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Solid organ transplant: *when & which variants do best?* Trials – *when?*

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Patient Workshop
October 31, 2015

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

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Hereditary systemic amyloidoses

Fibril name	Mutated precursor Protein	Target Tissues
ATTR	Transthyretin	PNS, ANS, heart, eye, leptomeninges, tenosynovium
AFib	Fibrinogen α-chain	Kidney
ALys	Lysozyme	Kidney, primarily
AApoAI	Apolipoprotein A-I	Heart, liver, kidney, PNS, testis, larynx, skin
AApoAII	Apolipoprotein A-II	Kidney
AGel	Gelsolin	PNS, cornea
ACys	Cystatin C	PNS, skin
ABri	Abri-PP	CNS
Aβ2M	β2-microglobulin	Musculoskeletal system

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Strange truths about hereditary amyloidosis

- **For most types, the source of the ‘disease driving’ building blocks (mutant proteins) is the liver, although the liver otherwise works fine**
- **For most types, the disease driving organ (liver) isn’t doesn’t ‘appear’ sick**

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Transplant Approaches

1. **Remove mutant protein producer**
   - **Liver transplant**
2. **Replace symptomatic organ**
   - **Possible for kidney or heart**
   - **Not possible for nerve or guts**
3. **Do both**

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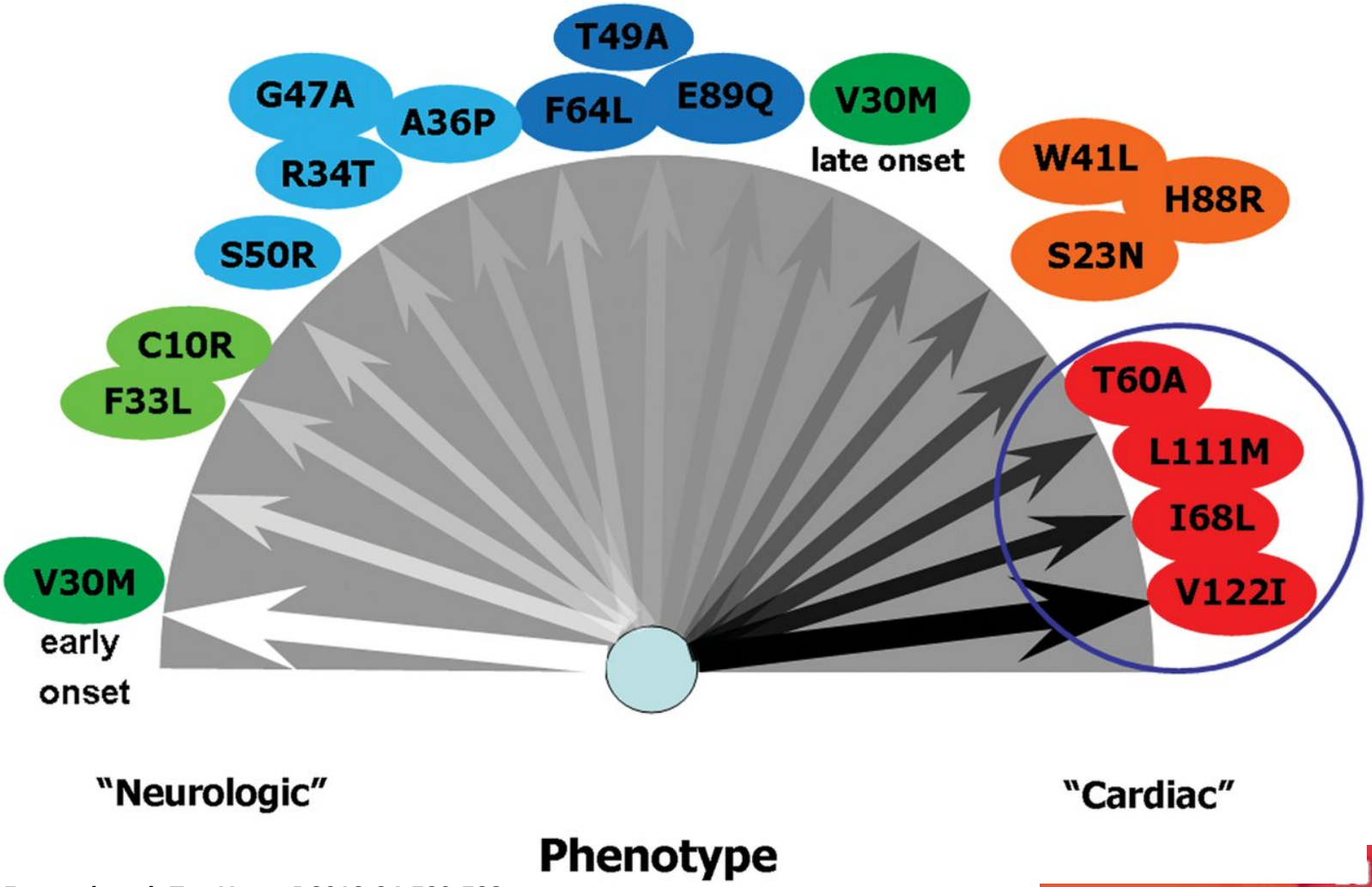
Spectrum of genotype–phenotype correlations in transthyretin-related amyloidosis.

