Managing Fabry disease: successes and challenges

Alberto Ortiz, MD, PhD
Chief of Nephrology and Hypertension, Fundación Jiménez Díaz
Professor of Medicine, Universidad Autónoma de Madrid
Coordinator, Spanish Kidney Research Network (REDINREN)

Conflict of interest

- Consultant: Sanofi Genzyme
- Speaker fees: Sanofi Genzyme, Shire, Amicus

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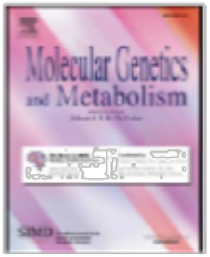


Minireview

Fabry disease revisited: Management and treatment recommendations for adult patients

Alberto Ortiz[a,*], Dominique P. Germain[b], Robert J. Desnick[c], Juan Politei[d], Michael Mauer[e], Alessandro Burlina[f], Christine Eng[g], Robert J. Hopkin[h], Dawn Laney[i], Aleš Linhart[j], Stephen Waldek[k], Eric Wallace[l], Frank Weidemann[m], William R. Wilcox[i]

Med Clin (Barc). 2017;148(3):132–138

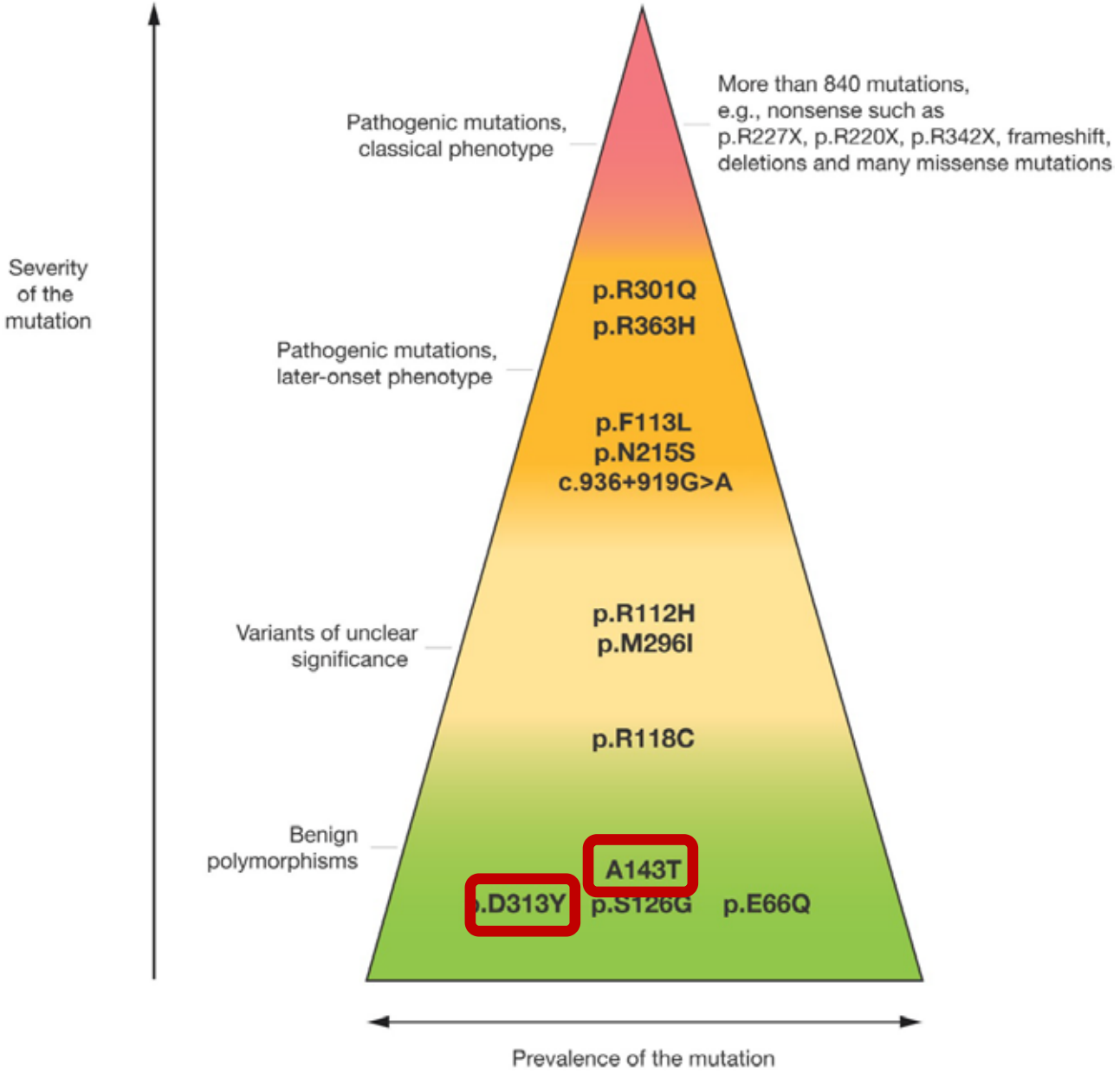
MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Diagnosis and treatment

Diagnosis and treatment of Fabry disease☆

Alberto Ortiz[a,b,*], Maria Dolores Sanchez-Niño[a,b]



Ortiz A, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 2018 Apr;123(4):416-427

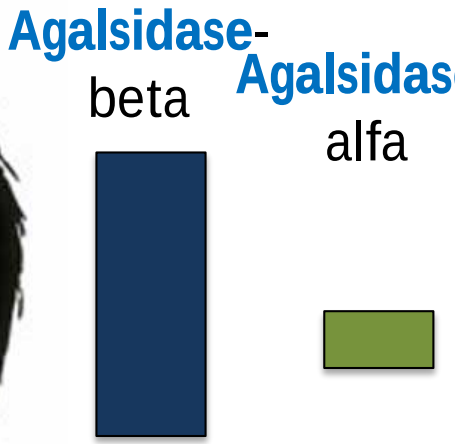
Spain D313Y:

1 in **100** males

1 in **50** females

http://csvs.babelomics.org/

What´s in a Fabry prescriber´s mind?



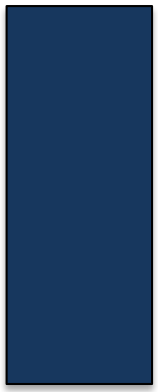
https://imgur.com/gallery/Am8qRh1

If you were using both preparations

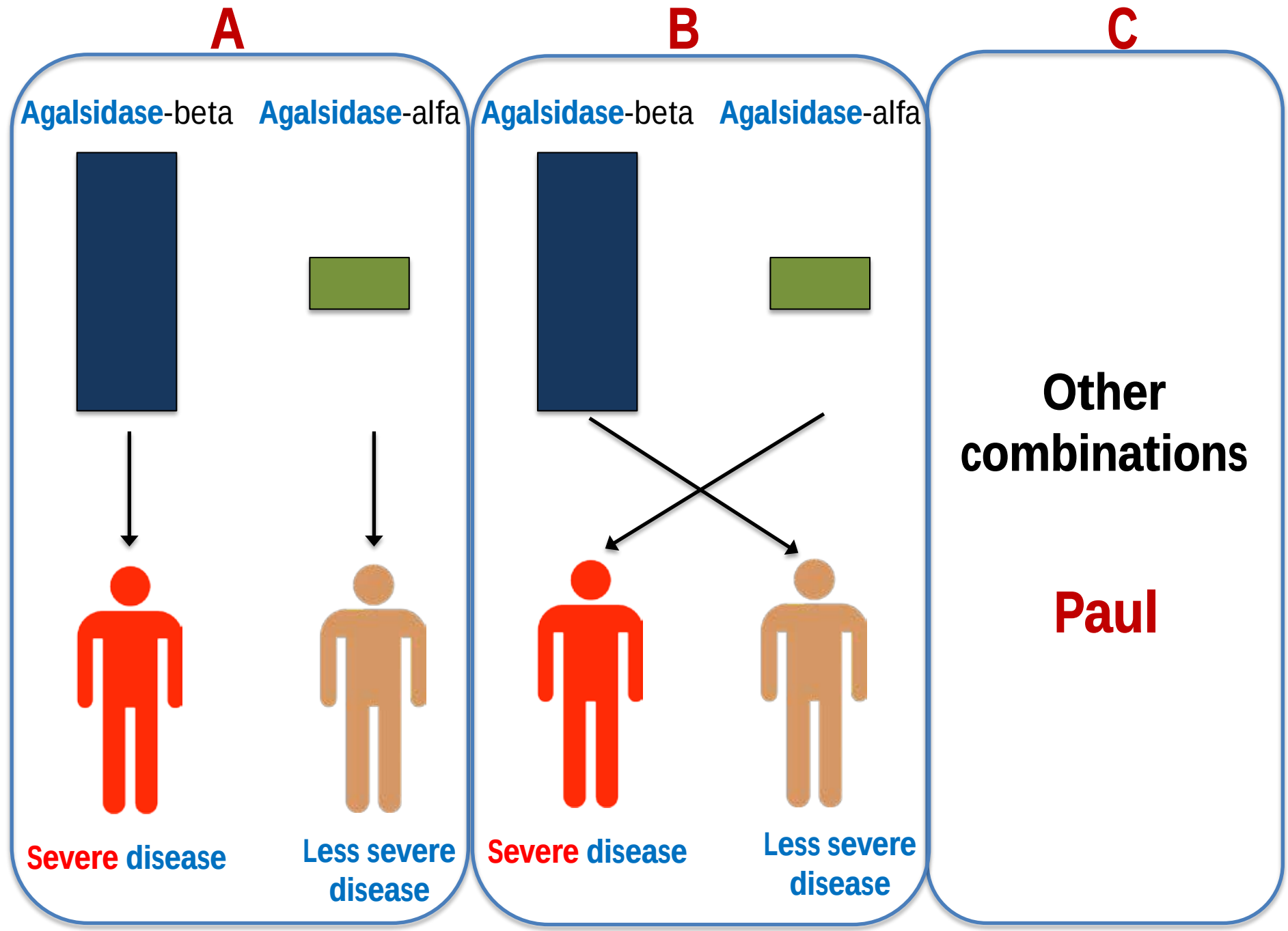
...

How would you **match**?

Agalsidase-beta



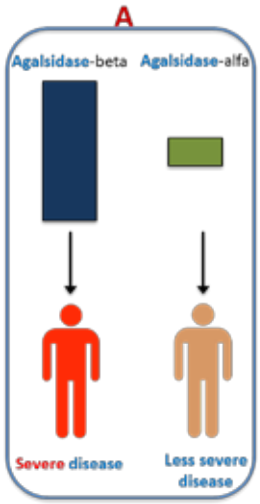
Agalsidase-alfa



Bars represent dose of ERT. Note that these are different molecules and differ by more than just dose.

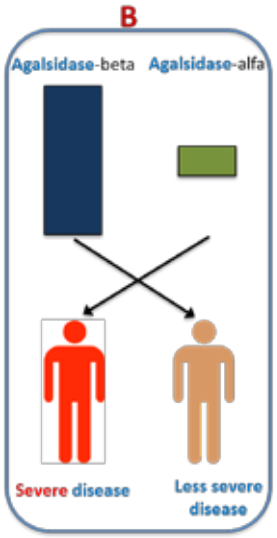

Paul

If you were using both preparations…
How would you **match**?



A?

B?



C?

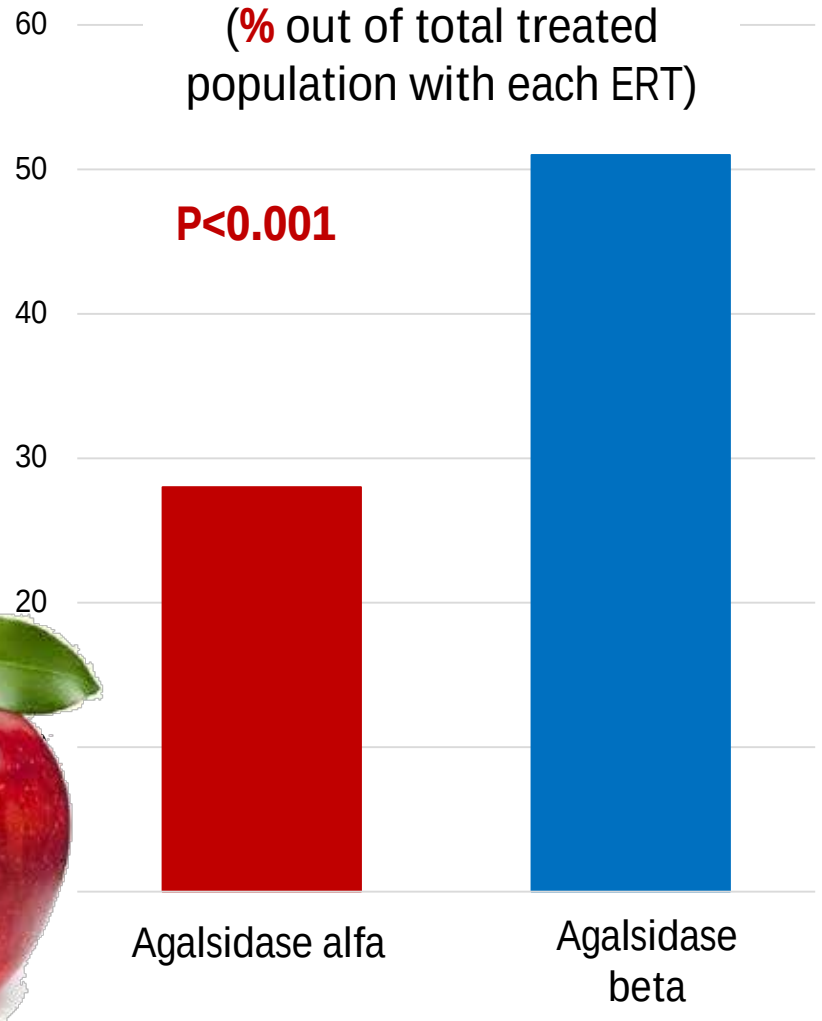
Expert opinion?

What are their choices?

How were patients distributed between **Agalsidase-alfa** 0.2 mg/kg/2weeks and **Agalsidase-beta 1.0** mg/kg/2 weeks in a recent multicenter observational study?

