

# **ATTRwt Amyloidosis**

Mat Maurer, MD

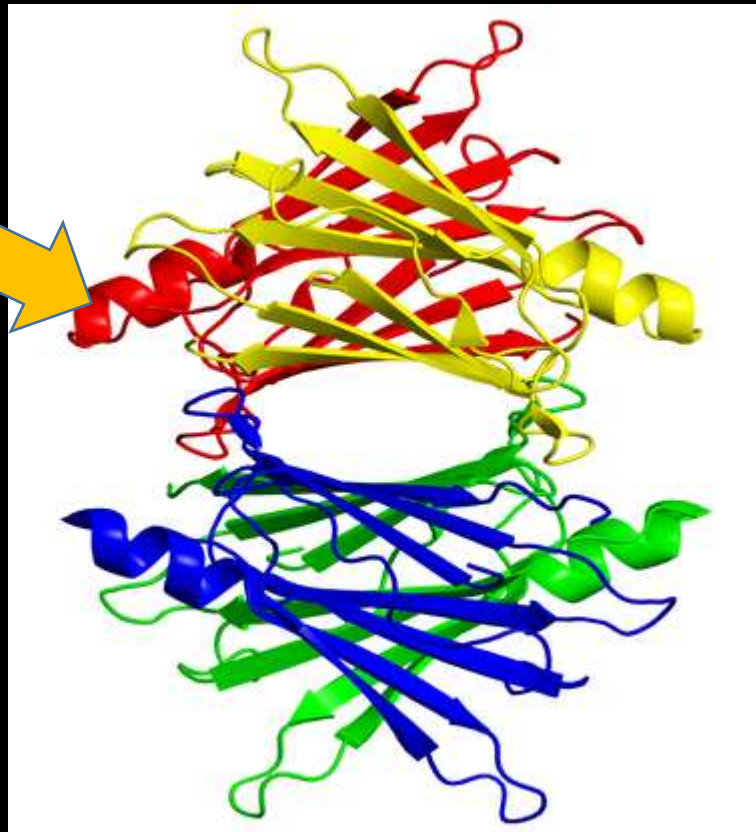
Columbia University Medical Center

New York Presbyterian Hospital

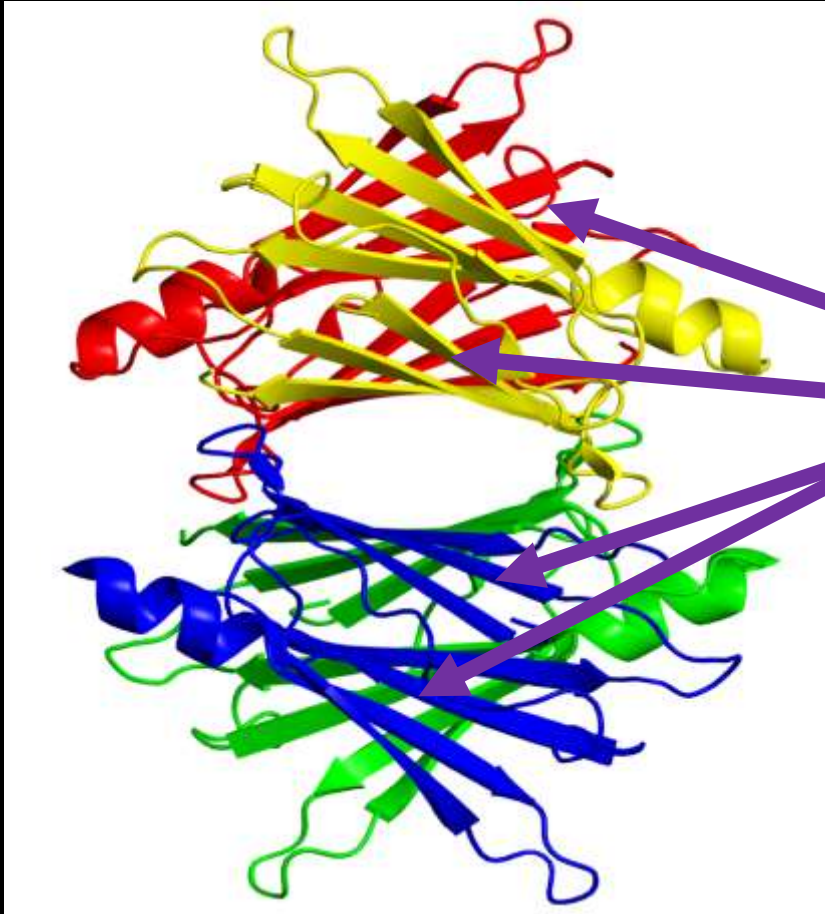
# This is the little bugger that causes the problem