112 mutations causing disease (2013)



Claudio Rapezzi et al. Eur Heart J 2013;34:520-528

European Heart Journal

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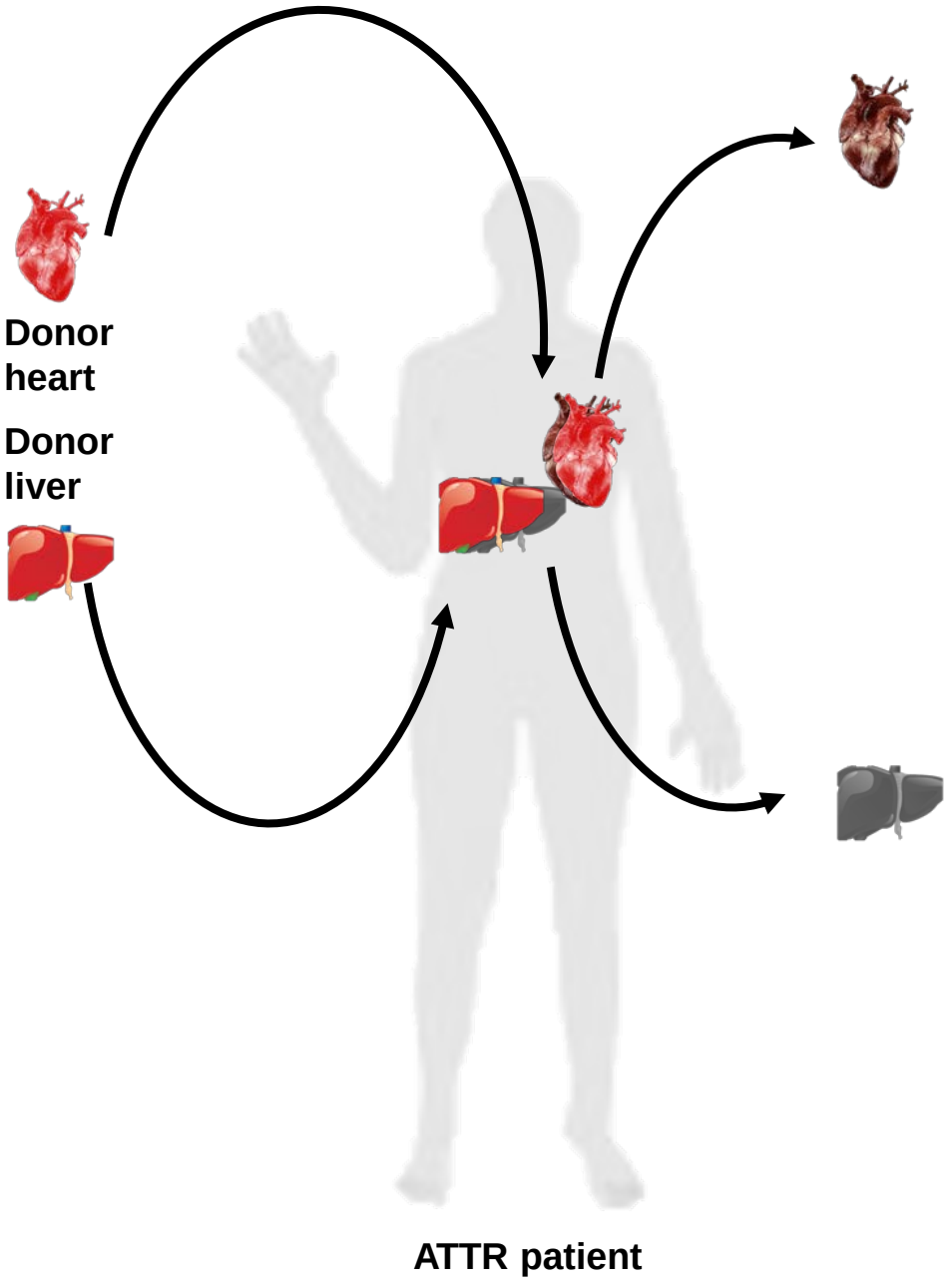
1. **Remove mutant protein producer (liver transplant)**

2. **Replace symptomatic organ kidney or heart)**

3. **Do 1 and 2?**



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ATTR Transplant Trivia

- First OLT for ATTR in 1990
- First domino liver transplant in 1995
- Partial liver transplants since 1995
- ATTR patients do not meet criteria for liver transplant since “normal” liver

Results from the Familial World Transplant Registry

Reporting centers and number of transplants performed (Dec 31, 2013)

COUNTRY	CITY	HOSPITAL	No of TX	No of TX/Country
Portugal	Lisbon	Hospital Curry Cabral	354	**948**
	Porto	Hospital Sto Antonio	327	
	Coimbra	Coimbra University Hospital	260	
	Porto	Hospital S João	7	
France	Villejuif	Hospital Paul Brousse/Kremlin Bicêtre	227	**267**
	Marseille	Hospital de la Conception	10	
	Strasbourg	Hospital Hautpierre	10	
	Lyon	Hospital Edouard Herriot	8	
	Clichy	Hospital Beaujon	7	
	Bordeaux	Pellegrin Hospital	5	
Sweden	Stockholm	Karolinska University Hospital Huddinge	130	**151**
	Gothenburg	Sahlgrenska University Hospital	21	
USA	Rochester	Mayo Clinic	47	**127**
	Burlington	Lahey Clinic Medical Center	21	
	Boston	NEDH/Harvard Medical School	14	
	San Francisco	UCSF Medical Center	11	
	Miami	Jackson Memorial	8	
	Phoenix	Mayo Clinic	6	
	Pittsburgh	Thomas E Starzl Transpl. Institute	4	
	Philadelphia	The Penn Transplant Center	3	
	Cleveland	Cleveland Clinic	2	
	Charleston	Medical University of South Carolina	2	
	Chicago	Northwestern Memorial Hospital	2	
	Chapel Hill	UNC Comprehensive Transplant Center	2	
	Baltimore	University of Maryland	2	
	Cleveland	University Hospitals of Cleveland	1	
	Denver	University Hospital	1	
	Durham	Duke University Medical Center	1	
Spain	Barcelona	Hospital de Bellvitge	35	**101**
	Murcia	Hospital Virgen de la Arrixaca	27	