- Academic Medical Center, The Netherlands;
- Royal Free London NHS Foundation Trust, UK
- University Hospital Wuerzburg, Germany
- Cohort 1b, CFDI, Canada

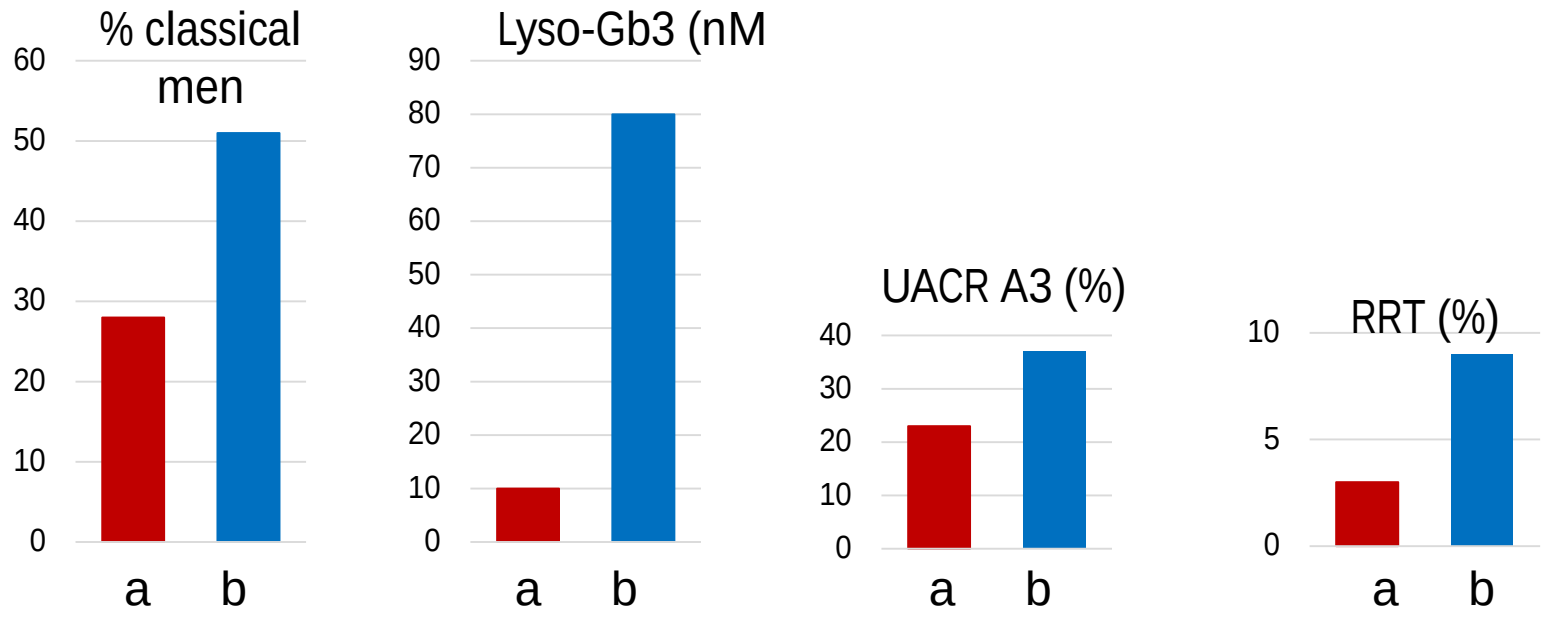
Classical men
(**%** out of total treated population with each ERT)



The correct response is **A**

Arends M et al. J Med Genet Published Online First: 07 February 20[illegible]/jmedgenet-2017-104863

The Fabry physician does separate pears from apples

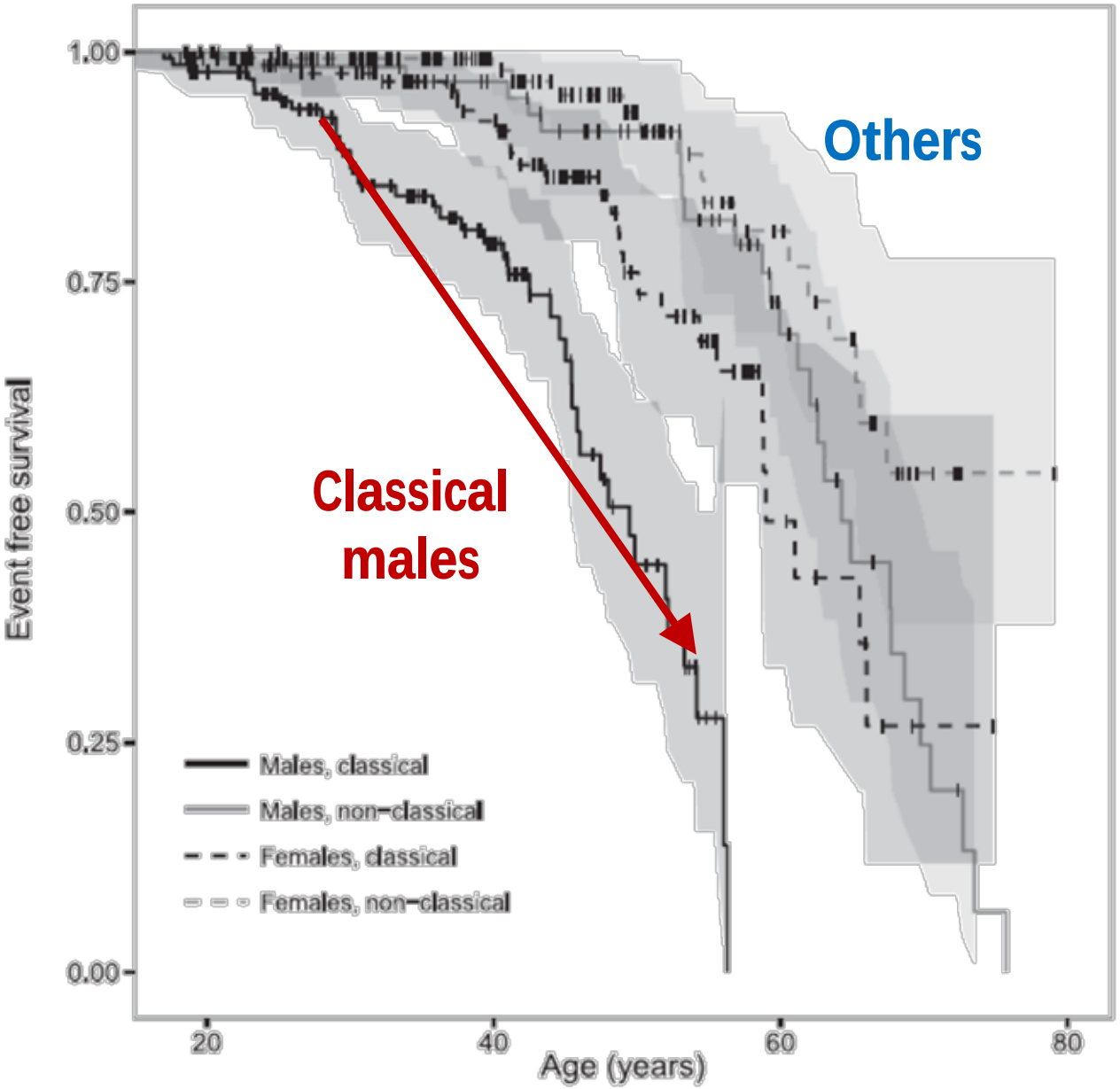


- Academic Medical Center (AMC), The Netherlands;
- Royal Free London NHS Foundation Trust, UK
- University Hospital Wuerzburg, Germany
- Cohort 1b, CFDI, Canada

Arends M et al. J Med Genet 2018 E Pub

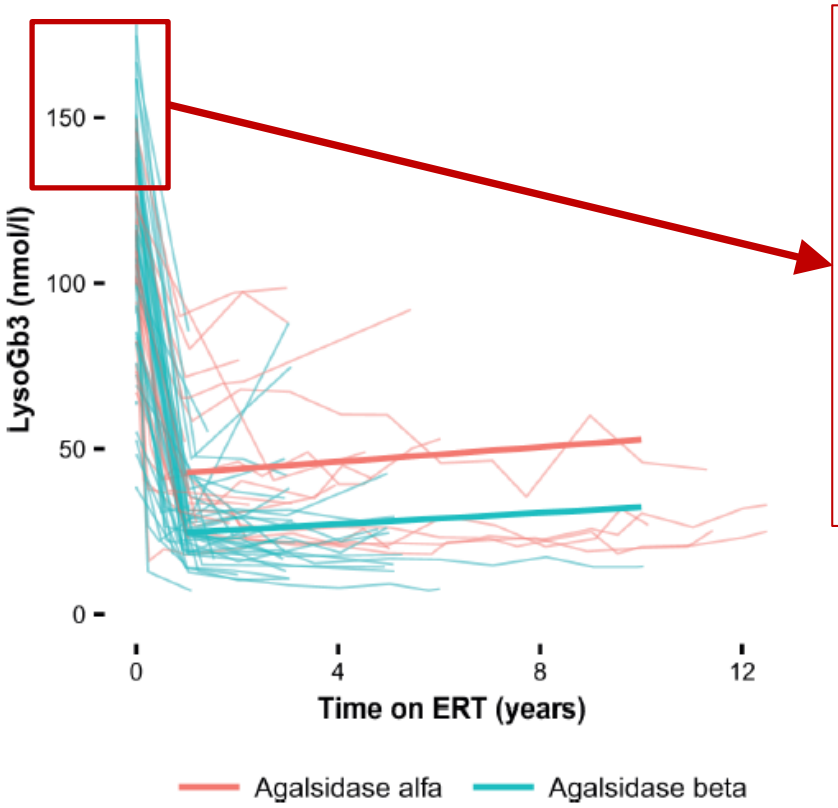
Classical males vs other Fabry patients

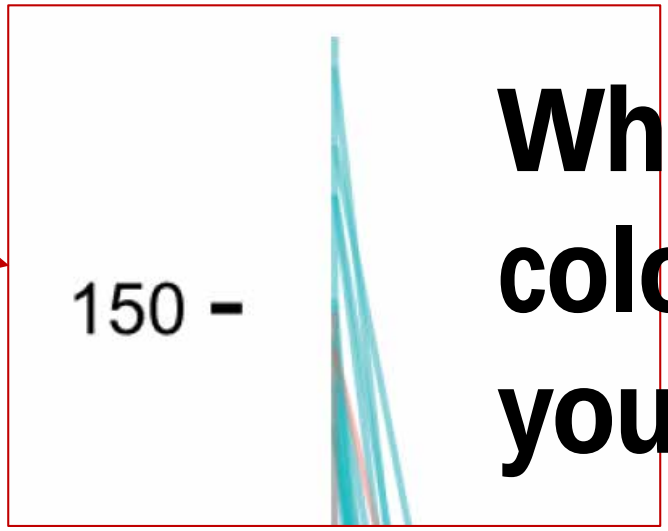
Natural history



Arends M, et al. J Am Soc Nephrol 2017 May;28(5):1631-1641

Let us look only at classical males!





What color do you see?

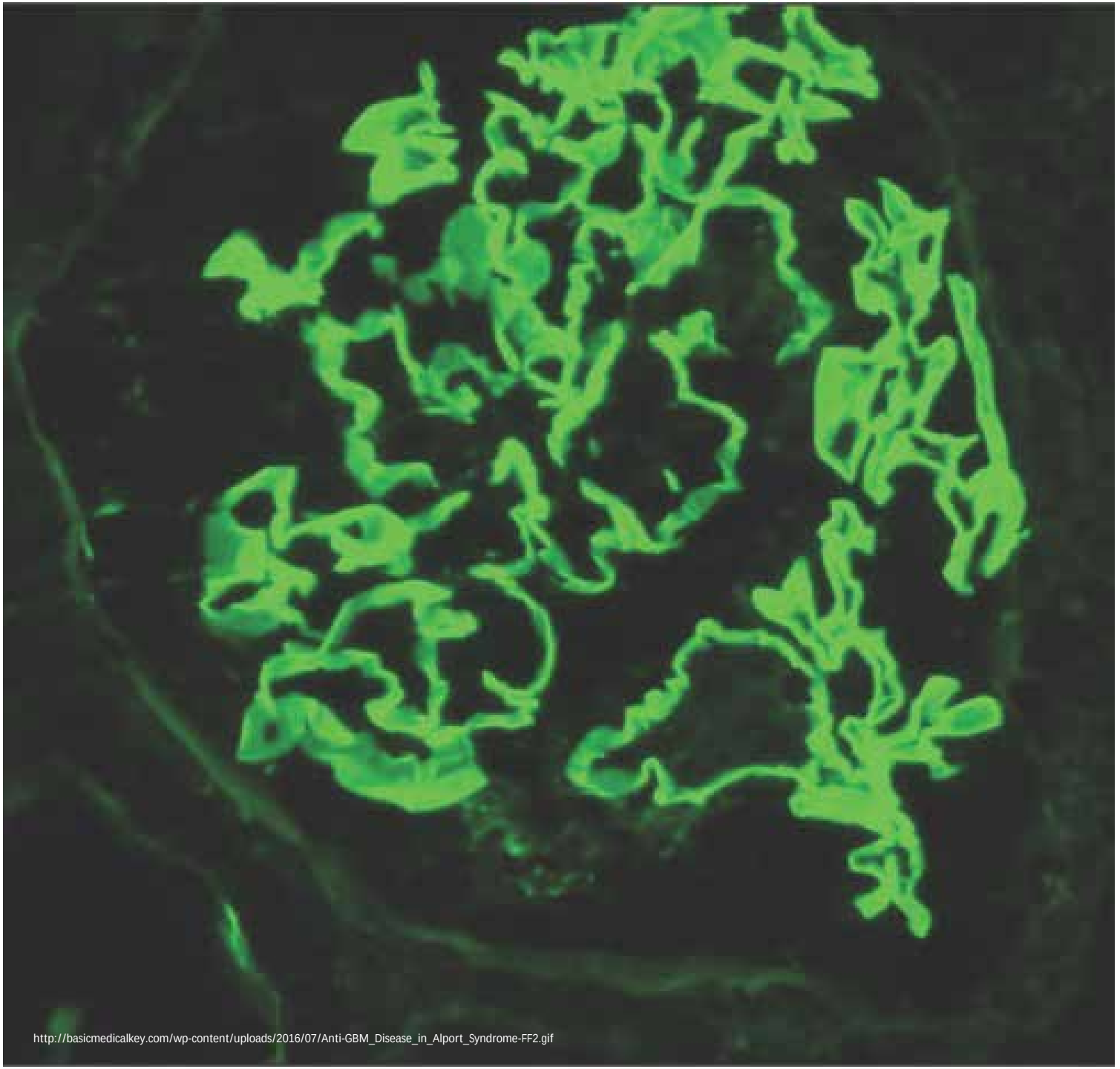
Beta color!

Arends M et al. J Med Genet Published Online First: 07 February 2018. doi: 10.1136/jmedgenet-2017-104863

Why is this important?

