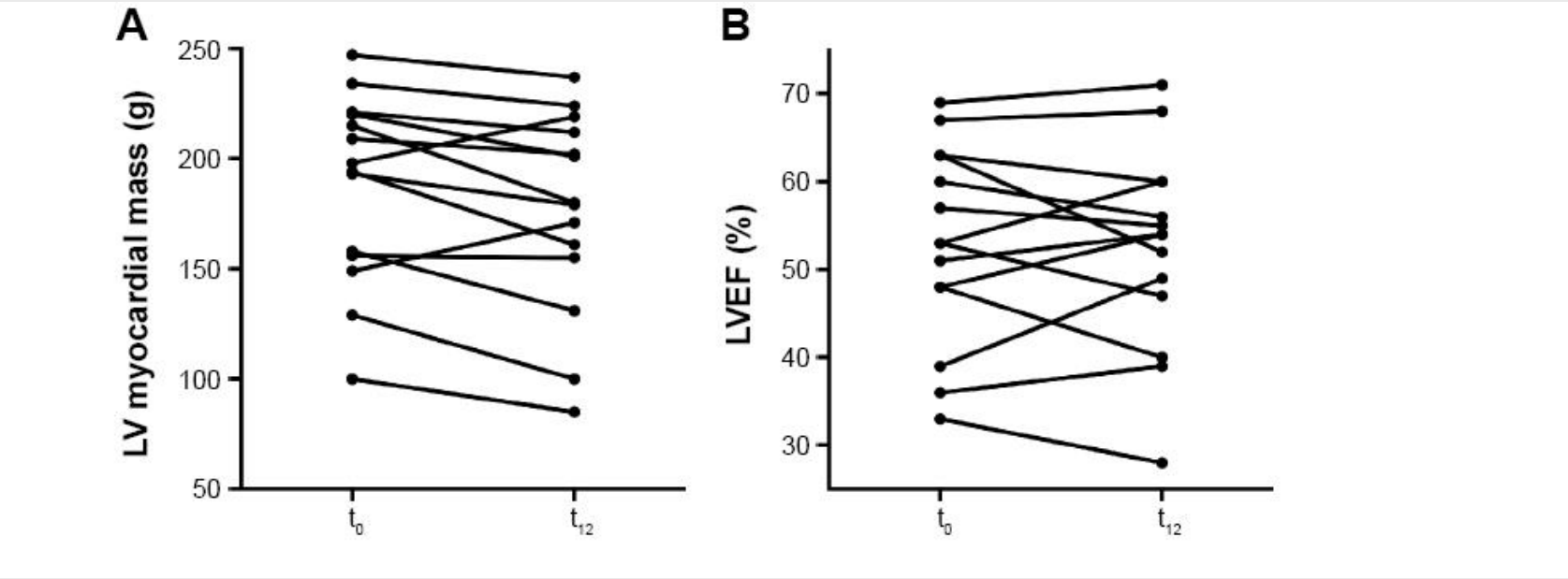


Grüner Tee Extrakt bei WT-Amyloidose

Siepen F et al, Drug Design 2015; 9: 6319-6325

cMRI findings

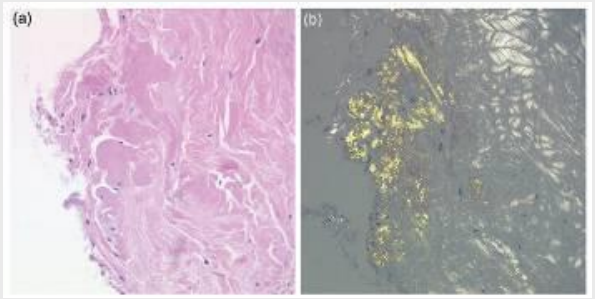
Stabilisierung



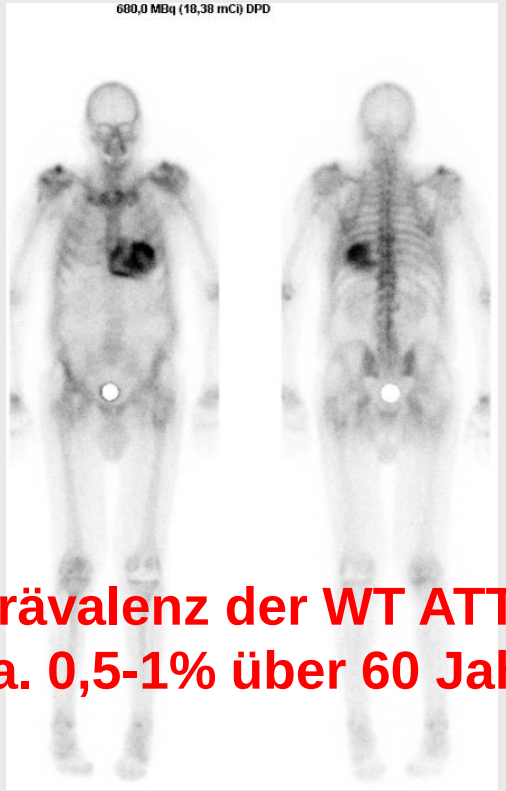
Frühdiagnose durch ...