- **Male 57%**
- **Age at transplant: 38.2 (range 21-73)**
- **Duration of disease: 3 years (0-30 years)**

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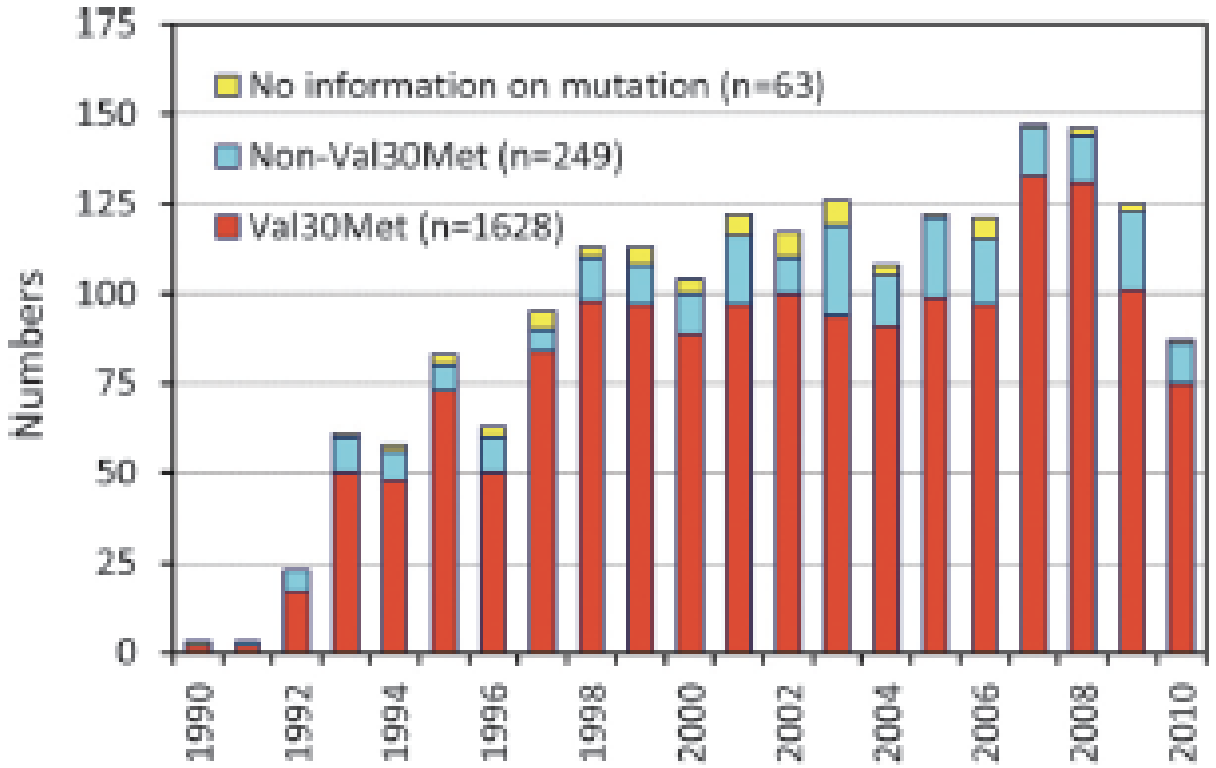
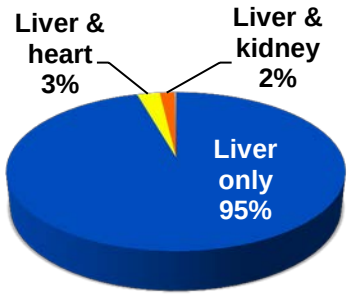
Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative?

1940 patients undergoing 2127 liver transplants





Ericzon, B.G., et al., Transplantation, 2015. 99(9): p. 1847-54.