Anti-GBM antibodies in Alport patient receiving a kidney graft

Alport patients **lack** certain **GBM** components (type IV collagen)

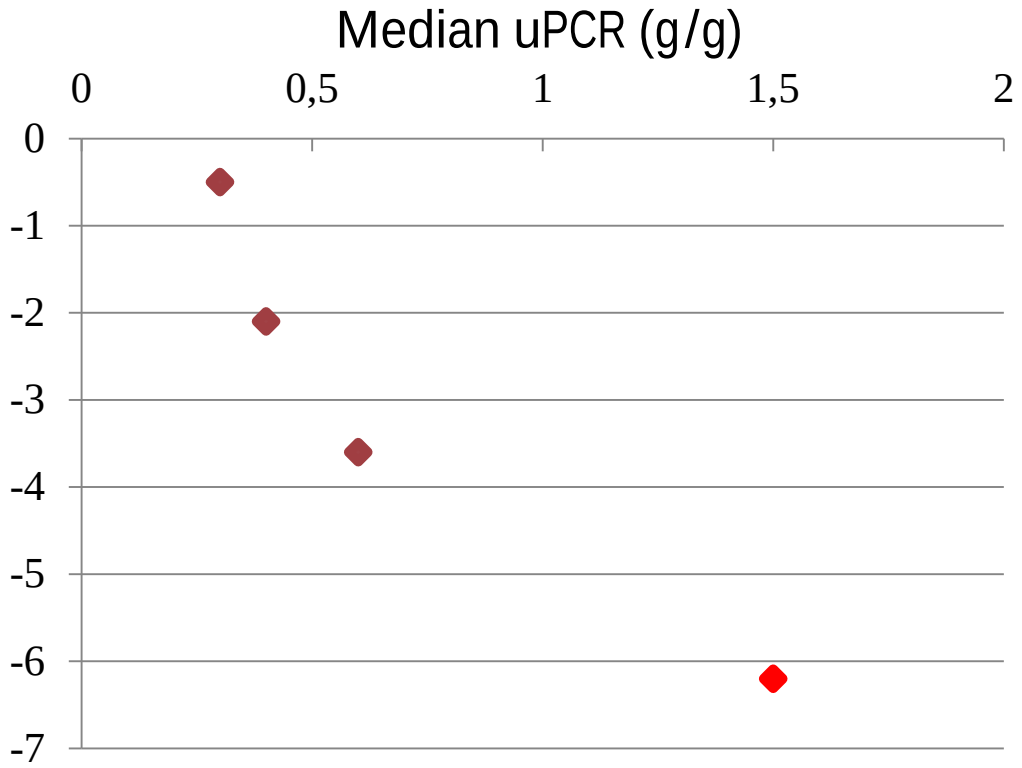


http://basicmedicalkey.com/wp-content/uploads/2016/07/Anti-GBM_Disease_in_Alport_Syndrome-FF2.gif

Albuminuria (proteinuria » albuminuria x 2) is a major **risk factor** for **progression** of CKD in Fabry disease

Nat history data

Median eGFR slope (ml/min/year)



Warnock, et al. Nephrol Dial Transplant. 2012 Mar;27(3):1042-9.,
Wanner, et al. Clin J Am Soc Nephrol. 2010 Dec;5(12):2220-8.?

This is not what it seems!!!!

Podocyte farewell ceremony by cell biology scientist

Trimarchi et al. J Transl Med (2016) 14:289
DOI 10.1186/s12967-016-1049-8

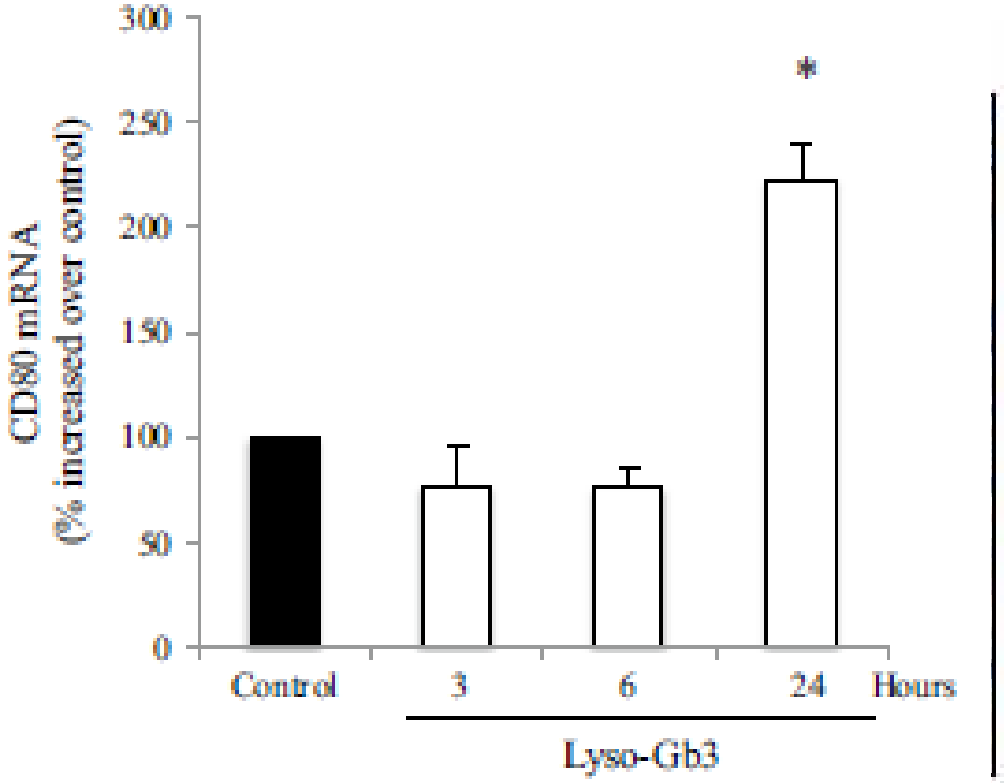
Journal of Translational Medicine

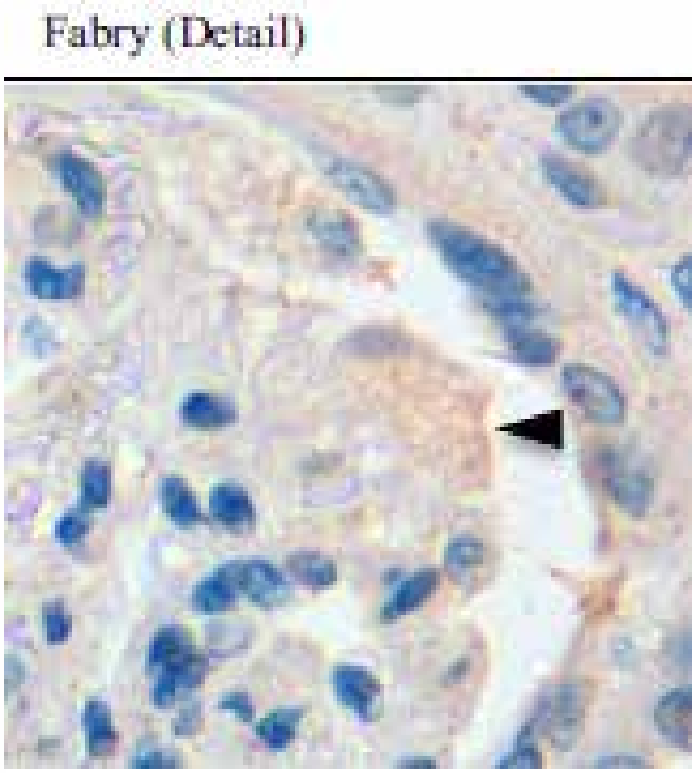
RESEARCH Open Access

Increased urinary CD80 excretion and podocyturia in Fabry disease

CD80 = B7-1

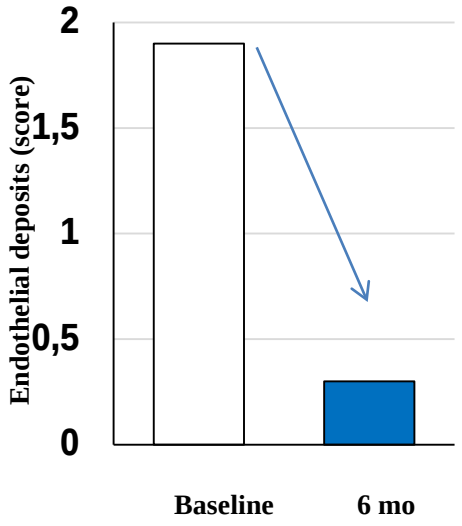
H. Trimarchi[1*], R. Canzonieri[2], A. Schiel[2], C. Costales-Collaguazo[3], J. Politei[4], A. Stern[2], M. Paulero[1], T. Rengel[1], J. Andrews[1], M. Forrester[1], M. Lombi[1], V. Pomeranz[1], R. Iriarte[1], A. Muryan[2], E. Zotta[3], M. D. Sanchez-Niño[5,6*†] and A. Ortiz[5,6†]



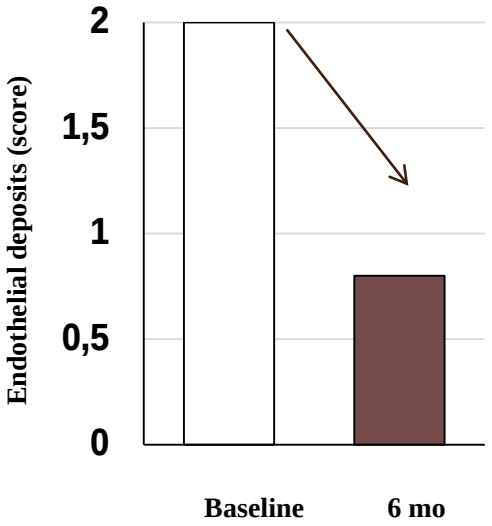


Sesame Street suggests endothelial findings may not apply to podocytes

Endothelial deposits in placebo-controlled phase II/III RCT of enzyme replacement therapy



agalsidase beta 1.0 mg/kg/2 weeks

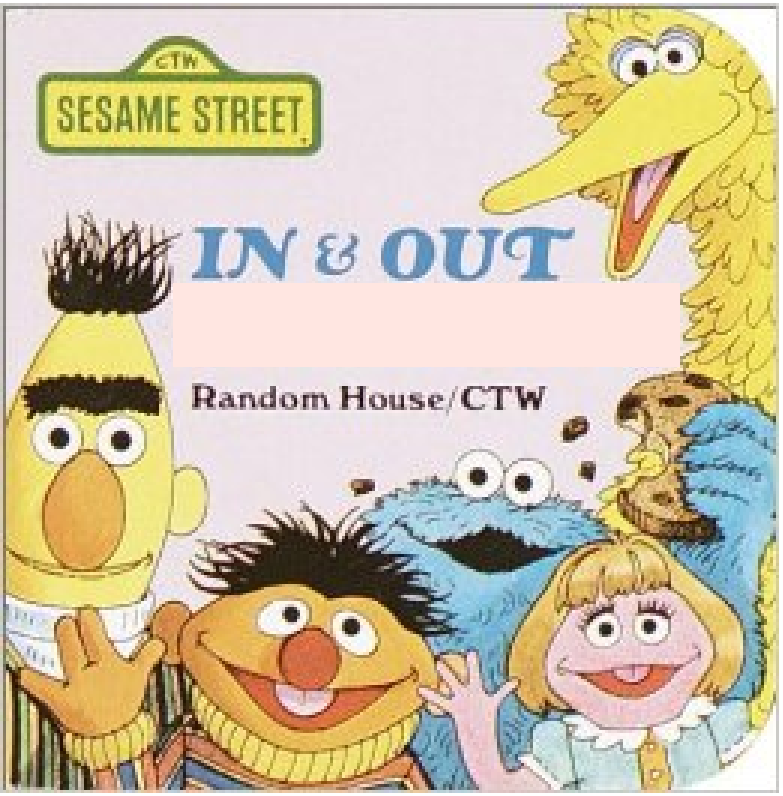


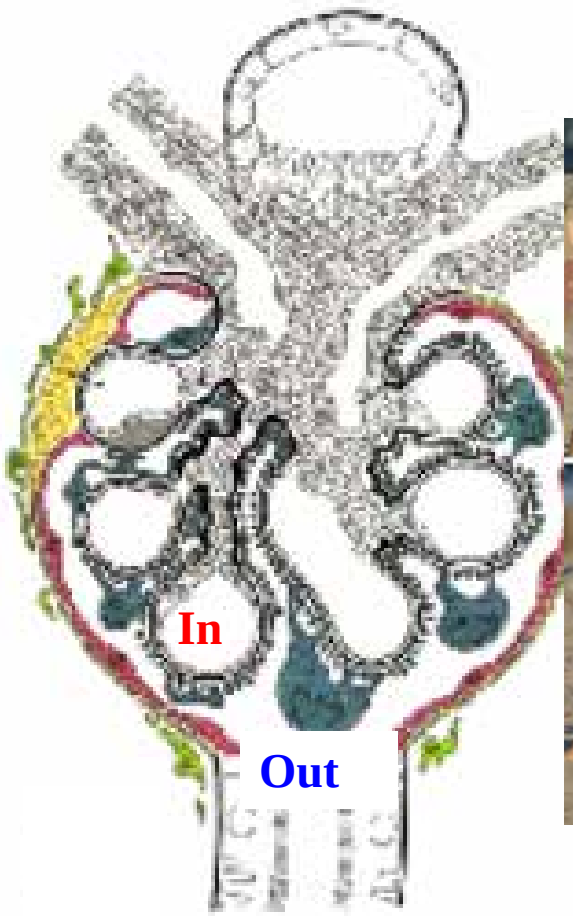
agalsidase alpha 0.2 mg/kg/2 weeks

Eng, Christine M., et al. *New England Journal of Medicine* 345.1 (2001): 9-16.
Schiffmann, Raphael, et al. *Jama* 285.21 (2001): 2743-2749.
Ortiz et al, Med Clin Med Clin (Barc). 148 (2017):132-138.

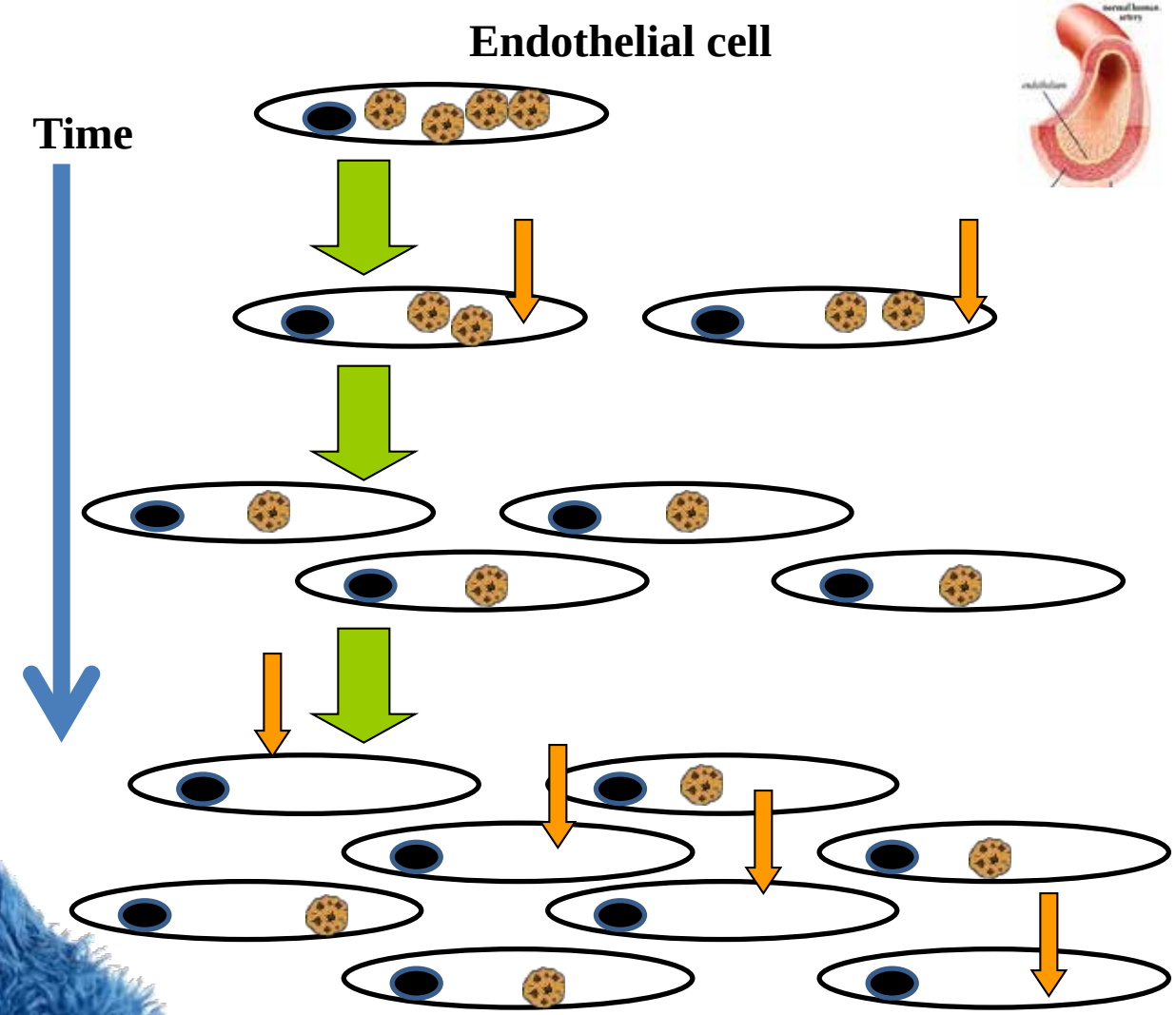
Sesame Street issues: In and out

Beware of **larger** molecules!