- A protein made of 4 identical subunits
- Has two names
  1. Prealbumin
  2. Transthyretin

The latter because it transports (trans), thyroid hormone (thy) and retinol (retin), which is Vitamin A.

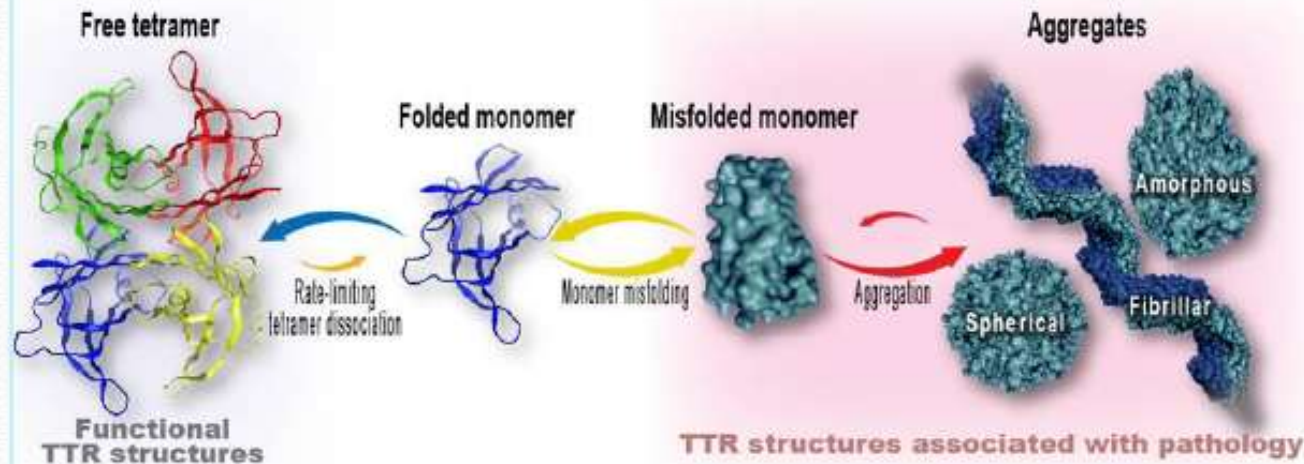


# Transthyretin (aka Prealbumin)



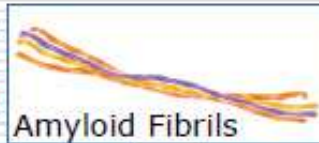
A protein with a lot  
of beta pleated sheets

# How does one get TTR amyloidosis?



Sensorimotor Polyneuropathy

*Deposition in Peripheral Nerves*



*Deposition in Cardiac Tissues*

Restrictive Cardiomyopathy

TTR Amyloid Polyneuropathy (ATTR-PN)

TTR Amyloid Cardiomyopathy (ATTR-CM)

