Società Medico Chirurgica di Ferrara dal 1846

La terapia emodialitica sostitutiva: l'esperienza consolidata

Yuri Battaglia, Phd

UOC di Nefrologia e Dialisi

AOU Sant'Anna

Therapy of Fabry disease

Specific Therapy

Support Therapy

Therapy of Fabry disease

Specific Therapy

Specific Therapy of Fabry disease

For all

nzyme Replacement Therapy (ERT): Agalsidase alfa

Agalsidase beta

econd generation ERT: Pegunigalsidase alfa (PRX-102)

ubstrate Reduction Therapy (SRT): Lucerastat, Venglustat

ene therapy

For some

haperones: Migalatat

Specific Therapy of Fabry disease

For all

nzyme Replacement Therapy (ERT): Agalsidase alfa

Agalsidase beta

ERT for Fabry Disease: Characteristics of Drug

	Agalsidase alfa (Replagal®)	Agalsidase beta (Fabrazyme®)
of production	Gene activated human α-GalA expressed in a continuous human cell line	Recombinant human α-GalA expressed in a continuous CHO line
ture	Homodimer consisting of two ~50kDa subunits. Aa sequence is identical to the endogenous human enzyme	Homodimer consisting of two ~50kDa subunits. Aa sequence is identical to the endogenous human enzyme
acid:galactose	0.56	0.88
ose-6-phosphate	1.8 ± 0.0 mol/mol protein	3.1 ± 0.1 mol/mol protein
ific activity	3.4 - 3.9 nmol/kg/h	3.8 nmol/kg/h
ded as	Sterile isotonic solution	Lyophilised powder
mmended dose	0.2 mg/kg bw	1 mg/kg bw

ERT: Characteristics of Drugs (2001)

	Agalsidase-α	Agalsidase-β
ure	Human recombinant protein	Human recombinant protein
ained from ilability	Human fibrosarcoma cells Worldwide, excluding USA	CHO cells Worldwide, including USA
ses tested in phase 1 ls	0.007; 0.014; 0.028; 0.056; 0.1 mg/kg (single dose)	0.1; 1.0; 3.0 mg/kg/2 weeks (5 consecutive doses)
se tested in pivotal cebo controlled trials	0.2 mg/kg/2 weeks	1.0 mg/kg/2 weeks

REPLAGAL®
agalsidase alfa

Fabrazyme®
agalsidase beta

Shiffmann et al, Kidney Inter

ERT: Dose

ients with Fabry Disease after Enzyme Replacement

ients with Fabry Disease after Enzyme
lacement Therapy Dose Reduction and

y disease under enzyme replacement therapy – new insights in efficacy of rent dosages

nnes Krämer[1,2§], Malte Lenders[3§], Sima Canaan-Kühl[4], Peter Nordbeck[1], Nurcan er[1,5], Daniela Blaschke[6], Thomas Duning[7], Stefanie Reiermann[3], Jörg ann[8], Stefan-Martin Brand[9], Timo Gottschling[10], Stefan Störk[1], Christoph er[1], Claudia Sommer[1,5], Eva Brand[3*] and Frank Weidemann[1,10*]

ntributed equally

rol Dial Transplant 2017 in minor revision

yme replacement therapy for Anderson-Fabry disease iew)