Sesame Street issues: sharing cookies

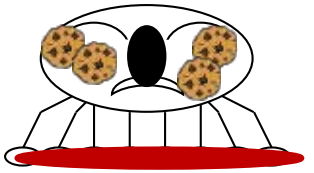


If you **don`t share** your cookies, you get to **keep all** of them!

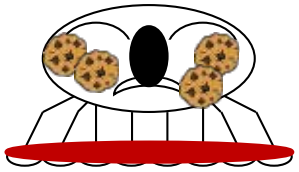
Time

Podocyte

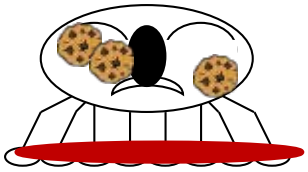
1 y



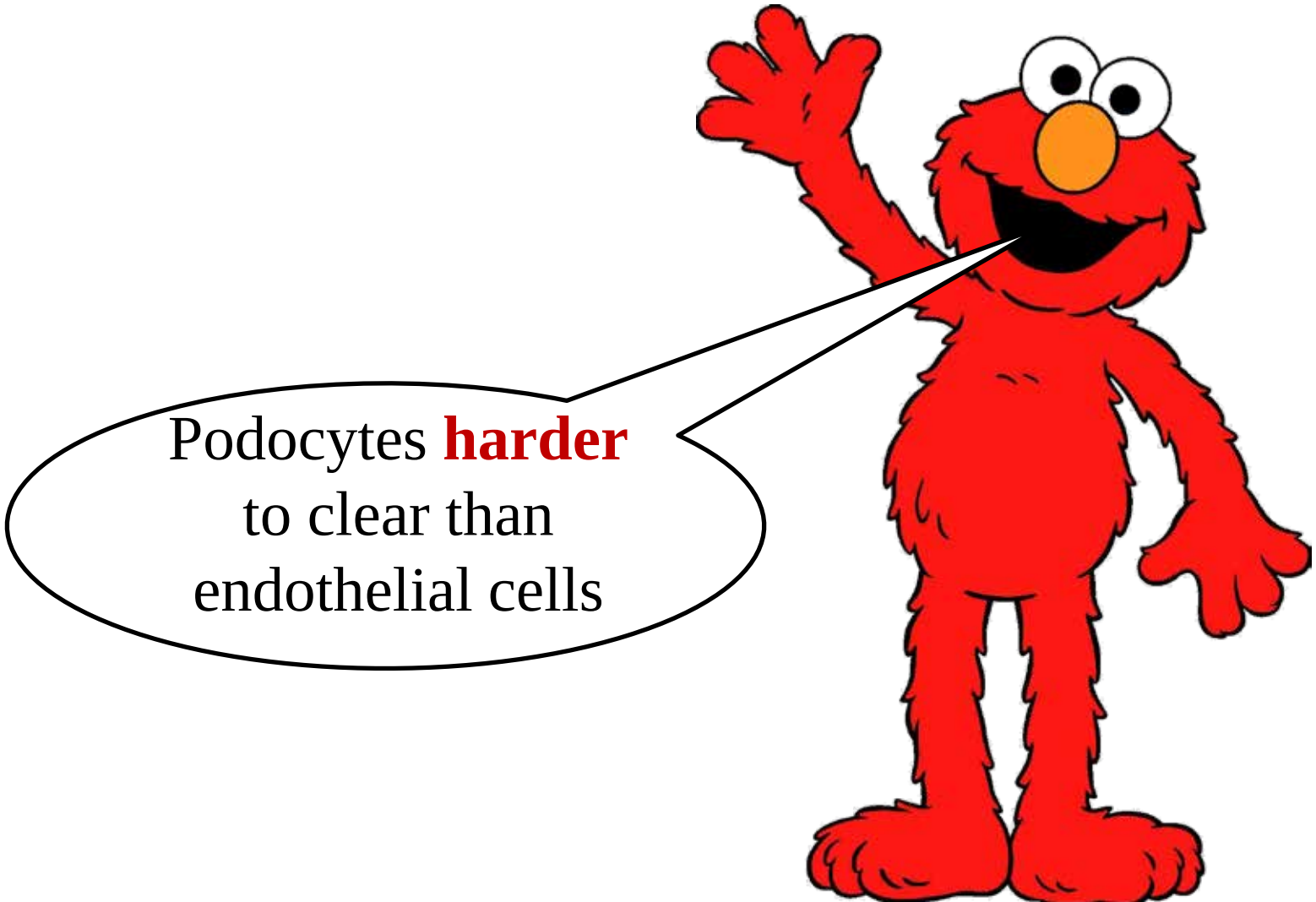
2 y



3 y



The **Sesame Street** prediction



ERT and GL-3 clearance from podocytes

Tøndel C, Bostad L, Larsen KK, Hirth A, Vikse BE, Houge G, **Svarstad E**. Agalsidase benefits renal histology in young patients with fabry disease. J Am Soc Nephrol. **2013**;24:137-48

- **5 years** of **ERT** with agalsidase **alfa or** agalsidase **beta** in **12** consecutive patients age 7-33 years (median **16 y**).
  - **agalsidase alfa, 0.2 mg/kg/EOW** (n=5), 0.2 mg/kg/EW (n=1), 0.4 mg/kg/EOW (n=1)
  - **agalsidase beta, 1.0 mg/kg/EOW** (n=3), 0.2 EOW (n=1)
  - agalsidase alfa, 0.4 mg/kg/EOW + then agalsidase beta, 1.0 mg/kg/EOW (n=1)
- After a median of 65 months **microalbuminuria normalized** in **5** patients.
- Bx findings

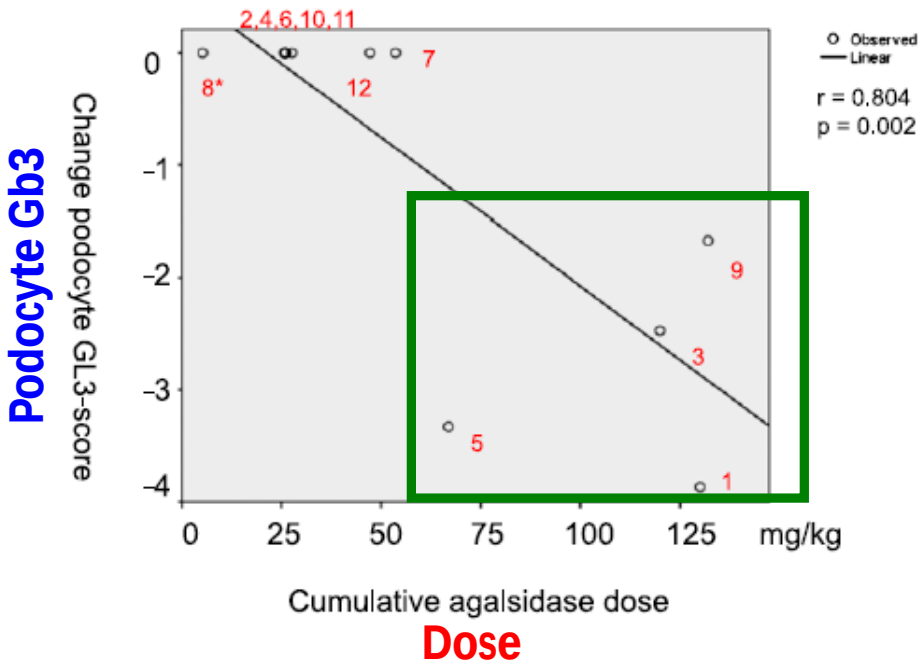
Please note: Fabrazyme (agalsidase beta) is indicated in patients >/= 8 years old (EU SmPC, Jan 2017).

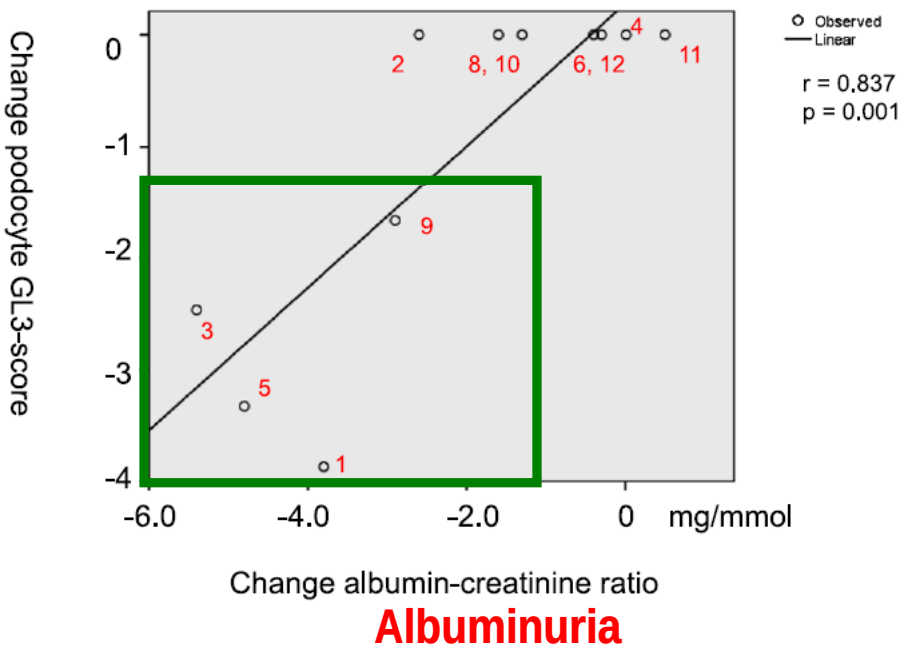
Early ERT in Fabry: Renal Bx after 5 years of ERT

Correlation between cumulative dose and podocyte Gb3 clearance

Endothelium cleared in all

Better podocyte clearance, more reduction in albuminuria

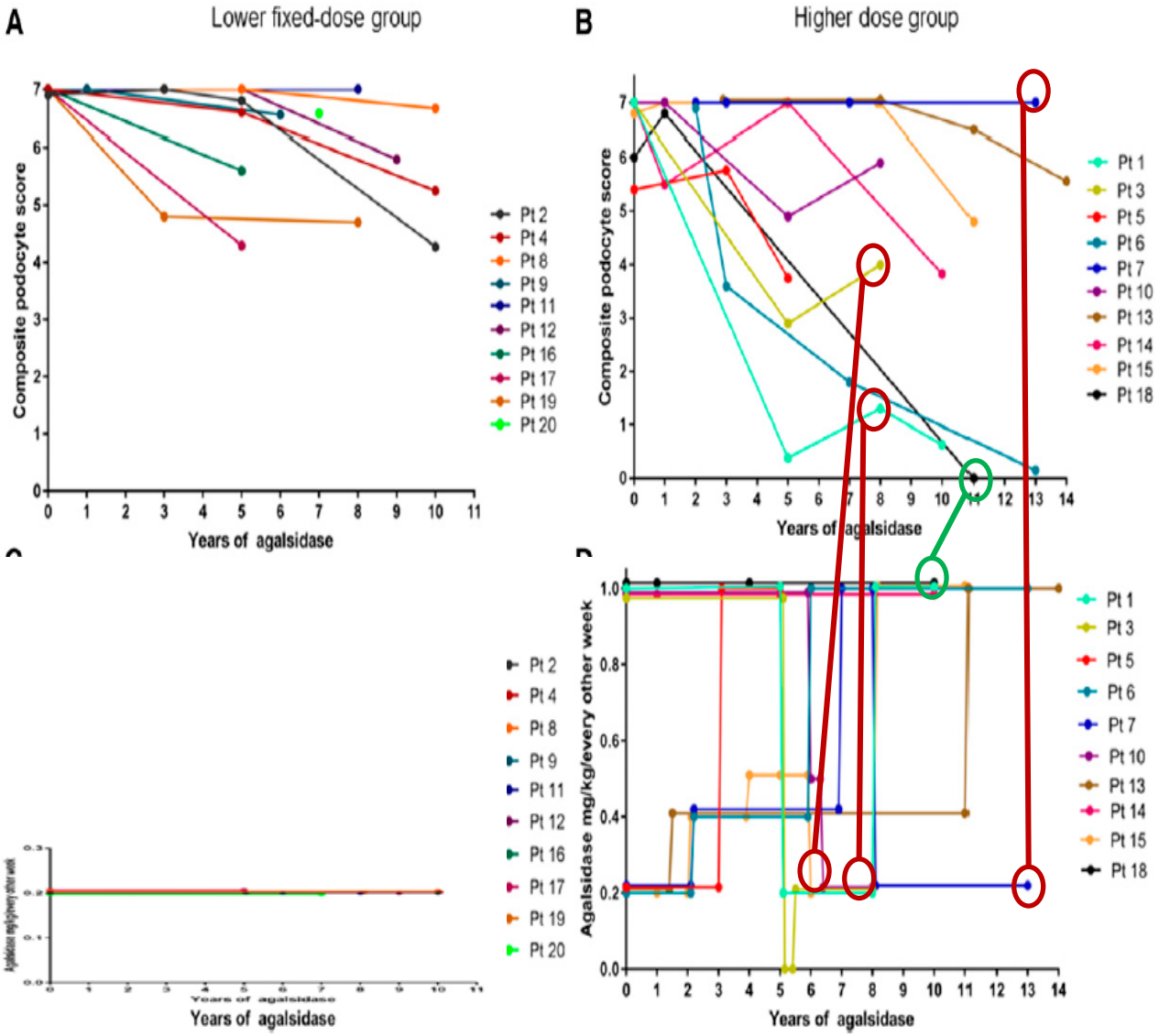




Fabrazyme (agalsidase beta) is indicated in patients >/= 8 years old (EU SmPC, Jan 2017)

Long-Term Dose-Dependent Agalsidase Effects on Kidney Histology in Fabry Disease

- Reduction of **podocyte Gb3** correlated with **cumulative dose**
- Residual plasma **Lyso-Gb3** correlated with **cumulative dose** in men



Efficacy and safety of Fabrazyme (agalsidase beta) in patients aged 0-7 years has not been established.
Per approved leaflet in Brazil, Fabrazyme (agalsidase beta 1mg/kg/every two weeks) is indicated in adults and adolescents aged 16 years and older.