Onset

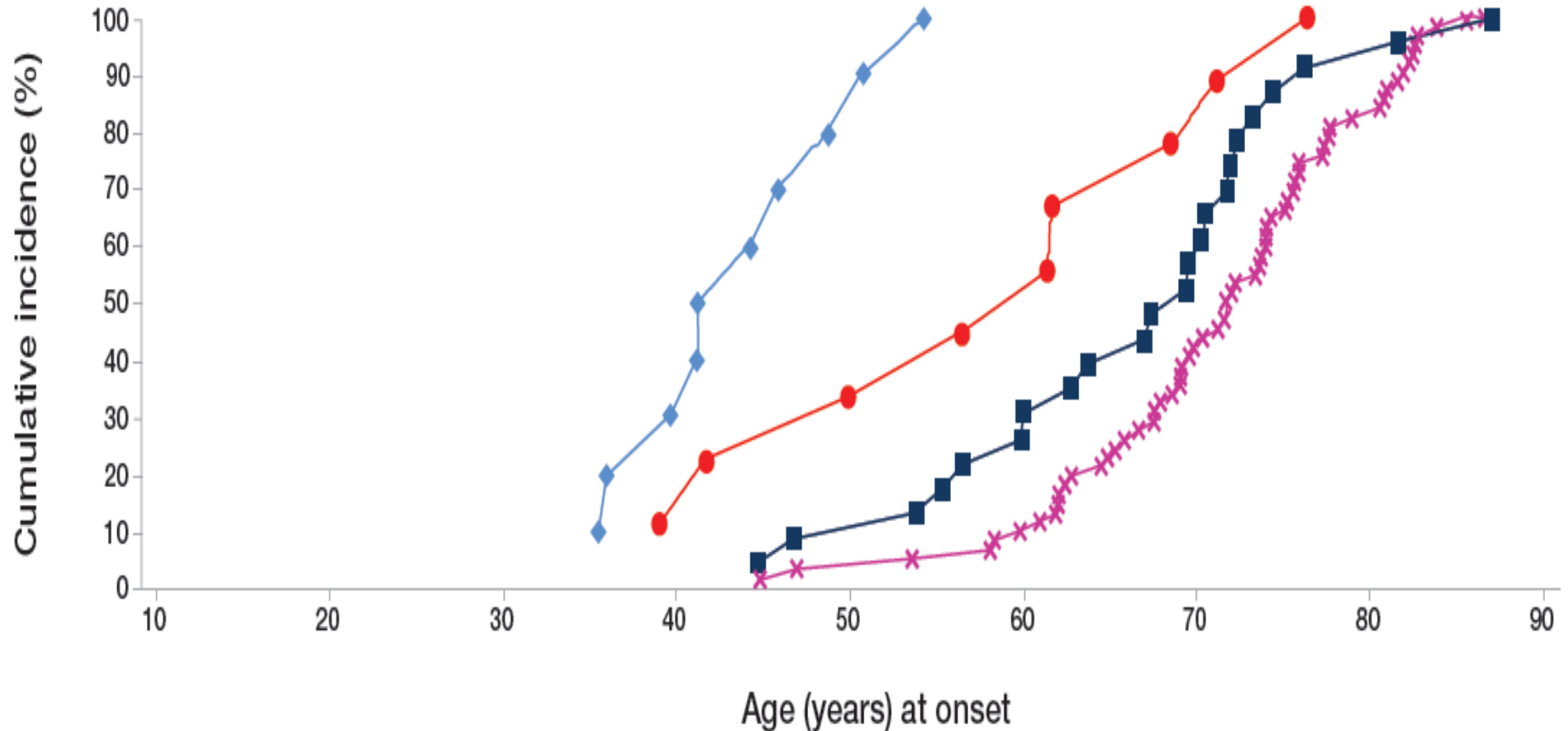
30-40s

60-70s

# Other names for Wild Type TTR Amyloidosis (note I am not responsible for them!)

- Senile Cardiac Amyloidosis (SCA)
  - Because patients are older not cognitively impaired
- Senile Systemic Amyloidosis (SSA)
  - Because while it affects mainly the heart other organs can have amyloid deposits
- Age Related Cardiac Amyloidosis

# Age Dependent Penetrance: A fancy term for, when does it show up?



N=62 for ATTRwt gene  
N=23 for Val122Ile mutation  
N=9 for Thr60Ala mutation  
N=10 for Leu111Met mutation

grpnum

***	ATTRwt gene	◆◆◆	Leu111Met mutation
●●●	Thr60Ala mutation	■■	Val122Ile mutation

# Production of Proteins



# Protein Folding: A Shout Out to Mother Nature

- Proteins - most abundant molecules in biology other than water.
- Must be converted into tightly folded compact structures in order to function.
- Single simple protein has  $10^{16}$  possible starting configurations
- Folding is usually extremely efficient - a remarkable testament to the power of mother nature (biology).