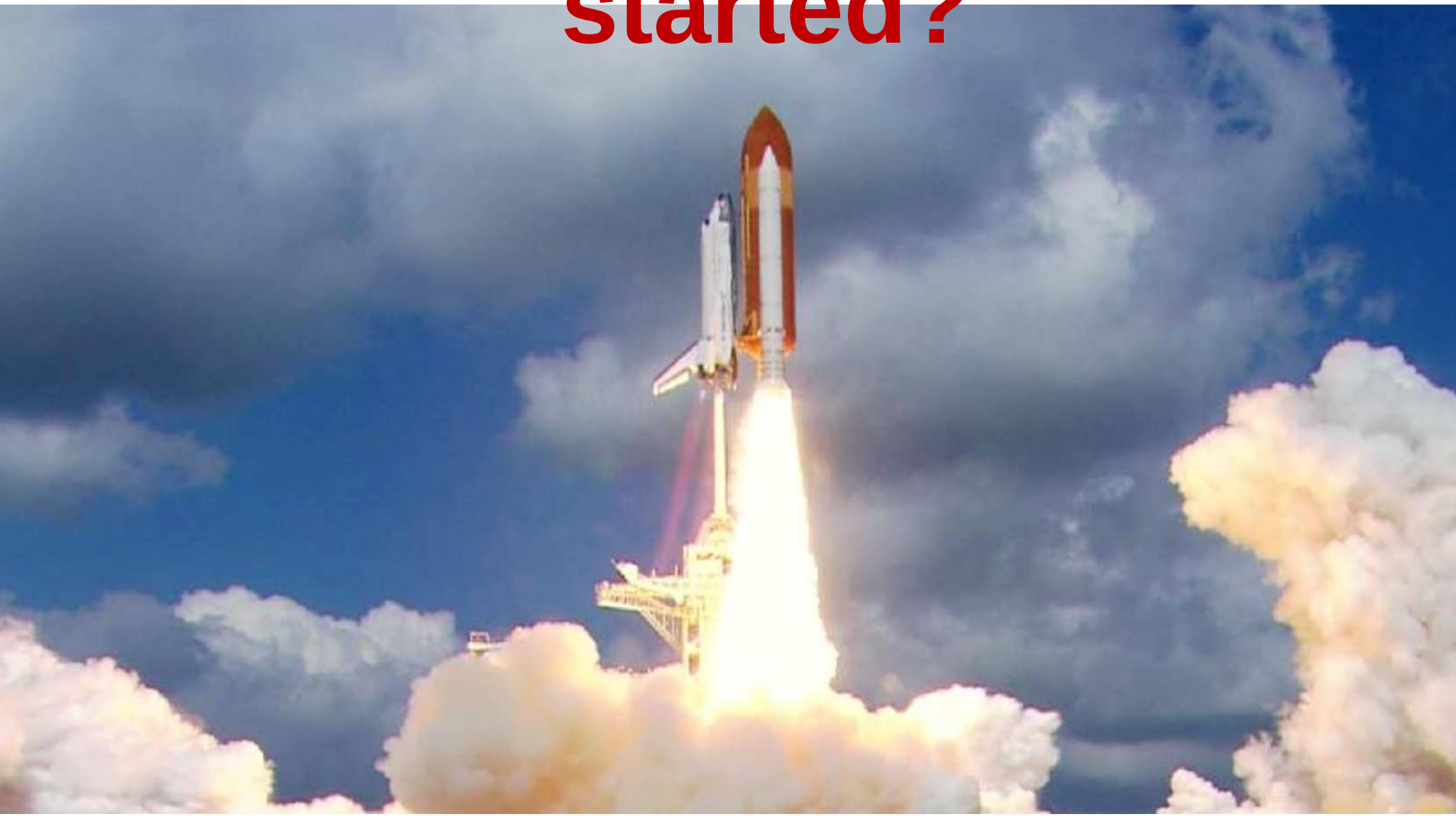
Cochrane Library
Cochrane Database of Systematic

R, Gomaa H, Carvalho RP, Camargo SE, Bazan R, Barretti P, Barreto FC

n pain-related quality of life. There is, however, no evidence iden-
ifying if the alfa or beta form is superior or the optimal dose or
requency of ERT. It is always difficult to study rare diseases, given
he limited population available to study and given that many of
hese disorders, such a AFD, are long-term, chronic illnesses and
long follow up is required. With regards to safety, adverse events

El Dib et al, 2

When should therapy be started?



abry Disease guidelines – Eng et al. Genet Med 2006

ecommendation and guidelines for diagnosis and treatment of Fabry nephropaty i

dults – Ortiz et al. Nature Clin Pract Nephrol 2008

tandard Operating procedure - Great Britain 2012

WMF Guidline, Germany 2013

uropean Renal Best Practise Guideline on Fabry Nephropathy - Terryn et al. NDT 2

n nefropatia in corso di malattia di Anderson-Fabry: nuove raccomandazioni sulla

agnosi, il follow-up e la terapia - Mignani et al. 2015

anadian Fabry Disease Treatment Guidelines - 2016

ry disease: Guidelines for the evaluation and nagement of multi-organ system involvement

e M. Eng, MD[1], Dominique P. Germain, MD[2], Maryam Banikazemi, MD[3], David G. Warnock, MD[4], h Wanner, MD[5], Robert J. Hopkin, MD[6], Jan Bultas, MD[7], Philip Lee, MD[8], Katherine Sims, MD[9], Brodie, MD[3], Gregory M. Pastores, MD[10], Joerg M. Strotmann, MD[5], and William R. Wilcox, MD, PhD[11]