Skrunes R et al. Clin J Am Soc Nephrol. 2017 Jun 16. pii: CJN.01820217. doi: 10.2215/CJN.01820217.

The shortage: dose matters?

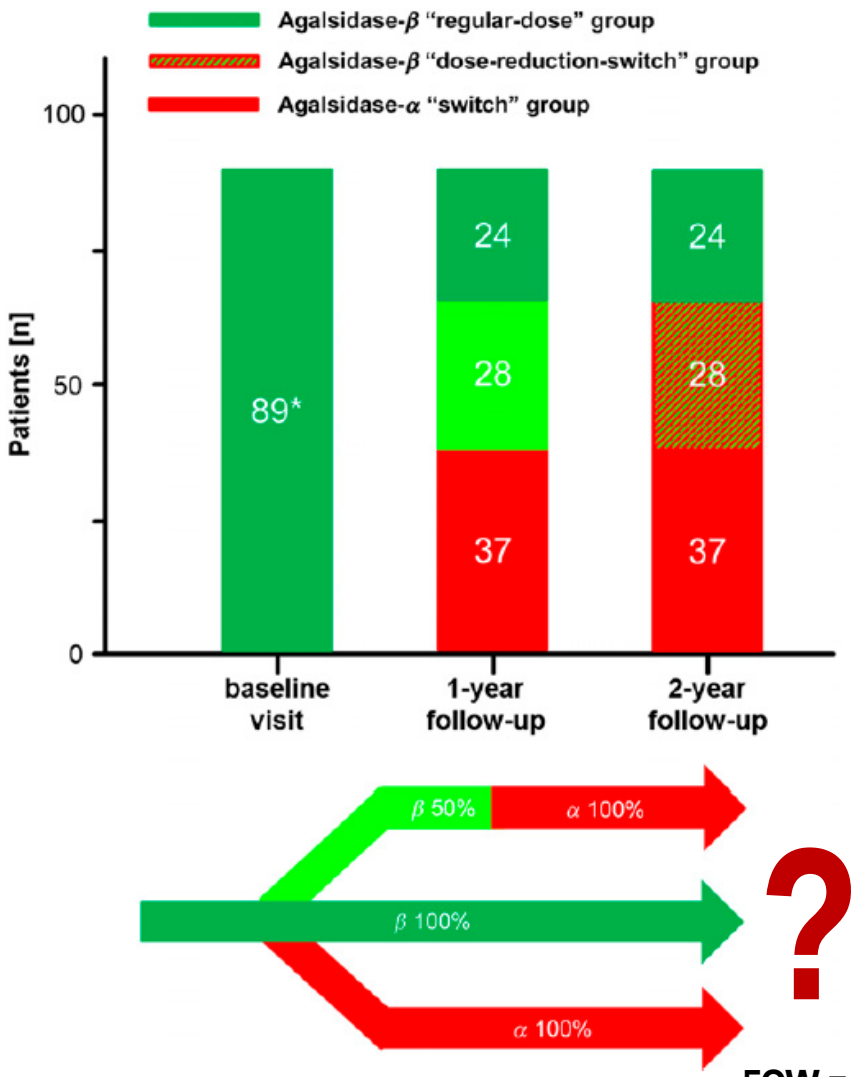
- June 2009: viral contamination of Manufacturer production facility

- Worldwide **shortage** of agalsidase beta

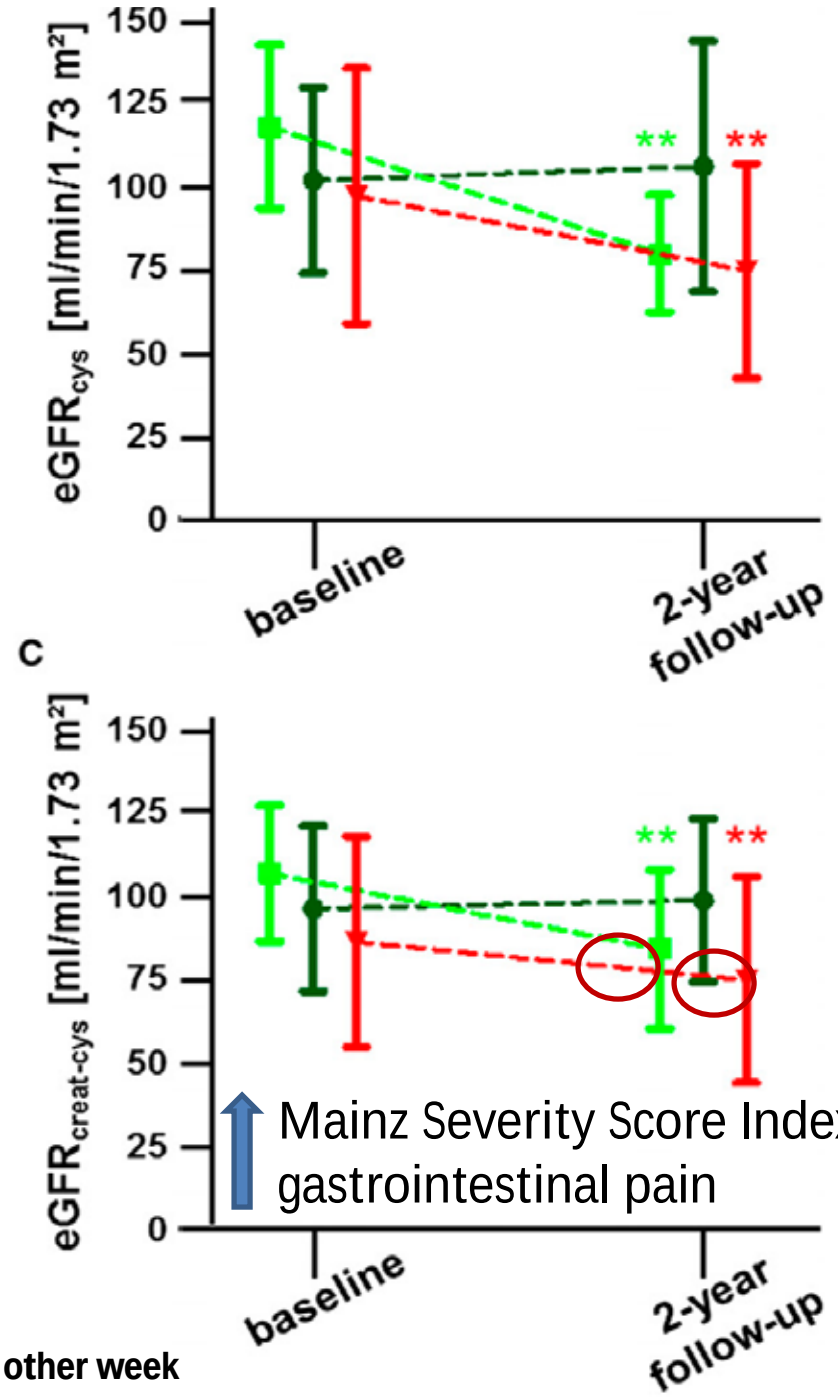
- Leading to involuntary **dose reductions** (approved dose 1.0 mg/kg/eow, reduced dose 0.5 mg/kg/eow), or **switch to** agalsidase alfa (administered dose 0.2 mg/kg/eow).

EOW = every other week

2 years of dose-reduction of agalsidase-b 1.0 mg/kg/eow and/or switch to agalsidase-a 0.2mg/kg/eow and eGFR



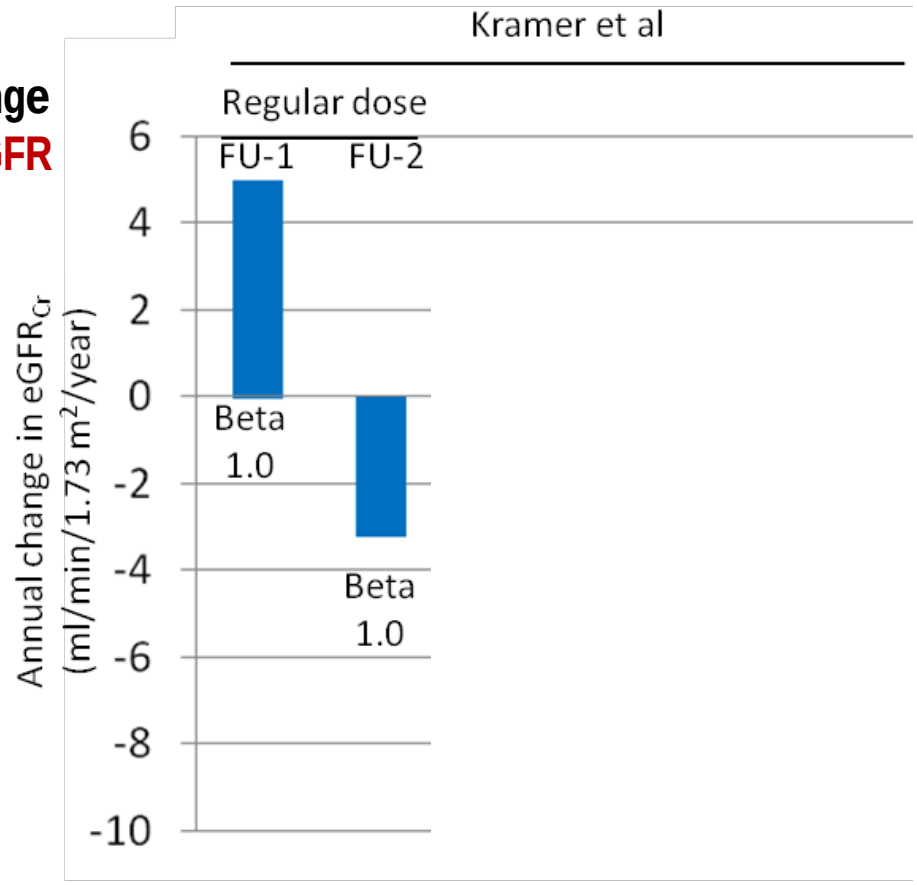
Lenders et al. JASN 2015



EOW = every other week

Dose and the shortage: impact of switching back to agalsidase beta 1.0 mg/kg/EOW

Change in eGFR



Ortiz et al. Nephrol Dial Trasplant 2018. Elaborated with data from:
Krämer J et al. Nephrol Dial Transplant 2017 Nov 23. doi: 10.1093/ndt/gfx319. [Epub ahead of print]
www.fda.gov/ohrms/dockets/ac/03/briefing/3917B2_01_TKT%20Replagal%20Background%20.pdf

Hard outcomes: severe clinical events

Myocardial infarction
Heart failure
Heart intervention

Dialysis/transplantation

Stroke

Death

What is the evidence on **ERT** and **severe** clinical events?

1. RCT

ERT for Fabry disease

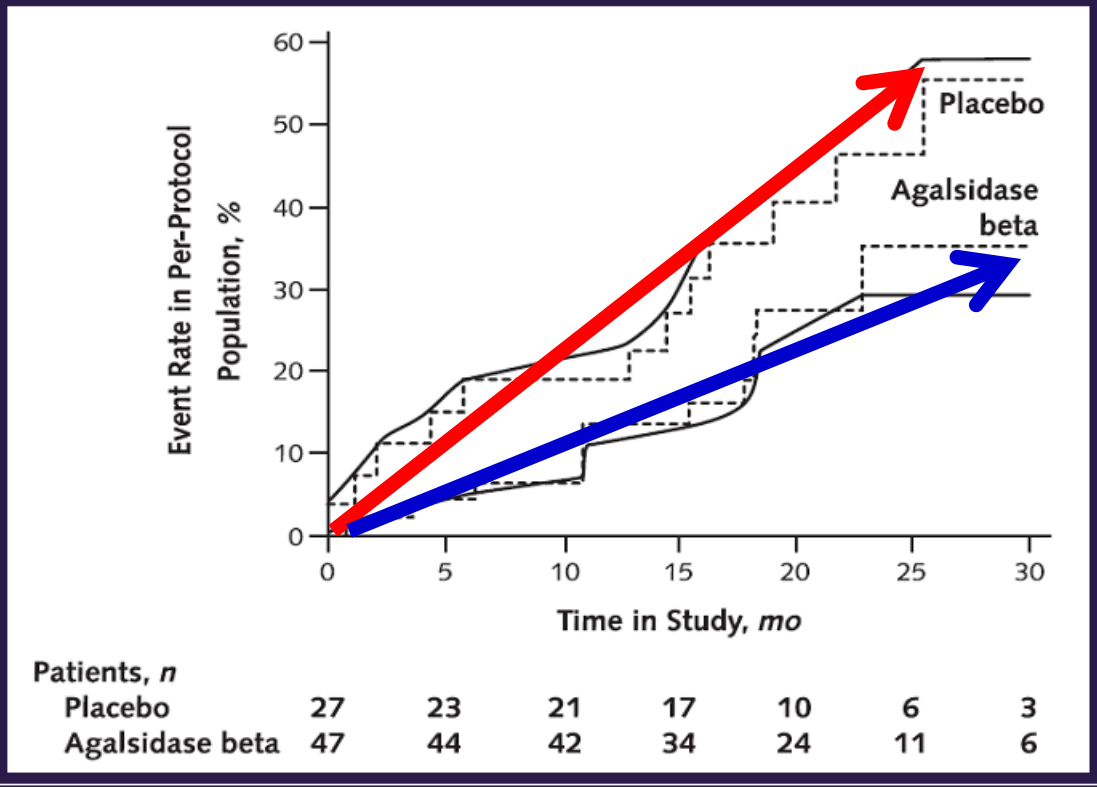
	Agalsidase alfa	Agalsidase beta
Approved dose	0.2 mg/kg/2w	1 mg/kg/2w
Phase II/III	YES	YES
Phase IV Placebo controlled Events as primary outcome	NO	YES

Agalsidase beta, phase IV 1 mg/kg/2 week

Mean age 47 years (ERT) vs 44 (placebo)

Mean UACR 1.3 g/g (ERT) vs 0.9 years (placebo)

- 82 adults with mild to moderate kidney disease



hazard ratio 0.39
P 0.034
adjusted for
baseline proteinuria

Events: composite clinical outcome of renal, cardiac, and cerebrovascular complications or death

Per protocol population

ITT population (HR 0.47, p=0.06)

Banikazemi et al. Ann Intern Med 2007.

1. RCT

2. Registry data

ERT at 1 mg/kg/2 weeks with agalsidase beta was associated with a decrease in incidence of severe clinical events* AFTER 6 months of treatment

Fabry registry data:
1044 patients

Median age at start ERT: 40 years = late!!

Non-classical mutations excluded from analysis!

* severe clinical events were defined as: death , renal, cardiac event or stroke.