# Protein Misfolding



# Tissue Tropism

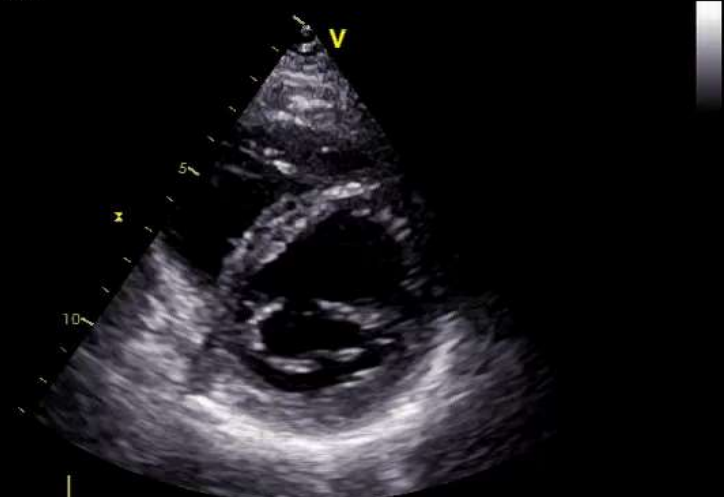
- Why does transthyretin like the heart?
- Or the ligaments?
- What factors affect the clinical manifestations and progression of the condition?