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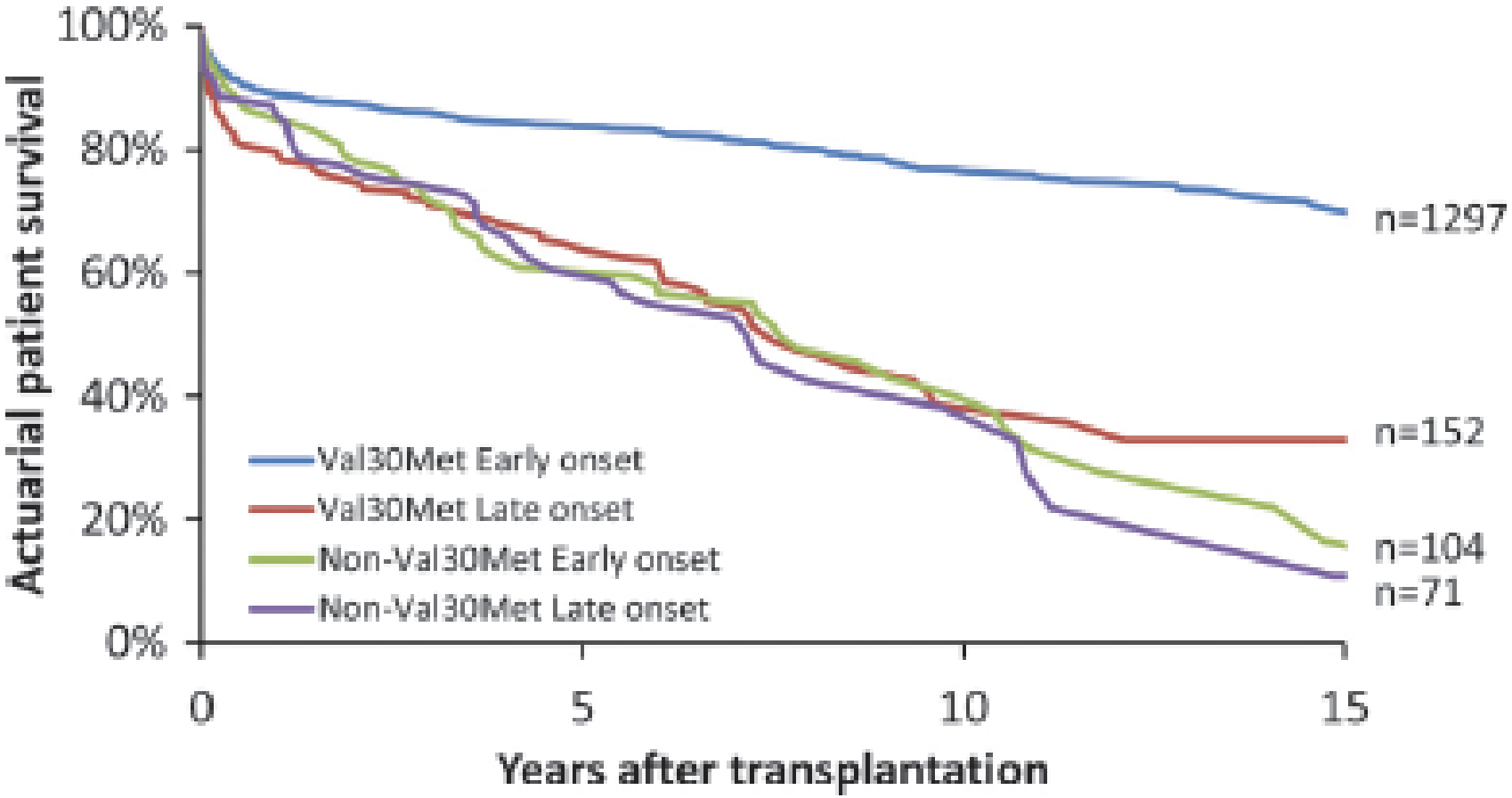
Survival post-OLT for Familial ATTR by mutation



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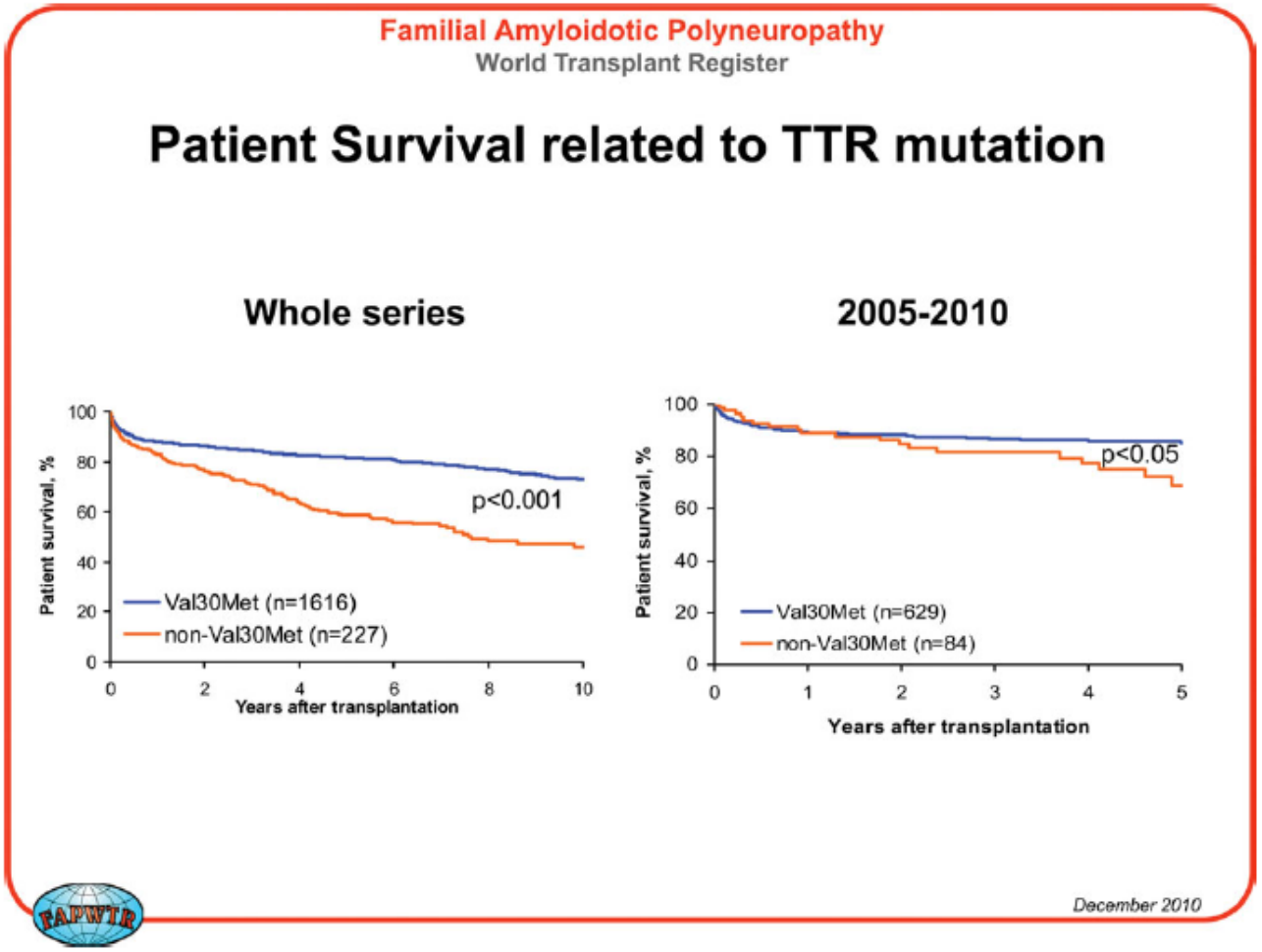

FIGURE 2. Patient survival after liver transplantation for TTR amyloidosis comparing data for Val30Met subjects with composite data for subjects with all other TTR mutations reported to the FAP World Transplant Registry. Used with permission.