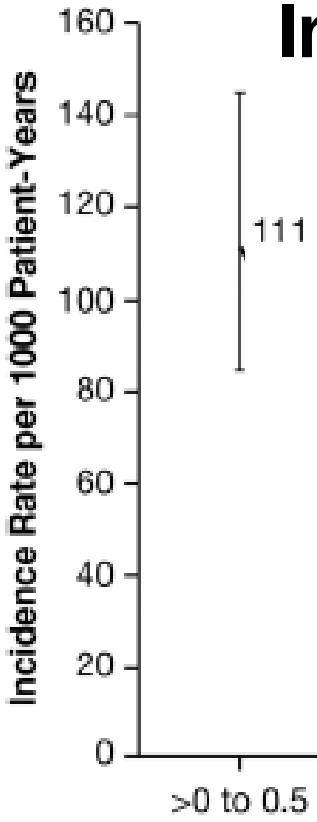
Ortiz at al J Med Genet. 2016 Jul;53(7):495-502.

ERT at 1 mg/kg/2 weeks with agalsidase beta was associated with a decrease in incidence of severe clinical events* AFTER 6 months of treatment

Fabry registry data:
1044 patients

Median age at start ERT: 40 years = late!!

Incidence rate within the first 6 months of ERT



* severe clinical events were defined as: death , renal, cardiac event or stroke.

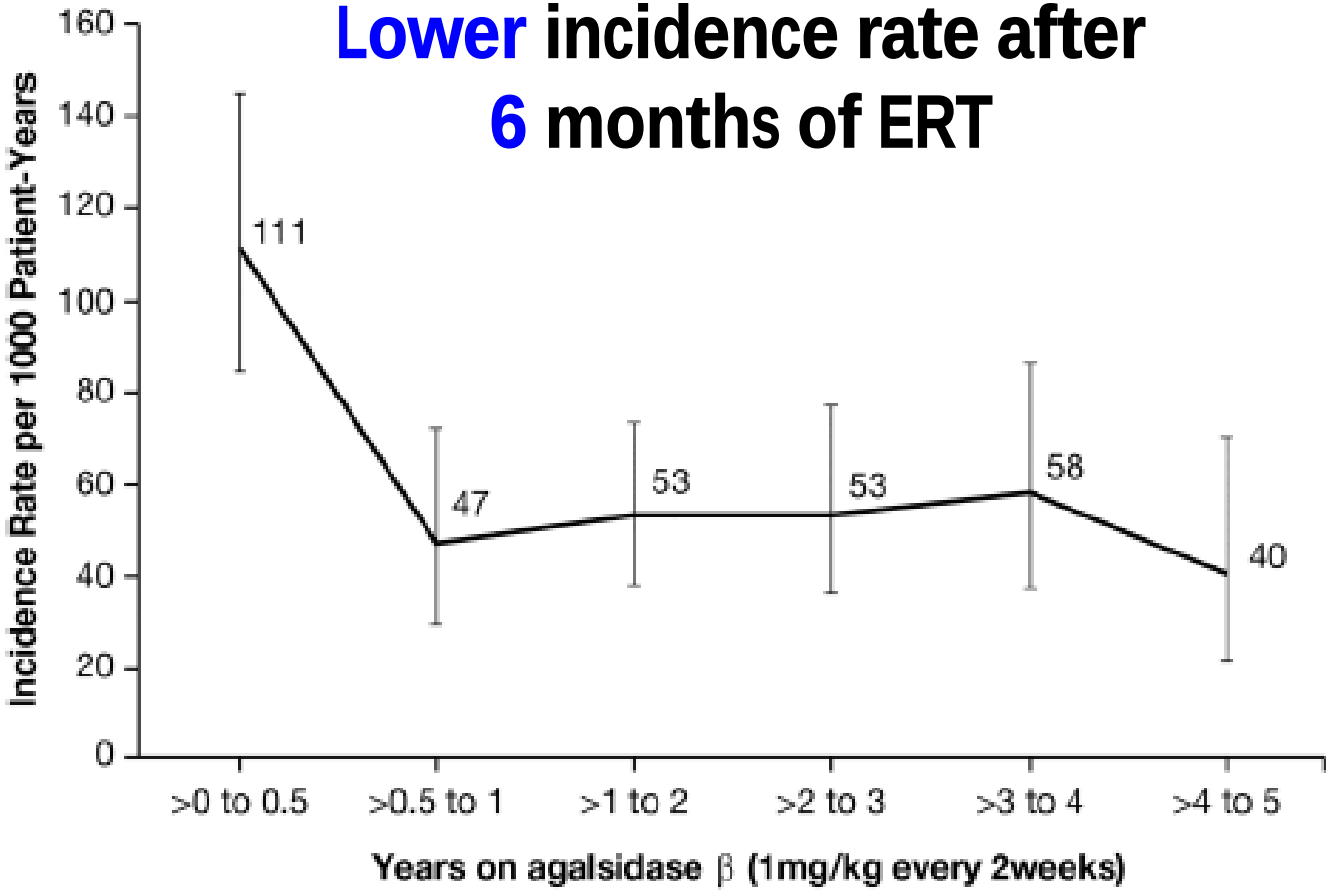
Ortiz at al J Med Genet. 2016 Jul;53(7):495-502.

ERT at 1 mg/kg/2 weeks with agalsidase beta was associated with a decrease in incidence of severe clinical events* AFTER 6 months of treatment

Fabry registry data:
1044 patients

Median age at start ERT: 40 years = late!!

Lower incidence rate after 6 months of ERT



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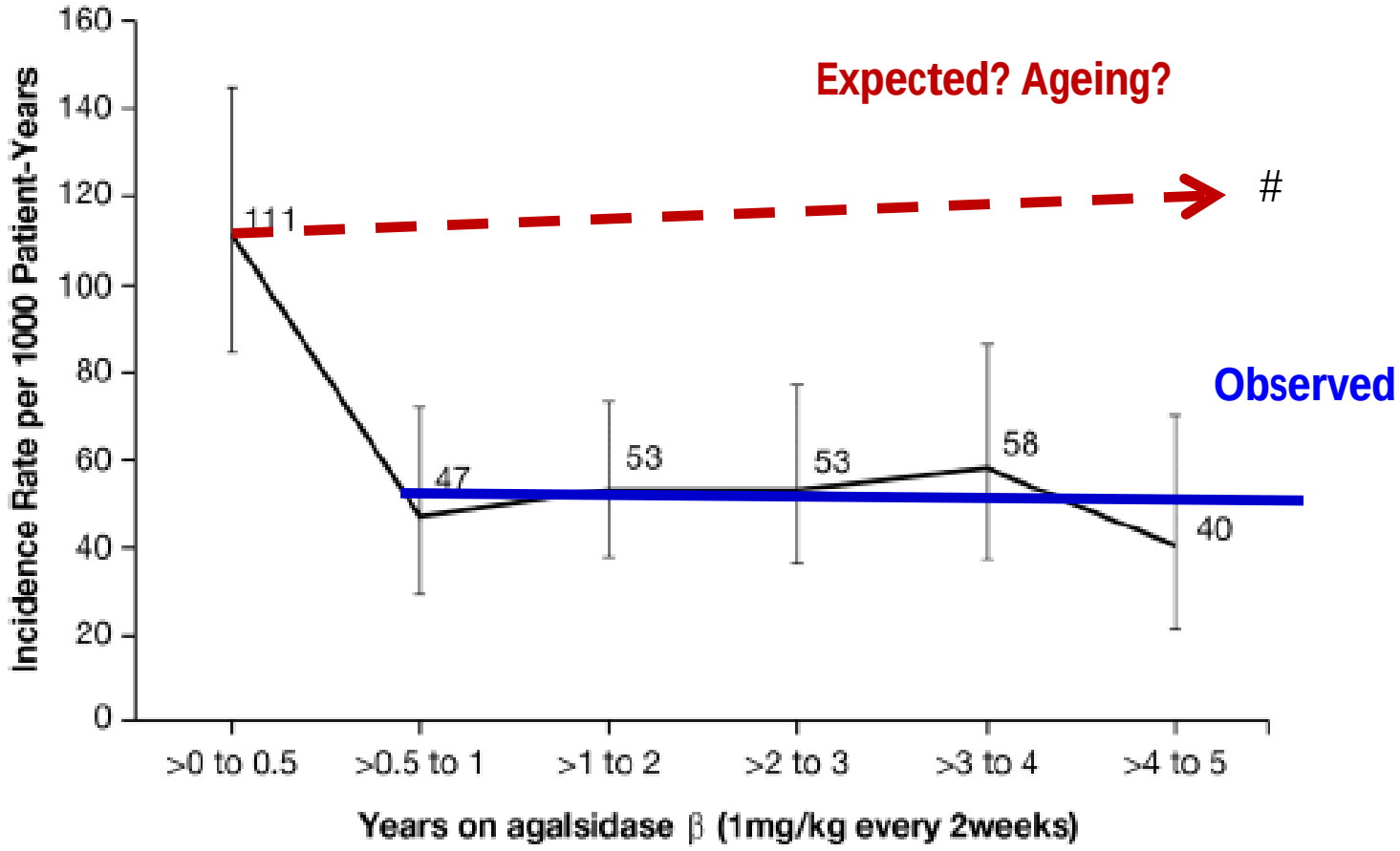
ERT at 1 mg/kg/2 weeks with agalsidase beta was associated with a decrease in incidence of severe clinical events* AFTER 6 months of treatment

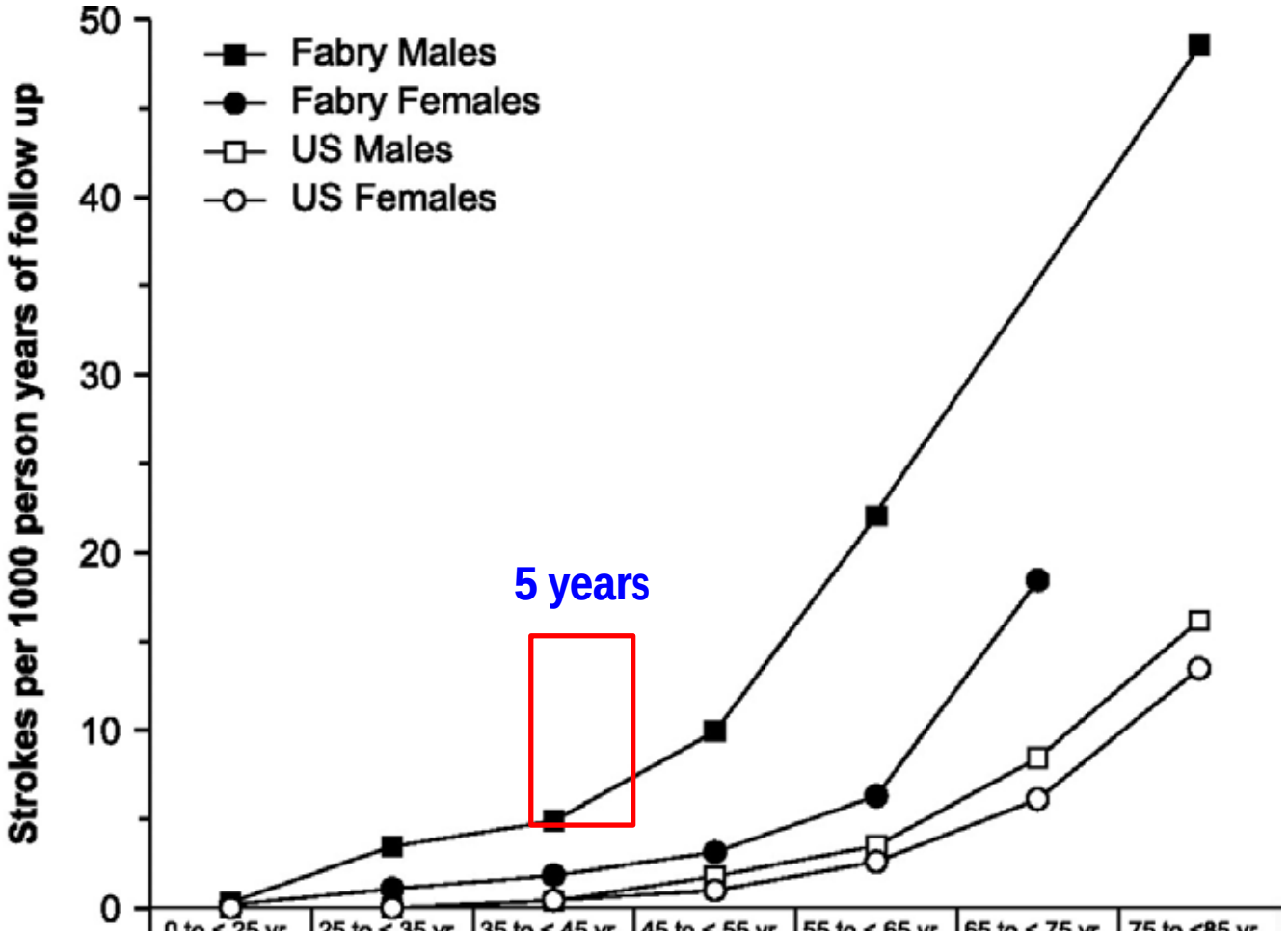


* severe clinical events were defined as: death , renal, cardiac event or stroke.

Ortiz at al J Med Genet. 2016 Jul;53(7):495-502.