# How does ATTRwt affect the heart?

## Normal

05/02/2017 11:58:36 AM



PSAX MV

72  
153/252 HR



Apical 4CH LV optimization

71  
189/235 HR

## Amyloidosis

M1: 1.5  
53  
19 JUNE 07  
11:04:57  
2/0/C/H5  
PHILIPS MEDICAL  
SYSTEMS  
NYP-COL ECHO

03445.00  
GAIN 65  
COMP 54  
69BPM

18CM  
48HZ

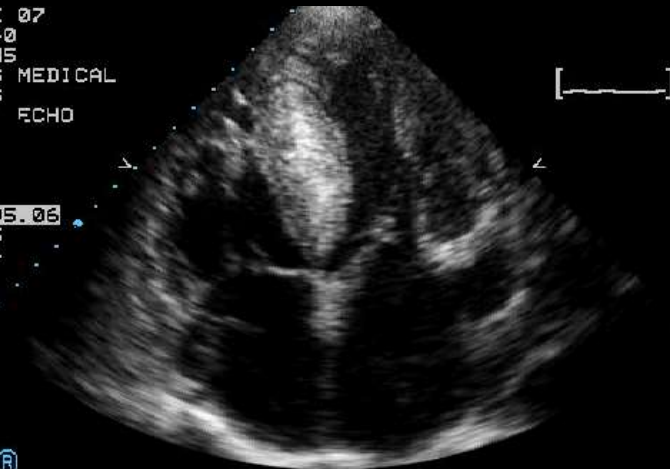
T  
P 1.5 3.2

M  
S  
19 JUNE 07  
11:06:40  
2/0/C/H5  
PHILIPS MEDICAL  