Progression noted in heart, vitreous opacities, autonomic nervous system
Typially less cardiac deposition if heart transplant done same time

Benson, M.D. Muscle & nerve, 2013. 47(2): p. 157-62.

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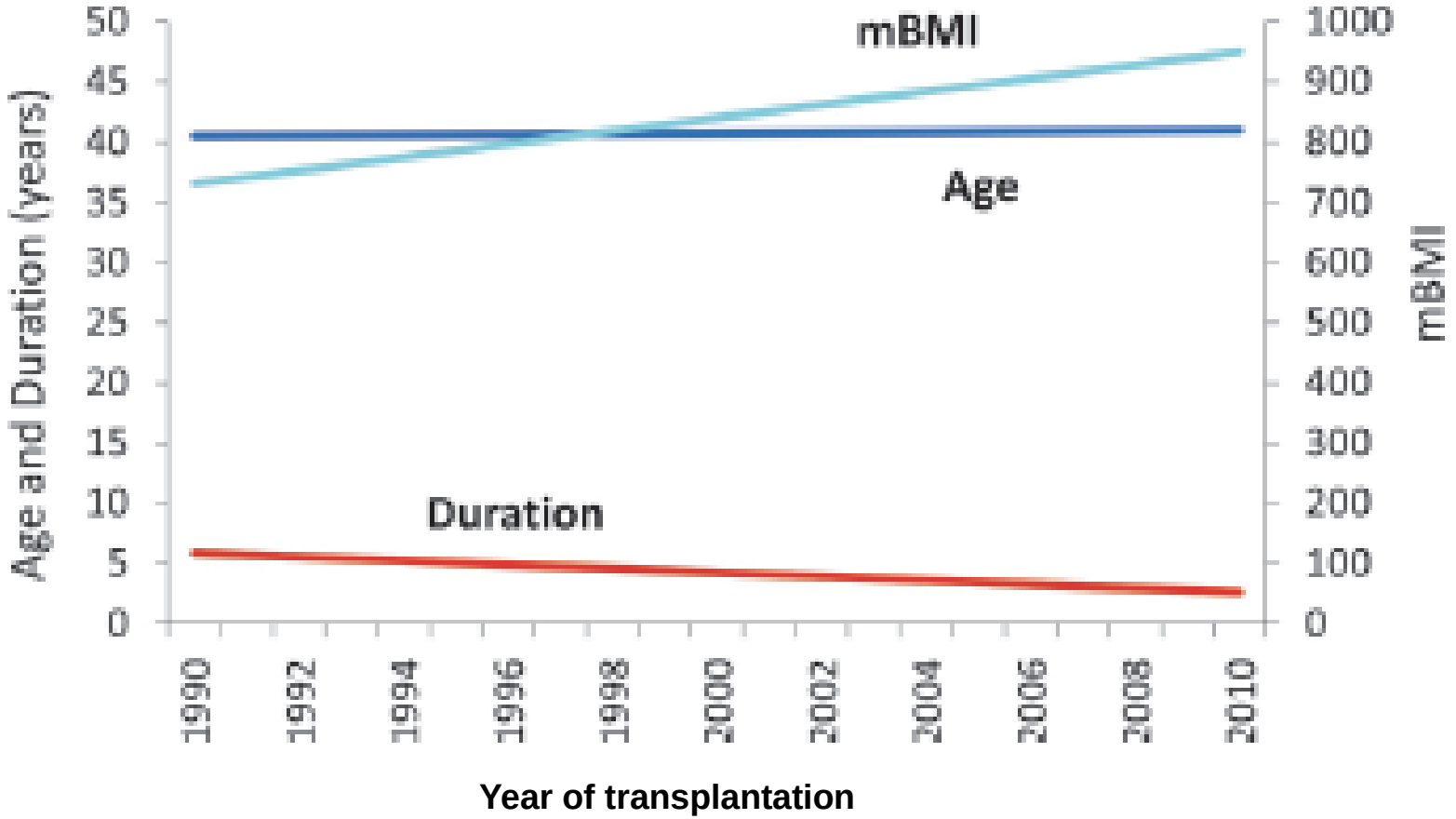
Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative?