Dr ortix's Estimates/ personal opinions based on **Katherine Sims et al. Stroke. 2009;40:788-794**

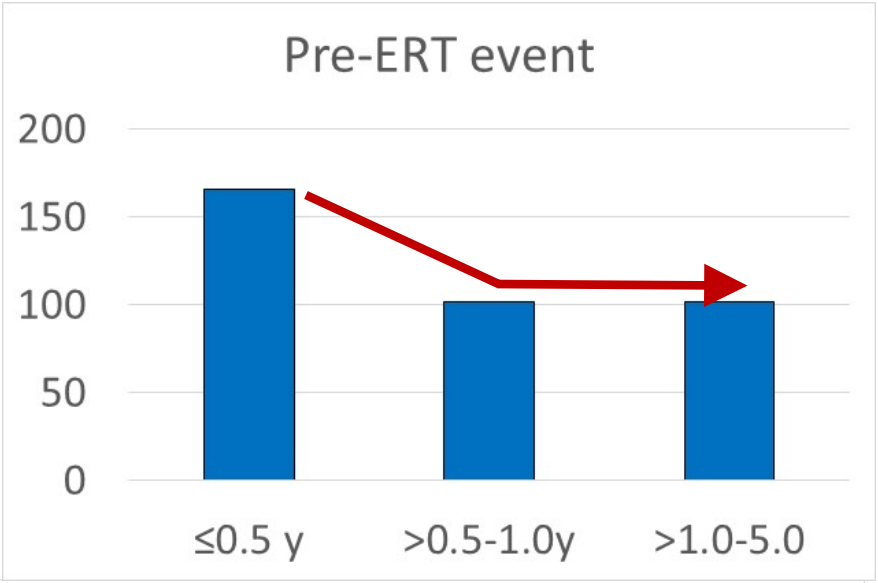
Incidence of strokes increases with age in untreated Fabry patients and the general population

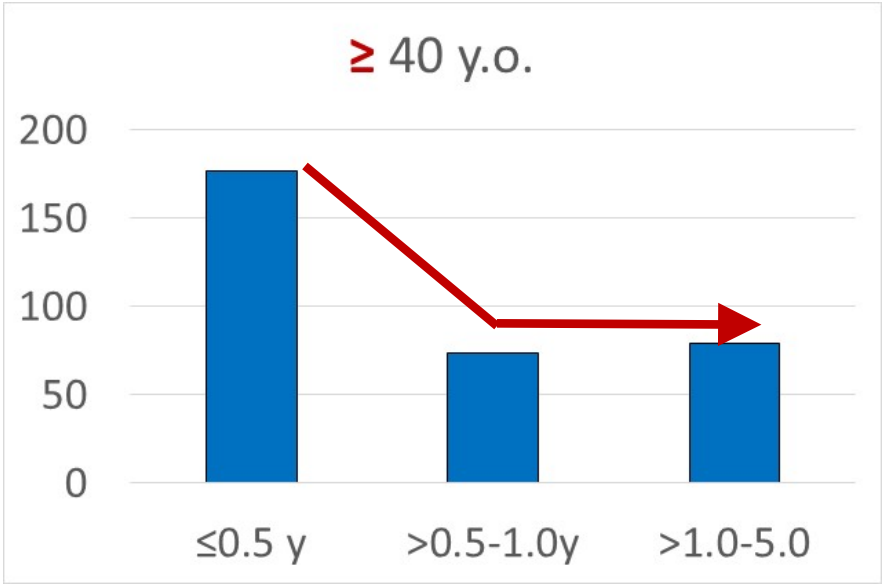


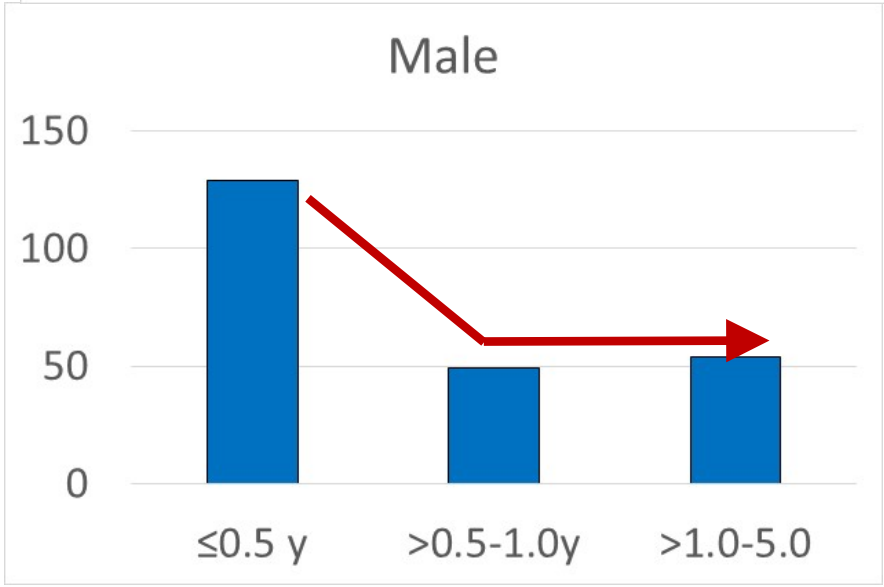
	0 to < 25 yr	25 to < 35 yr	35 to < 45 yr	45 to < 55 yr	55 to < 65 yr	65 to < 75 yr	75 to <85 yr
Fabry Males	0.32	3.47	4.89	9.92	22.05	*	48.58
Fabry Females	0.18	1.09	1.83	3.14	6.30	18.43	#
US Males	0.00	0.00	0.40	1.79	3.50	8.43	16.17
US Females	0.00	0.00	0.44	0.99	2.60	6.12	13.46

Katherine Sims et al. Stroke. 2009;40:788-794

Incidence rates of severe clinical events per 1000 patient years while on agalsidase beta: higher risk populations







Ortiz at al for the Fabry Registry, J Med Genet 2016

1. RCT

2. Registry data

3. Meta-analysis

ERT and **hard** outcomes

El Dib R et al. **Cochrane** Database of Syst Rev 2016;7:CD006663

- The long-term influence of ERT on **risk of morbidity and mortality** related to Anderson-Fabry disease remains **to be established**

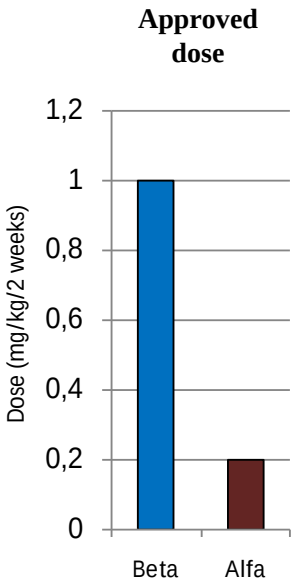
- There is **no evidence** identifying if the alfa or beta form is superior or the optimal dose or frequency of ERT.

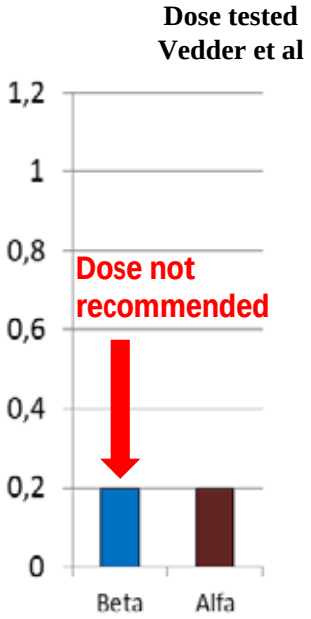
Cochrane Selection criteria:
- Randomized controlled trials
- of agalsidase alfa or beta

a. This is a **rare** disease with 40 year natural history: health authorities requested **Registries**

b. **only 1** completed head-to-head RCT alfa vs beta

Cochrane: only 1 completed head-to-head RCT agalsidase alfa vs agalsidase beta





Vedder CONCLUSION:

Treatment failure occurred

frequently

in **both** groups

Vedder AC et al. PLoS ONE. 2007;2:e598

ERT and **hard** outcomes

Observational studies meta-analysis

CONCLUSIONS: “Agalsidase **beta** is associated to a

significantly lower incidence of renal, cardiovascular and cerebrovascular events **than no ERT**

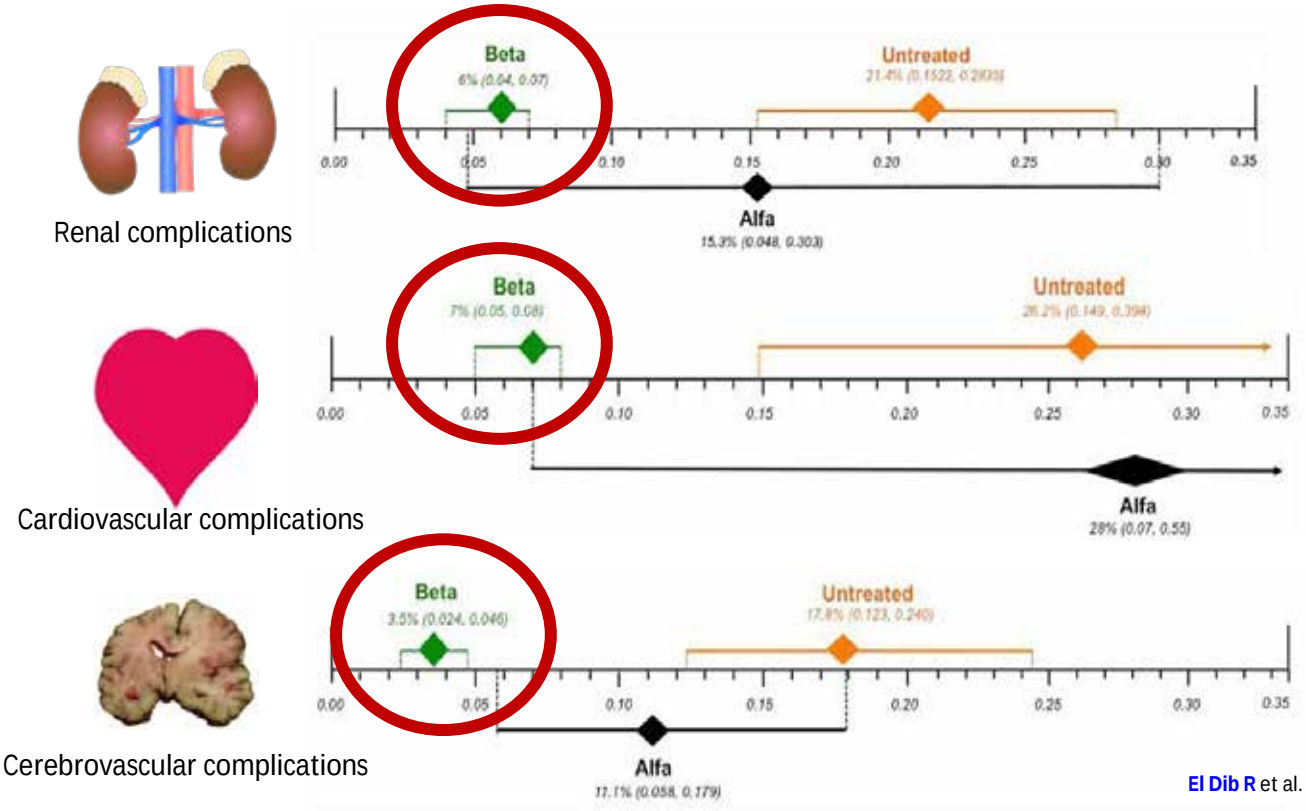
significantly lower incidence of cerebrovascular events **than agalsidase alfa**

El Dib R et al. PLoS One. **2017 Mar 15**;12:e0173358

ERT and hard outcomes: fresh news!

Enzyme replacement therapy for Anderson-Fabry disease: A **complementary** overview of a **Cochrane** publication through a linear regression and a pooled analysis of proportions from **cohort studies**

Comparison of the plotted proportional meta-analysis, according to ERT regimens, for severe complications



El Dib R et al. PLoS One. 2017 Mar 15;12:e0173358

Take home message

How to **treat**? with **optimal dose** to halt progression

- **Podocytes** should be immortal: **published data suggests ERT may clear them in dose-dependent manner**
- Lessons from the **shortage: dose** and preservation of **GFR**
- Long-term **agalsidase beta 1 mg/kg/EOW** results in **a reduction of incidence** of **severe clinical events** (evidence from RCT, the largest Fabry disease Registry study and meta-analysis)

And remember conventional **nephroprotection**!!

3 key concepts

1. Fabry nephropathy is a form of CKD

What is chronic kidney disease?

Criteria for CKD (**either** of the following present for **>3 months**)

1. Markers of **kidney damage** (one or more)

- **Albuminuria (>30 mg**/g creatinine) A c
- Urine sediment abnormalities
- Electrolyte and other abnormalities du
- **Abnormalities detected by histology**
- Structural abnormalities detected by imagin
- History of kidney transplantation

or

Albuminuria **>30** mg/g diagnoses **CKD**

Histology diagnoses **CKD**

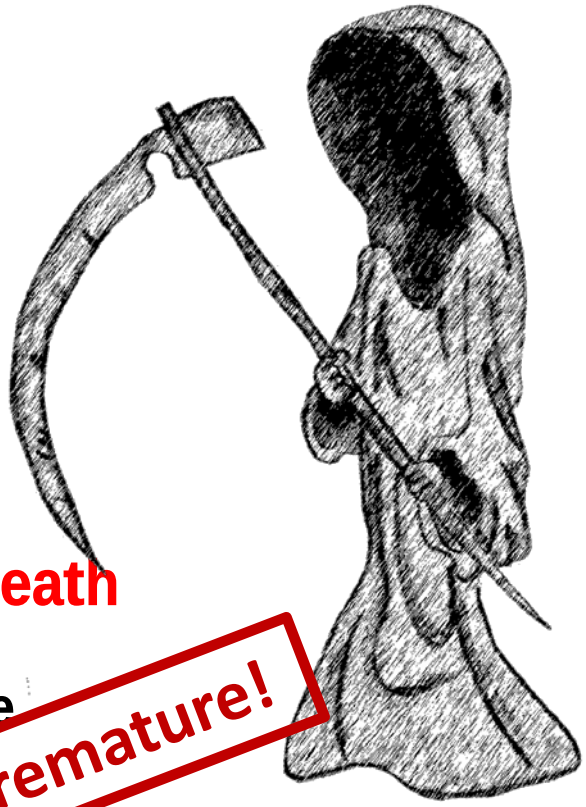
2. Decreased GFR: <60 ml/min/1.73 m^2 (GFR categories G3a–G5)

KDIGO CKD 2012. Kidney Int 2013. CKD, chronic kidney disease; GFR, glomerular filtration rate.

Where do the GFR and albuminuria thresholds come from?

Risk

- For CKD progression



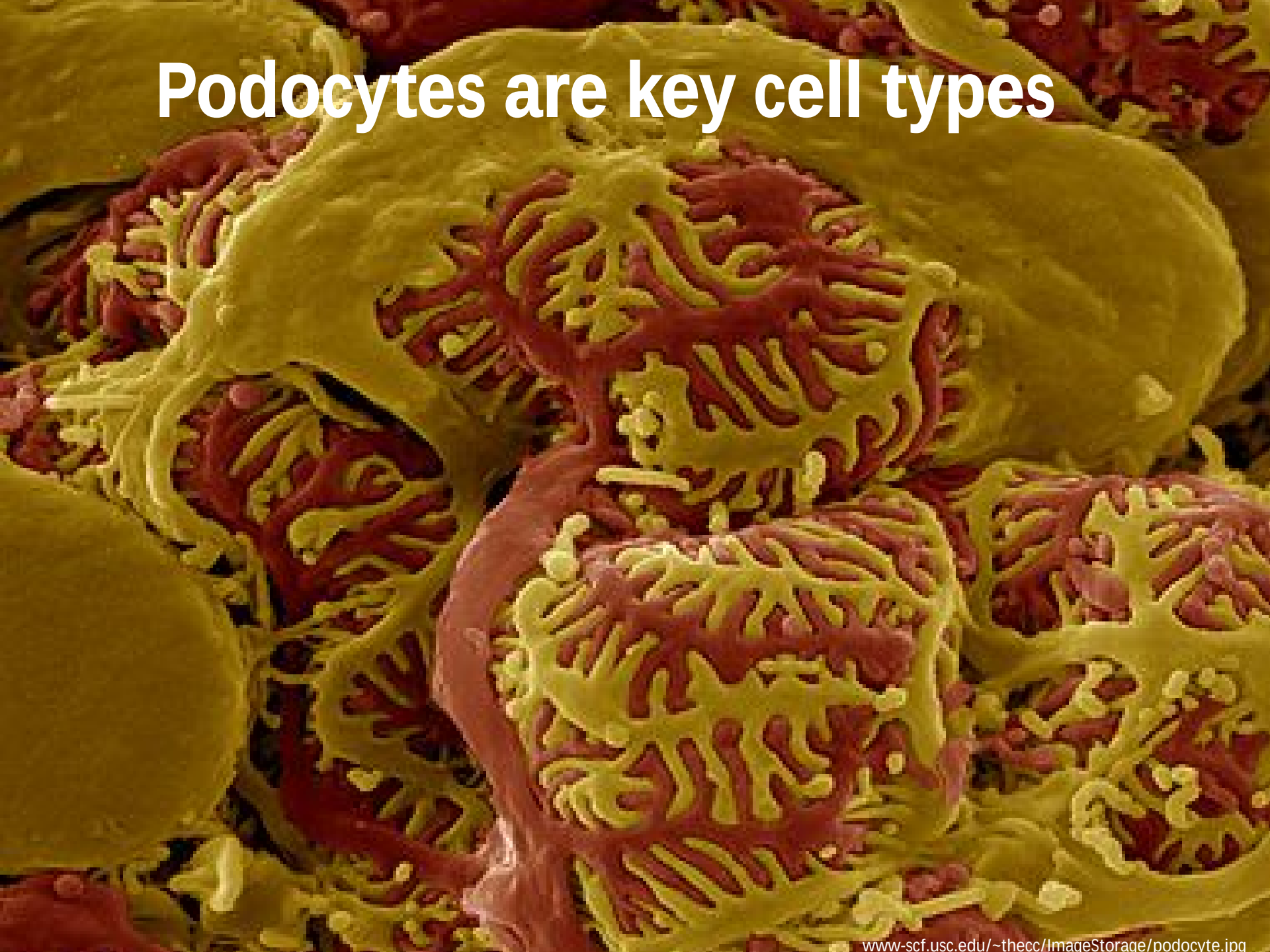
- For all-cause and cardiovascular death
  - Death, the **ultimate outcome**
  - The issue is not if, but when