SYSTEMS  
NYP-COL ECHO

03495.06  
GAIN 65  
COMP 54  
68BPM

18CM  
48HZ

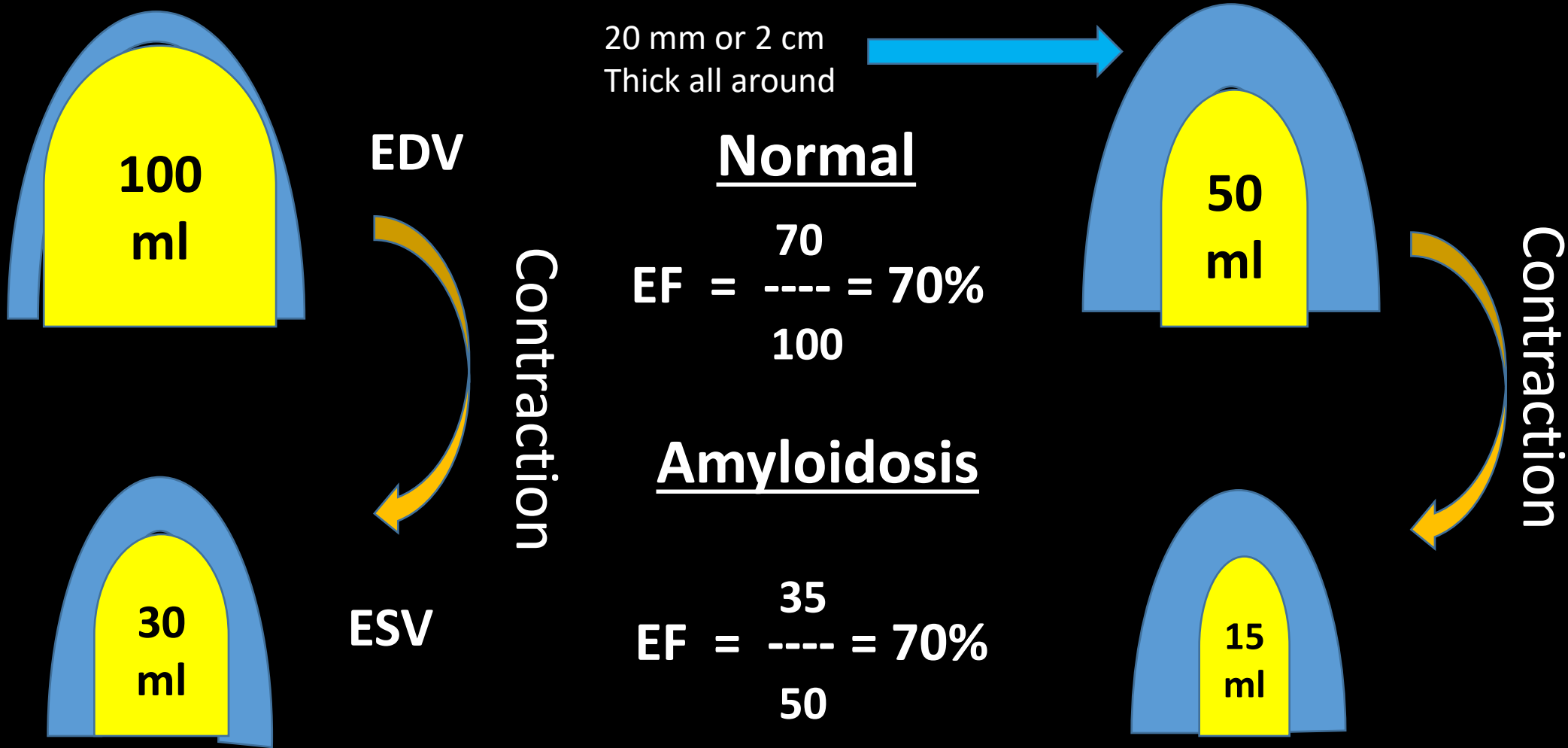
T  
P 1.5 3.2



# ATTRm and ATTRwt

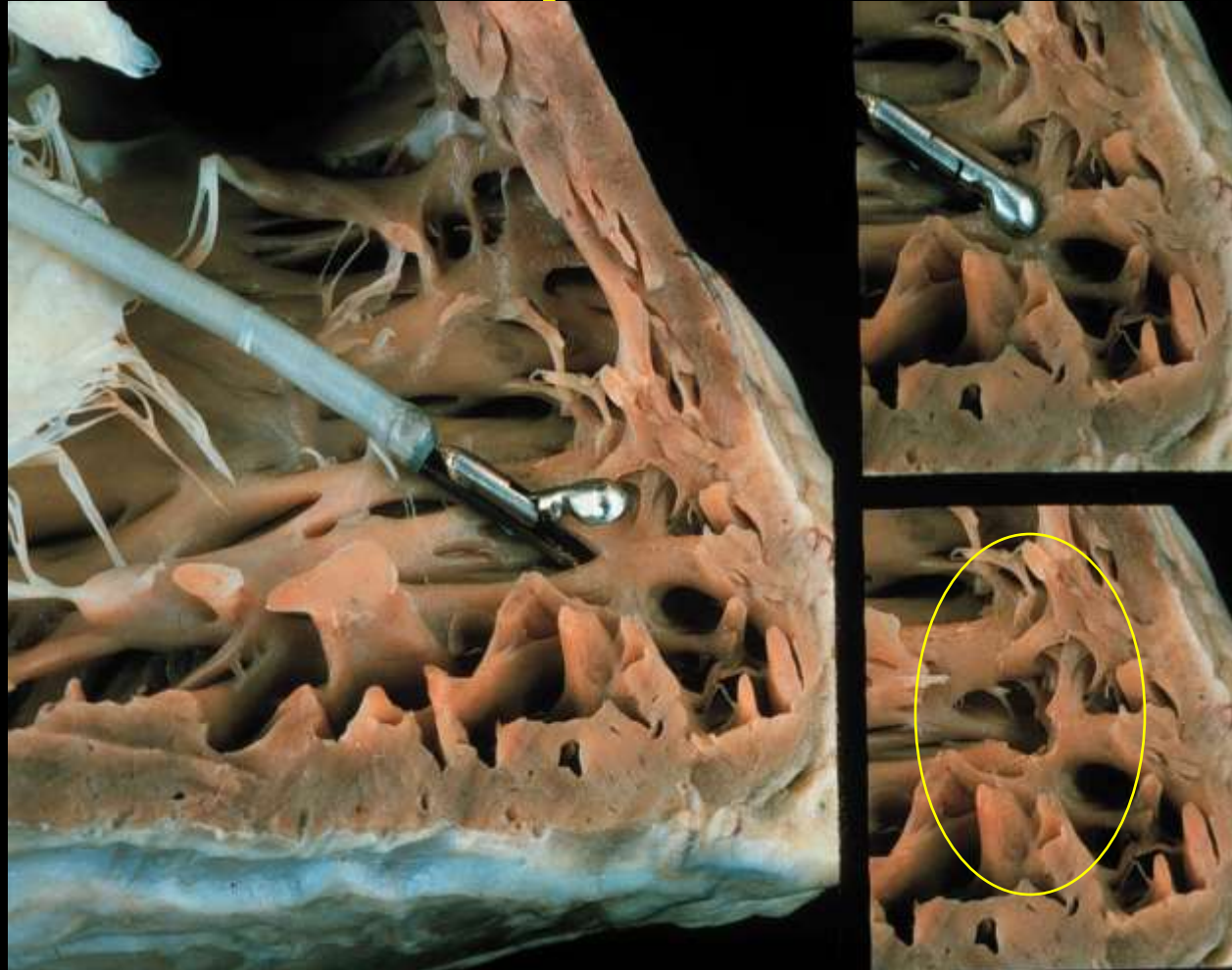
	<b>ATTRm</b>	<b>ATTRwt</b>
<b>Age (years)</b>	Variable (depends on mutation)	>65
<b>Gender (%M/%F)</b>	50%/50%	95%/5%
<b>Race</b>	Depend on mutation	Predominately Caucasians (To date)
<b>Affected Organs</b>	Nerves Heart Eyes	Heart