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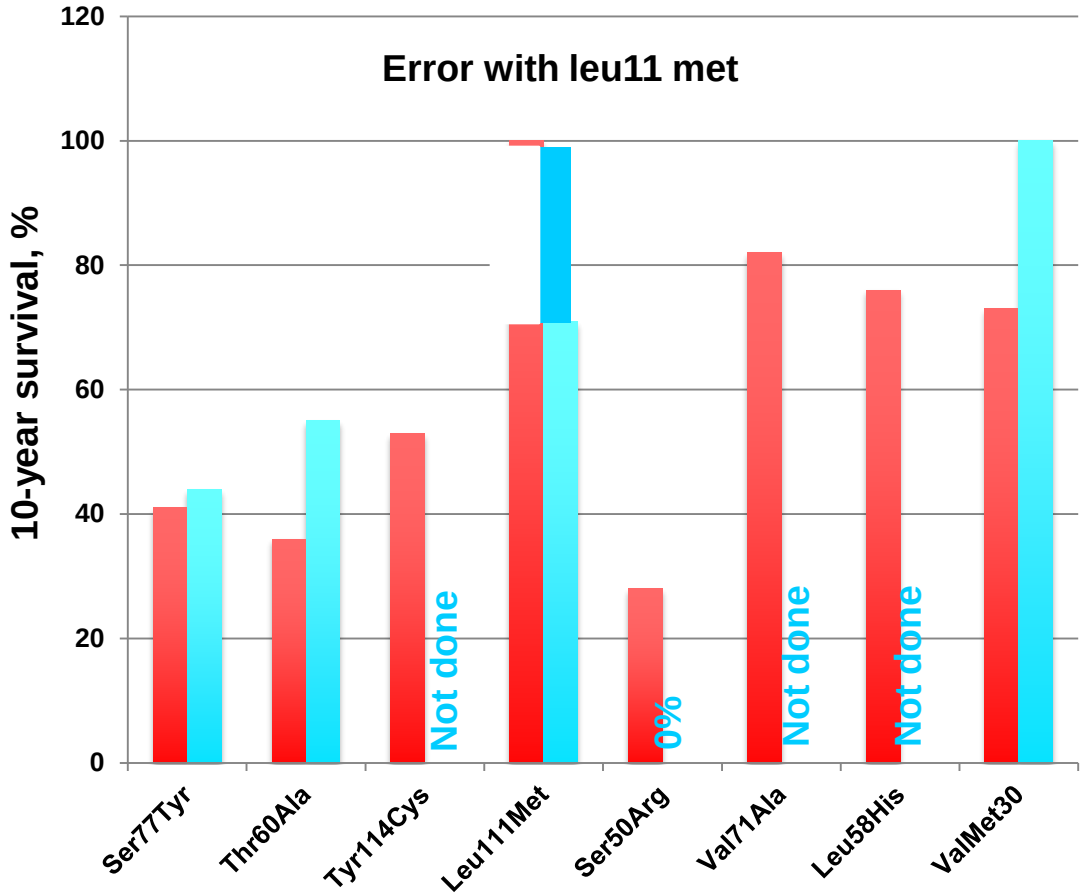
10-year Survival with Liver or Liver/Heart Transplants FAPWTR



Only part of story; QOL not accounted for in this graph

Ericzon, B.G., et al., Transplantation, 2015. 99(9): p. 1847-54.

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Heart Transplantation for Hereditary ATTR

- **Mayo series of 40 liver transplants including 21 who had heart and liver**
- **Trend for a superior 5-year overall survival among those receiving heart and liver transplant (85%) versus those receiving liver transplant only (52%), p=0.057**

Unpublished data

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V30M Outcomes

- Neuropathy stable or improved in up to 40%
- Nutrition improves in up to 80%
- Cardiac progresses in ~50%
- Kidney involvement unaffected
- Eye deposits progress

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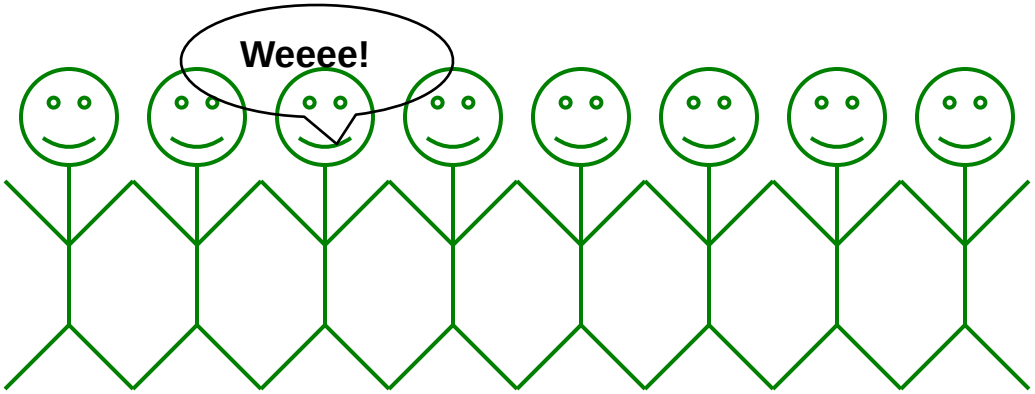
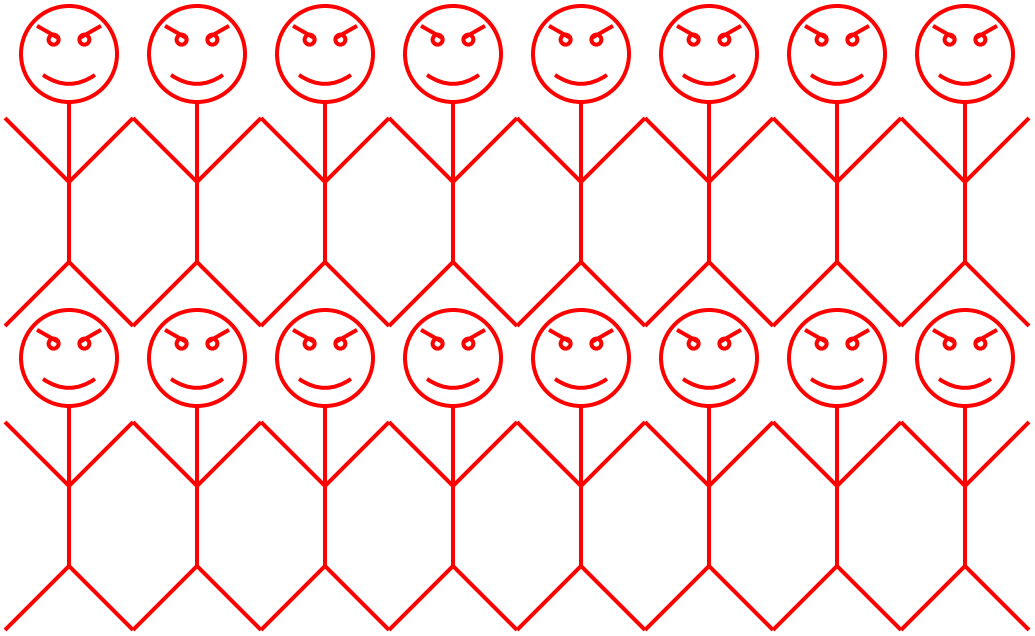