… Neurologen (Neurochirurgen)

Karpaltunnel-syndrom



… Nuklearmediziner

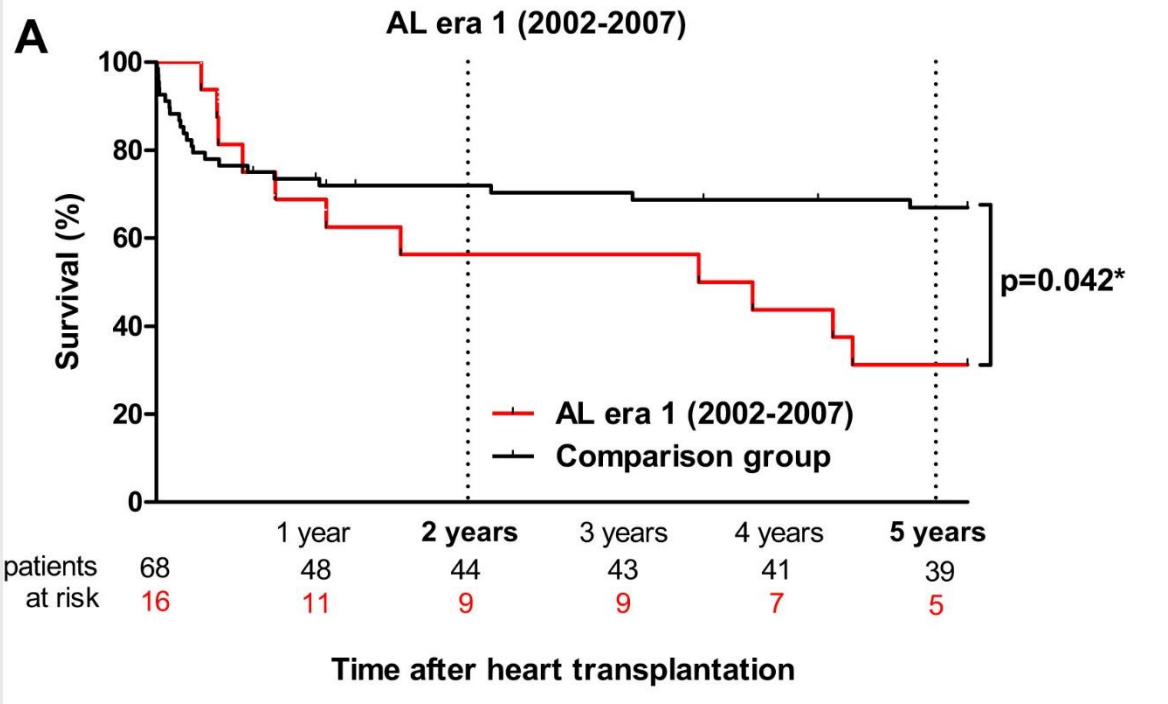


Prävalenz der WT ATTR: ca. 0,5-1% über 60 Jahre

AL Amyloidose und Herztransplantation

Kristen et al J Lung Heart Transplant 2017

Deutlich verschlechterter Transplantationserfolg 2002-2007
AL* vs non-Amyloidose



DANGER Kriterien für den Ausschluss einer Transplantation einer kardialen Amyloidose

Gilstrap et al J Lung Heart Transplant 2014

1. **Diarrhea** (**D**; weight loss, malabsorption),

2. Signs of **autonomic (A) nervous system** involvement (decreased heart rate variability, syncopes, polyneuropathy),

3. Impaired **nutritional (N)** status (assessed by serum protein, body mass index),

4. **Gastrointestinal (G)** tract involvement (history of gastrointestinal bleeding, gut biopsy),