# Why Ejection Fraction (EF) Sucks in Cardiac Amyloidosis

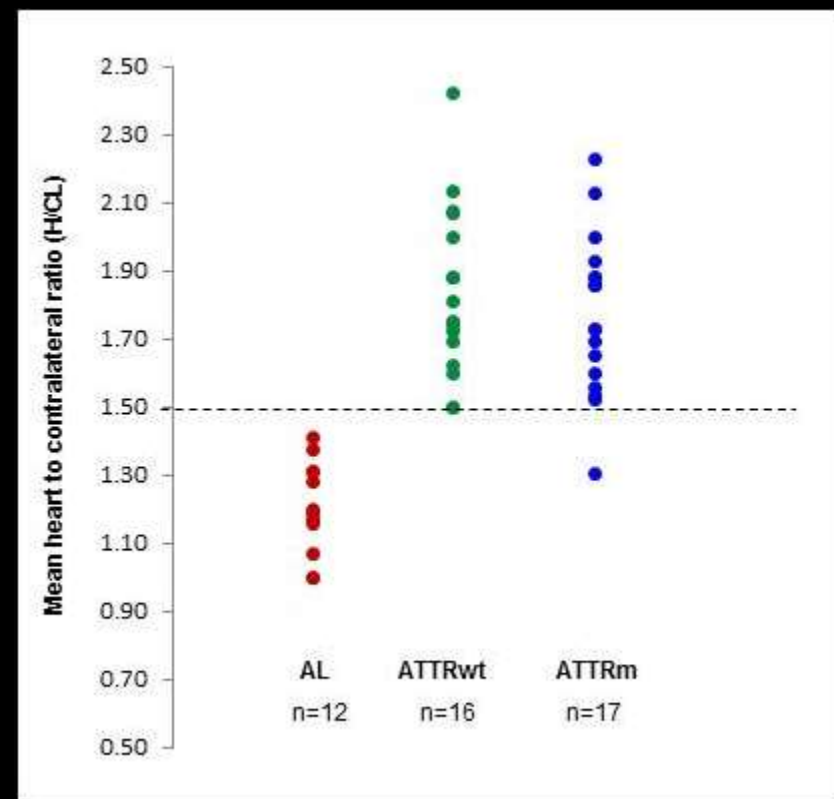
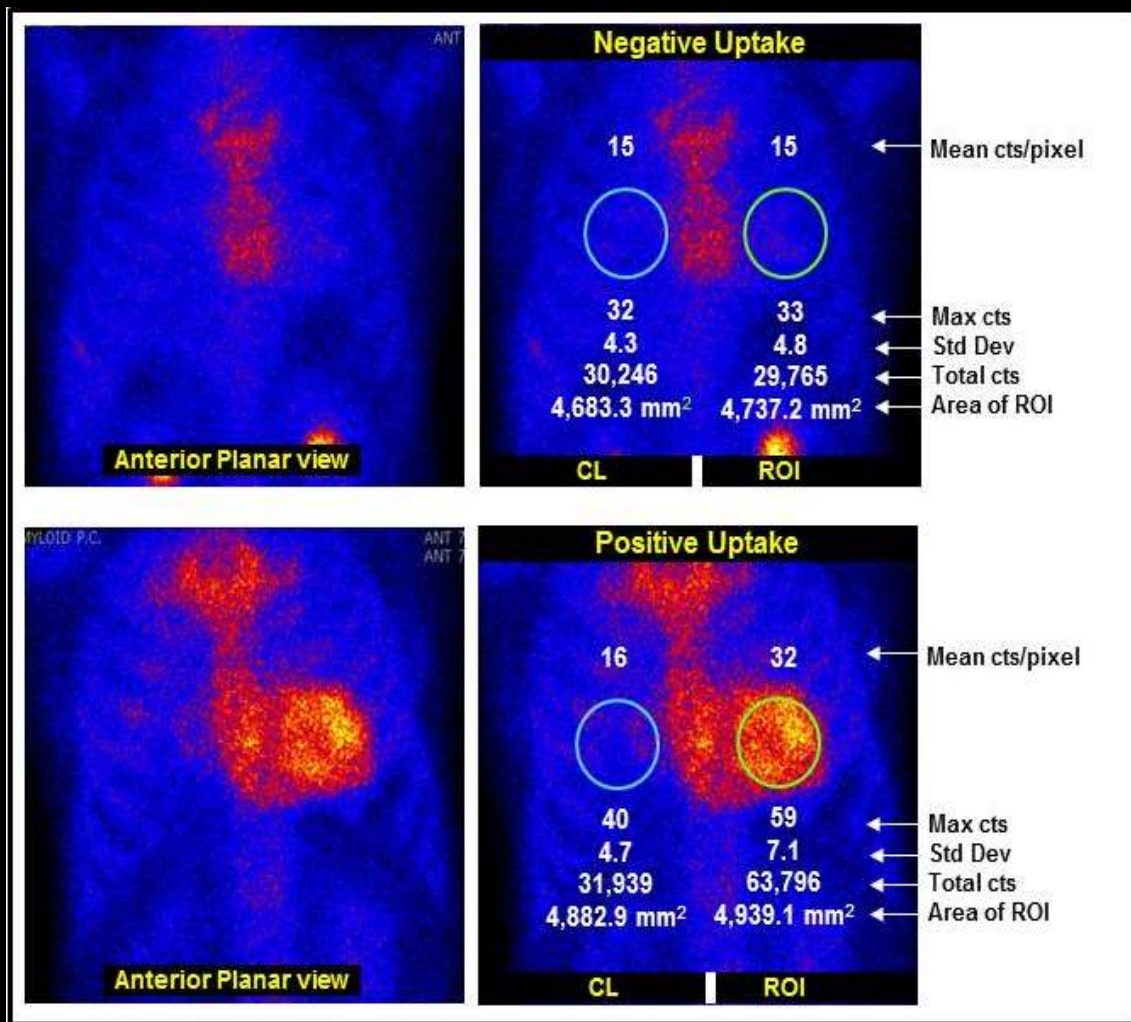