Normal ATTR
joining the party



Mutant ATTR fibrils
Made of mutant TTR

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FAPWTR Liver Transplantation Conclusions

- **OLT for familial amyloidotic polyneuropathy at 120/year worldwide**
- **Modified body mass index, disease duration, type of mutation, and degree of autonomic involvement are important risk factors**
- **Infection and cardiac causes account for approximately 45% of deaths**

Ericzon, B.G., et al., Transplantation, 2015. 99(9): p. 1847-54.

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What Does It All Mean?

- **Known:**
  - **Survival improved with liver transplant in V30M**
  - **Most effective if early**
  - **Major benefit is nutrition**
  - **Combined liver + heart and liver + kidney feasible**

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What Does It All Mean?

- **Unknown:**
  - **When is it futile?**
  - **Which mutations benefit?**
  - **If heart involved need combined heart + liver?**
  - **Is amyloid halted, slowed, reversed or accelerated?**

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Drug Trials for ATTR

NCT Number	Title
NCT01777243	A Study to Evaluate the Safety of GSK2398852 When Co-administered With GSK2315698 in Patients With Systemic Amyloidosis
NCT02510261	The Study of an Investigational Drug, Patisiran (ALN-TTR02), for the Treatment of Transthyretin (TTR)-Mediated Amyloidosis in Patients Who Have Already Been Treated With ALN-TTR02 (Patisiran)
NCT01960348	APOLLO: The Study of an Investigational Drug, Patisiran (ALN-TTR02), for the Treatment of Transthyretin (TTR)-Mediated Amyloidosis
NCT02175004	Open-Label Extension Assessing Long Term Safety and Efficacy of ISIS-TTR Rx in Familial Amyloid Polyneuropathy (FAP)
NCT01737398	Efficacy and Safety of ISIS-TTR Rx in Familial Amyloid Polyneuropathy
NCT00925002	Safety And Efficacy Evaluation Of Fx-1006A In Subjects With Transthyretin Amyloidosis
NCT02191826	Study of SOM0226 in Familial Amyloid Polyneuropathy

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AGel	Gelsolin	PNS, cornea
ACys	Cystatin C	PNS, skin
ABri	Abri-PP	CNS
Aβ2M	β2-microglobulin	Musculoskeletal system

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Fibrinogen A α

- Most common of hereditary renal amyloidoses (Ostertag 1932)
- First mutation described by Dr. Benson, 1993
- Middle age presentation
- If kidney replacement alone, graft fails in 1-7 years with 10-year graft survival of 5% (vs 65%)

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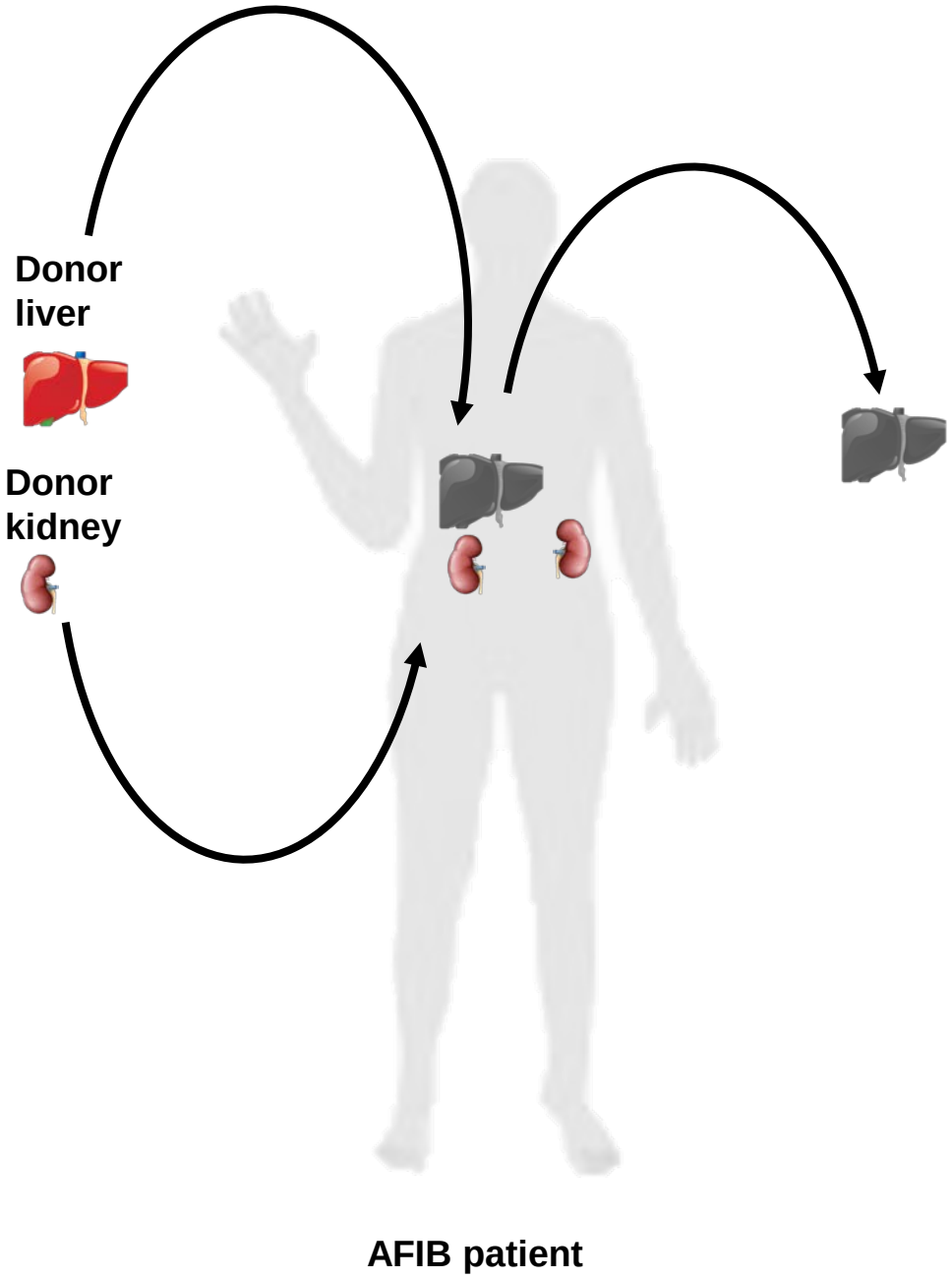
1. **Remove mutant protein producer (liver transplant)**