3 key concepts

1. Fabry nephropathy is a form of CKD

2. Fabry CKD is proteinuric

Podocytes are key cell types



www-scf.usc.edu/~thecc/ImageStorage/podocyte.jpg

Fabry podocytes are fuuuuull of glycolipids

Renal Biopsy Findings in Children and Adolescents With Fabry Disease and Minimal Albuminuria

Camilla Tøndel, MD,[1] Leif Bostad, MD,[2,3] Asle Hirth, MD,[4,5] and Einar Svarstad, MD, PhD[6,7]

Am J Kidney Dis. 2008 May;51(5):767-76

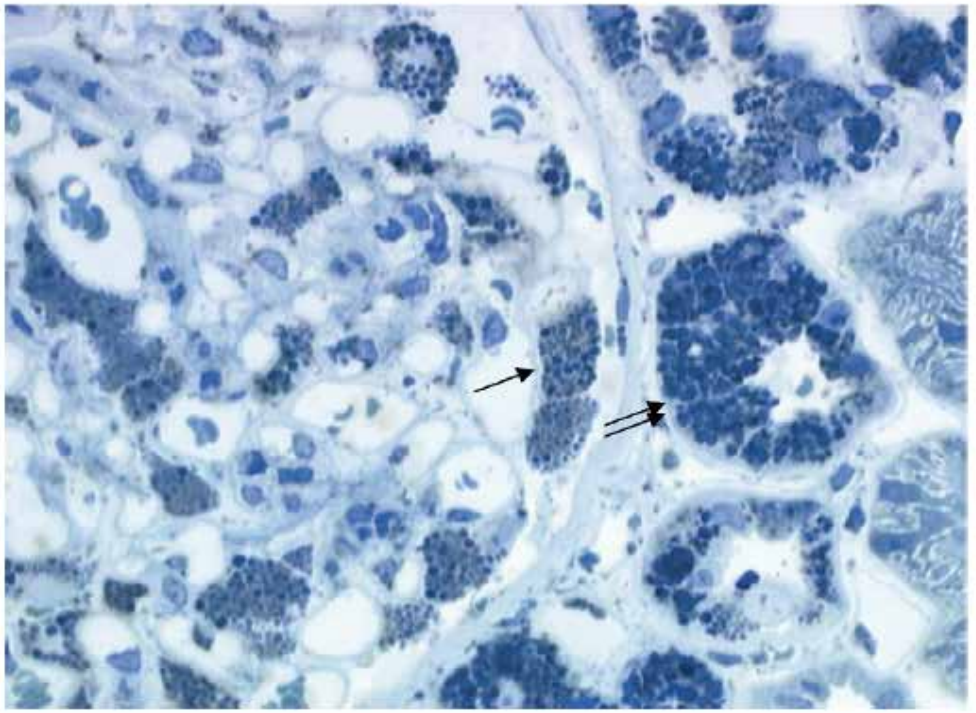
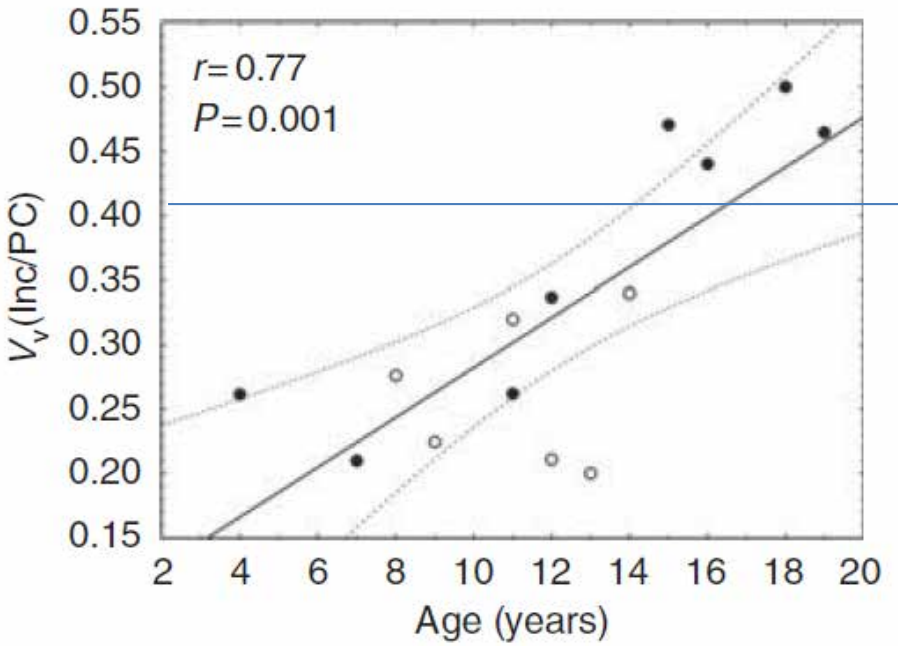


Figure 2. Patient 6. Dark-blue inclusion bodies in podocytes (arrow) and distal tubule epithelial cells (doub
'ound in all our patients who underwent biopsy. (Osmicated toluidine-stained semi-thin section.)

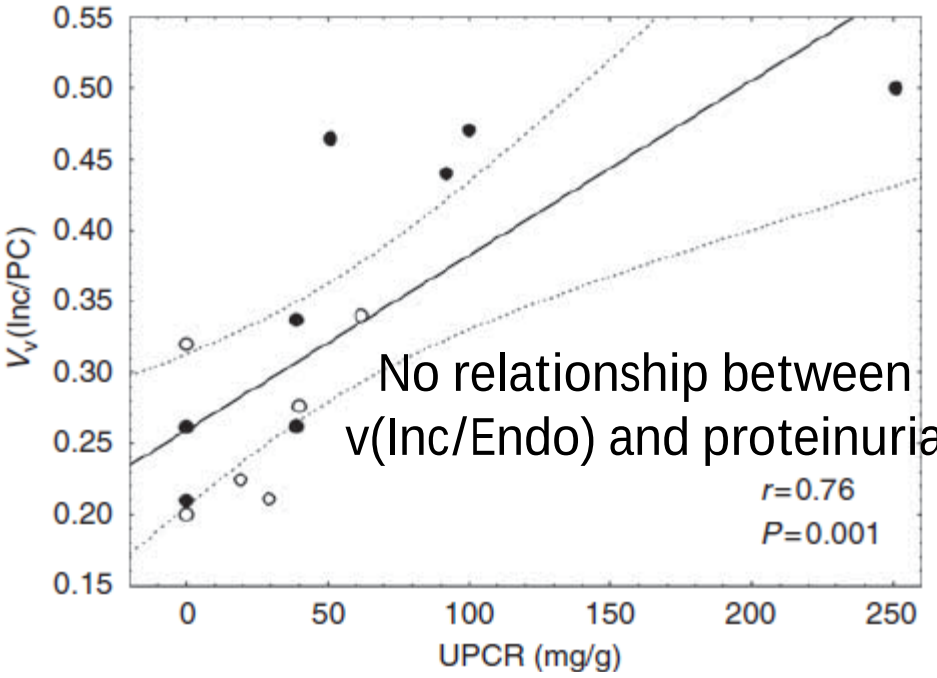
Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease

Behzad Najafian[1], Einar Svarstad[2,3], Leif Bostad[4,5], Marie-Claire Gubler[6], Camilla Tøndel[3,7], Chester Whitley[8] and Michael Mauer[8,9]

Podocyte inclusions vs age



Podocyte inclusions vs proteinuria

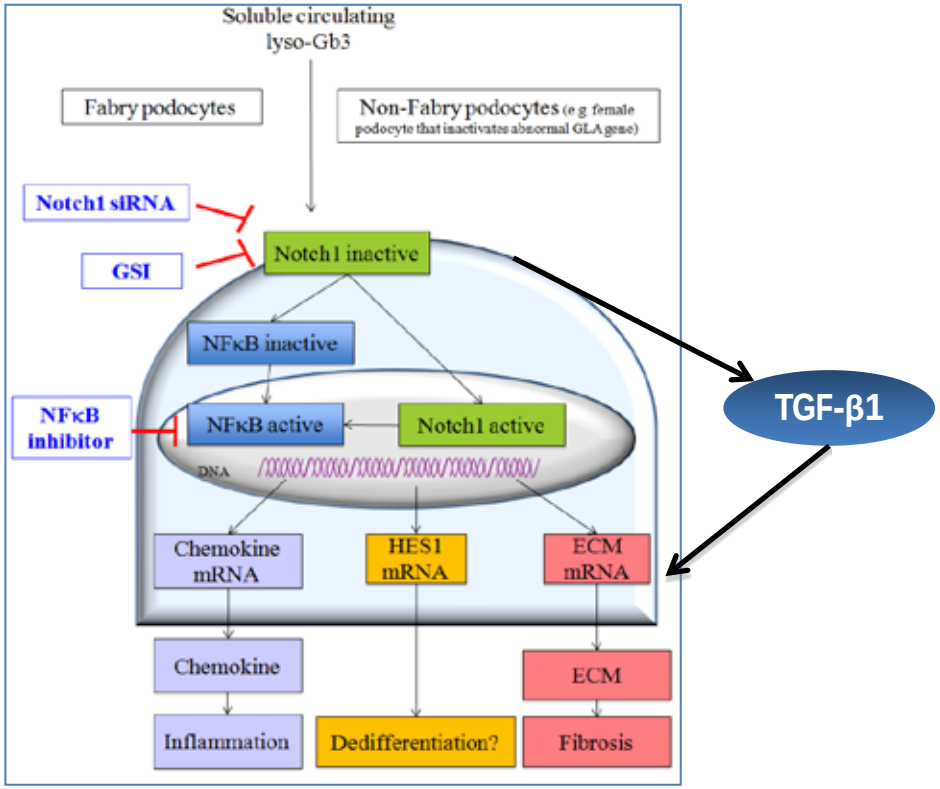


Relationship between age and podocyte (Vv(Inc/PC)), and endothelial cell (Vv(Inc/Endo)) GL-3 fractional volume of inclusions per cytoplasm

Segmental foot process effacement was present in **all glomeruli**

Najafian et al. Kidney International
Volume 79, Issue 6, 2 March 2011, Pages 663–670

Lyso-Gb3 Promotes Podocyte Stress



TGF-β1

Effect of lyso-Gb3 on Fabry nephropathy[1,2]

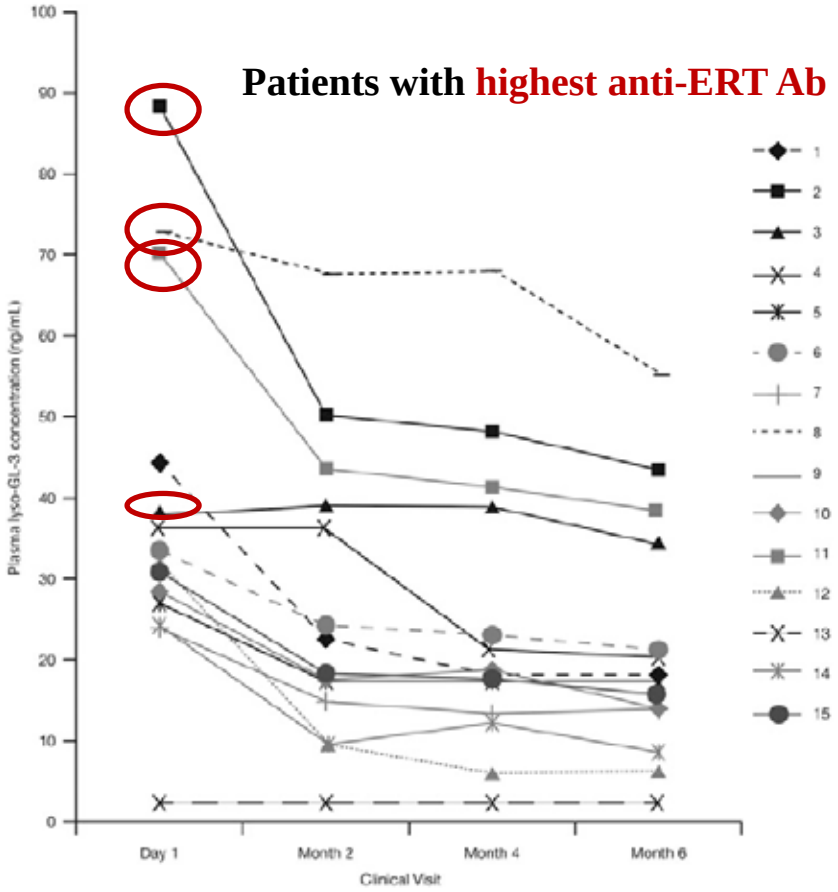
TGF-β1, transforming growth factor beta 1.

100 nM lyso-Gb3

1. Sanchez-Niño MD, et al. Nephrol Dial Transplant. 2011;26:1797-802.
2. Sanchez-Niño MD, et al. Human Mol Genet. 2015;24:5720-32.

Monitoring

Plasma lyso-Gb3 decreased when ERT switched from agalsidase alfa 0.2 mg/kg/EOW to agalsidase beta 1.0 mg/kg/EOW



Goker-Alpan, et al. Reduction of Plasma Globotriaosylsphingosine Levels After Switching from Agalsidase Alfa to Agalsidase Beta as Enzyme Replacement Therapy for Fabry Disease. *JIMD Rep*. 2016;25:95-106.

3 key concepts

1. Fabry nephropathy is a form of CKD

2. Fabry CKD is proteinuric

3. Fabry CKD is progressive

of proper monitoring and goal setting in Fabry patients' management. Pending on whether at that moment you could disclose the upcoming Therapeutic Goals for Fabry disease or not, this would be an excellent addition to your lecture