# Endomyocardial Biopsy

The previous way to diagnose TTR cardiac amyloidosis



# PYP Scan for Diagnosing TTR cardiac amyloidosis



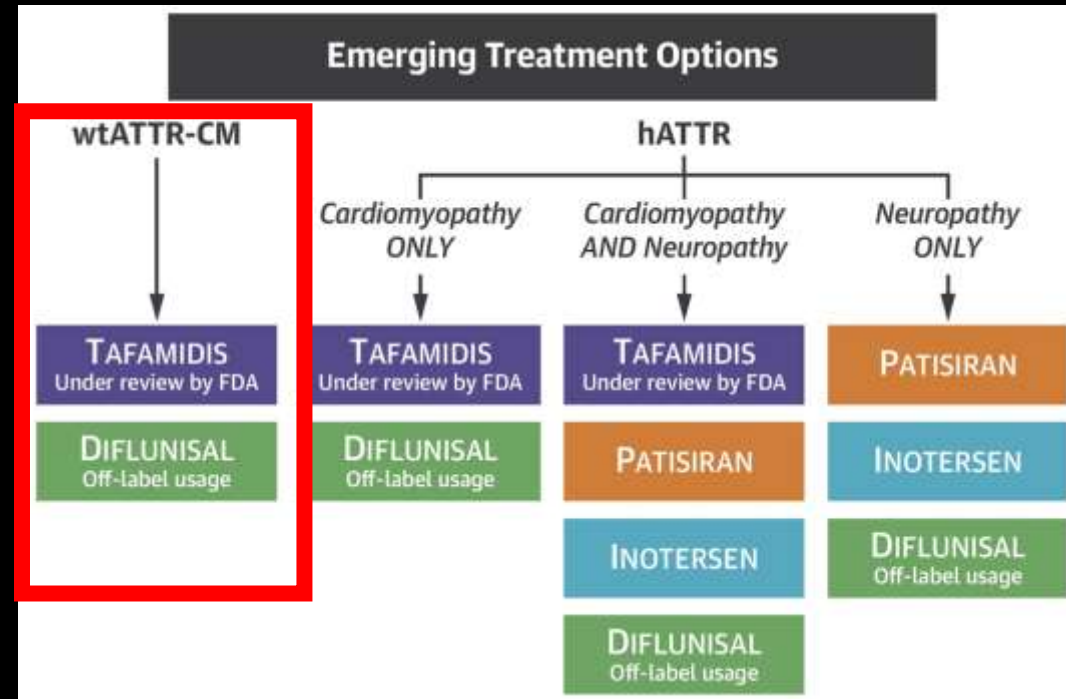
# General Treatment for Amyloid Cardiomyopathy

- Diuretics and Salt Restriction – Mainstay of therapy
  - Aldosterone Antagonists and Bioavailable Loop Diuretics
- Atrial Fibrillation – Nearly Universal Over Time
  - Prevalence - At least 1/3 in large series and 53% in the ATTR-ACT study
  - Incidence- ~90% develop AF over time
  - Anticoagulation in atrial fibrillation irrespective of CHADs-Vasc Score
- Calcium channel blockers – some contraindicated
- Hypotension – compression stockings and midodrine.
- AICD / pacemaker - More of a role for pacing



# ATTRwt Cardiomyopathy Clinically Available Options

- Tafamidis -
  - Approved
  - Cost could limit access
- Diflunisal
  - Off label use
  - NSAID – use cautiously
    - No recent decompensation
    - Good renal function
    - Daily diuretic dose < 80 mg Lasix, no metolozone
    - ? Use with anticoagulation



# **Trials Currently or Soon to be at an Amyloid Center Near You for ATTRwt**

<b>Drug</b>	<b>Mechanism /Delivery</b>	<b>Trial Name</b>	<b>Trial Design</b>
AG10 (Eidos)	Stabilizer Oral	ATTRIBUTE-CM	Placebo controlled, RCT: 2:1 allocation
Patisiran (Alnylam)	Silencer Intravenous	APOLLO-B	Placebo controlled, RCT; 1:1 allocation
ION-682884 (Ionis/Akcea)	Silencer: SQ	IONIS LICA-CM	Placebo controlled, RCT; 1:1 allocation
Vutrisiran (Alnylam)	Silencer; SQ	HELIOS-B	Placebo controlled, RCT; 1:1 allocation