2. **Replace symptomatic organ kidney or heart)**

3. **Do 1 and 2**



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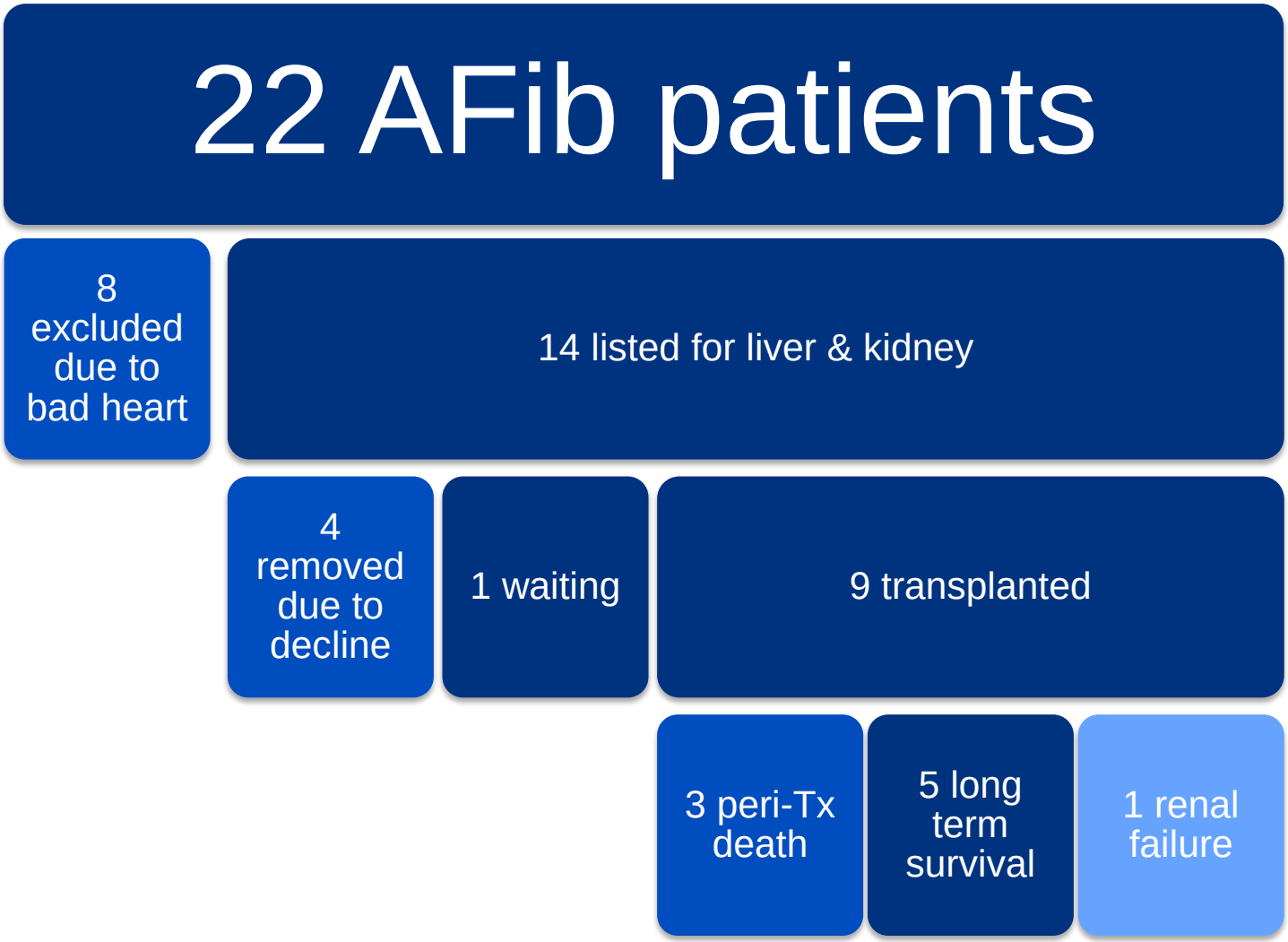
Hereditary fibrinogen A alpha-chain amyloidosis.



Stangou AJ, Banner NR, Hendry BM, et al. *Blood*. 2010;115(15):2998-3007.

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Conclusions

- Liver (± heart) transplant still plays a role in ATTR ValMet30 patients
  - Other mutations, less certain
- Exciting that other means of reducing the ATTR may be on the horizon
- For AFIB, liver + kidney is best
- Early diagnosis, better data collection is imperative regardless

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Thank you for your attention

And Happy Halloween☺!