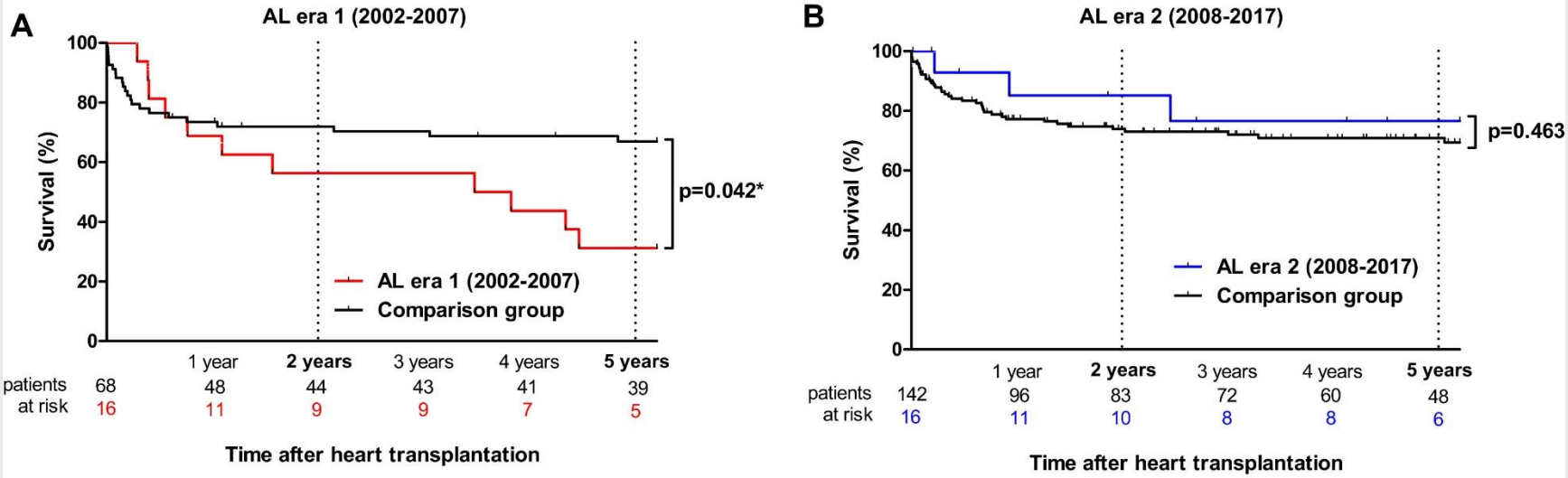
5. **Impaired elimination (E**; renal function; nephrotic syndrome, increased creatinine),

6. **Respiratory (R)** tract involvement (spirometry, diffusion capacity, computed tomography)

AL Amyloidose und Herztransplantation

Kristen et al J Lung Heart Transplant 2017

Dekadenvergleich: Transplantationserfolg AL* vs non-Amyloidose

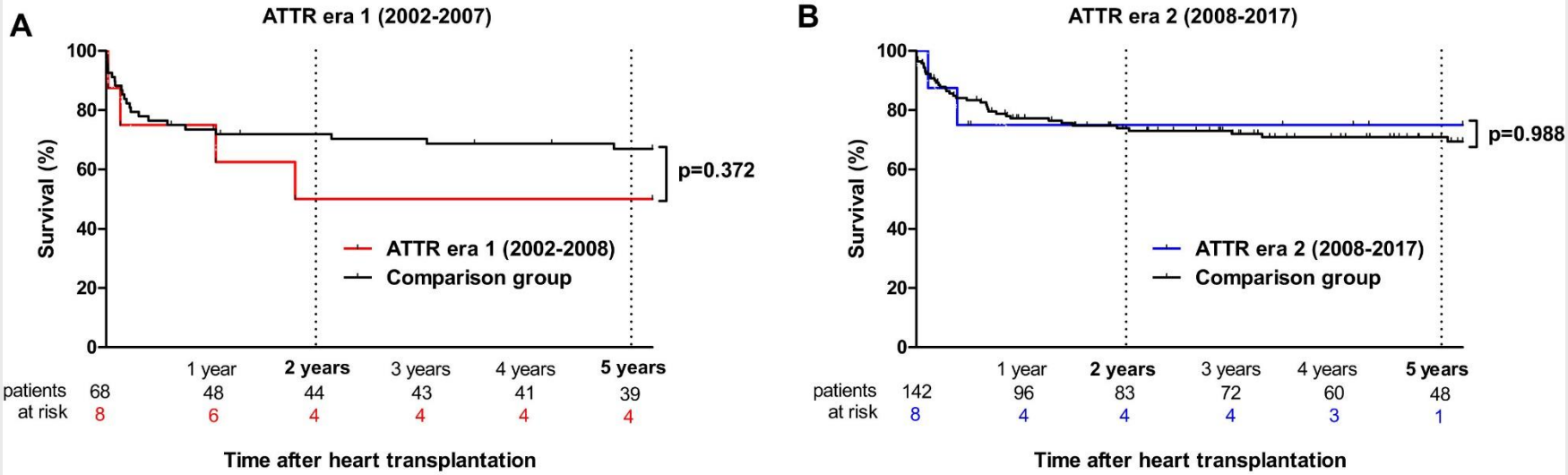


*** Ohne bedeutsamen systemischen Befall**

ATTR Amyloidose und Herztransplantation

Kristen et al J Lung Heart Transplant 2017

Dekadenvergleich: Transplantationserfolg ATTR* vs non-Amyloidose



*** Ohne bedeutsamen systemischen Befall**

Fazit für die Praxis

- 30% der LVH oder HFpEF Pat haben eine Amyloidose
- Früherkennung ist entscheidend (AL vs ATTR) – DD: HFpEF
- Low Volatage EKG, apikaler Strain, BNP, GFR - > Score
- Szinitigraphie (bei ATTRs positive , auch wenn asymptomatisch
- Med.- Therapie zur Zeit nur zugelassen bei neurologischer Beteiligung
- Herztransplantation heute mit besseren Daten

Diskussion
Kardiale Amyloidose