Current guidelines for instituting enzyme replacement therapy in Fabry disease patients

Fabry Population	Guideline for Instituting ERT
Adult males (>16 y)	At time of diagnosis of Fabry disease
Pediatric males	At time of development of significant symptoms[a] or If asymptomatic, consider at 10–13 yr
Females (all ages)	Monitor; institute if significant symptoms[a] or evidence of progression of organ involvement

Eng et al, Genet Med

aaten *et al. Orphanet Journal of Rare Diseases* (2015) 10:36
1186/s13023-015-0253-6

ORPHANET JOURN
OF RARE DISEASES

SEARCH Open Acce

commendations for initiation and cessation of zyme replacement therapy in patients with bry disease: the European Fabry Working oup consensus document

ke Biegstraaten[1*], Reynir Arngrímsson[2], Frederic Barbey[3], Lut Boks[4], Franco Cecchi[5], Patrick B Deegan[6], eldt-Rasmussen[7], Tarekegn Geberhiwot[8], Dominique P Germain[9], Chris Hendriksz[10], Derralynn A Hughes[11], Kantola[12], Nesrin Karabul[13], Christine Lavery[4], Gabor E Linthorst[1], Atul Mehta[11], Erica van de Mheen[14], P Oliveira[15], Rossella Parini[16], Uma Ramaswami[17], Michael Rudnicki[18], Andreas Serra[19], Claudia Sommer[20], Sunder-Plassmann[21], Einar Svarstad[22], Annelies Sweeb[14], Wim Terryn[23], Anna Tylki-Szymanska[24], la Tøndel[25], Bojan Vujkovac[26], Frank Weidemann[27], Frits A Wijburg[28], Peter Woolfson[29] and Carla EM Holla

	No signs or symptoms	Renal*	Cardiac*	CNS*	Pain*	GI*
cal s	if ≥ 16 years of age (Class IIB)	- microalbuminuria† (Class I)	- cardiac hypertrophy (MWT > 12 mm) without (or only minimal signs of) fibrosis (Class I)	- WMLs (Class IIB)	- neuropathic pain (Class IIA)	GI sympt (Class IIA 16 years age, Clas if > 16 ye age)
		- proteinuria† (Class I)		- TIA/stroke (Class IIA)		
		- renal insufficiency (GFR 60–90)# (Class I)	- signs of cardiac rhythm disturbances$ (Class I)	- hearing loss, corrected for age (Class IIB)	- neuropathic pain even if completely controlled (not interfering with daily activities) with pain medication (Class IIB)	
		- renal insufficiency (GFR 45–60)# (Class IIB)				

	No signs or symptoms	Renal*	Cardiac*	CNS*	Pain*	GI*
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nefropatia in corso di malattia di derson-Fabry: nuove raccomandazioni sulla gnosi, il follow up e la terapia

Mignani[1], Maurizio Gallieni[2], Sandro Feriozzi[3], Antonio Pisani[4], Nicola Marziliano[5], Amelia Morrone[6]

NG DELLA TERAPIA ENZIMATICA SOSTITUTIVA NEL PAZIENTE NEFROPATICO

ziare agalsidasi α alla dose standard di 0.2 mg/kg ogni 2 settimane o agalsidasi β alla dose standard di 1 mg/kg ogni 2 settimane na fatta diagnosi clinica o istologica di nefropatia in entrambi i sessi

onostante non ci siano al momento evidenze robuste di efficacia, nel paziente con proteinuria >1 g/die o con insufficienza renale ca o in dialisi/trapianto, si può considerare l'introduzione o il mantenimento della terapia enzimatica sostitutiva alle dosi standard igliate per la prevenzione del danno d'organo cardiaco o cerebro-vascolare

Mignani et al, G Ital Nefrol 2015

y nephropathy: indications for screening and guidance for nosis and treatment by the European Renal Best Practice

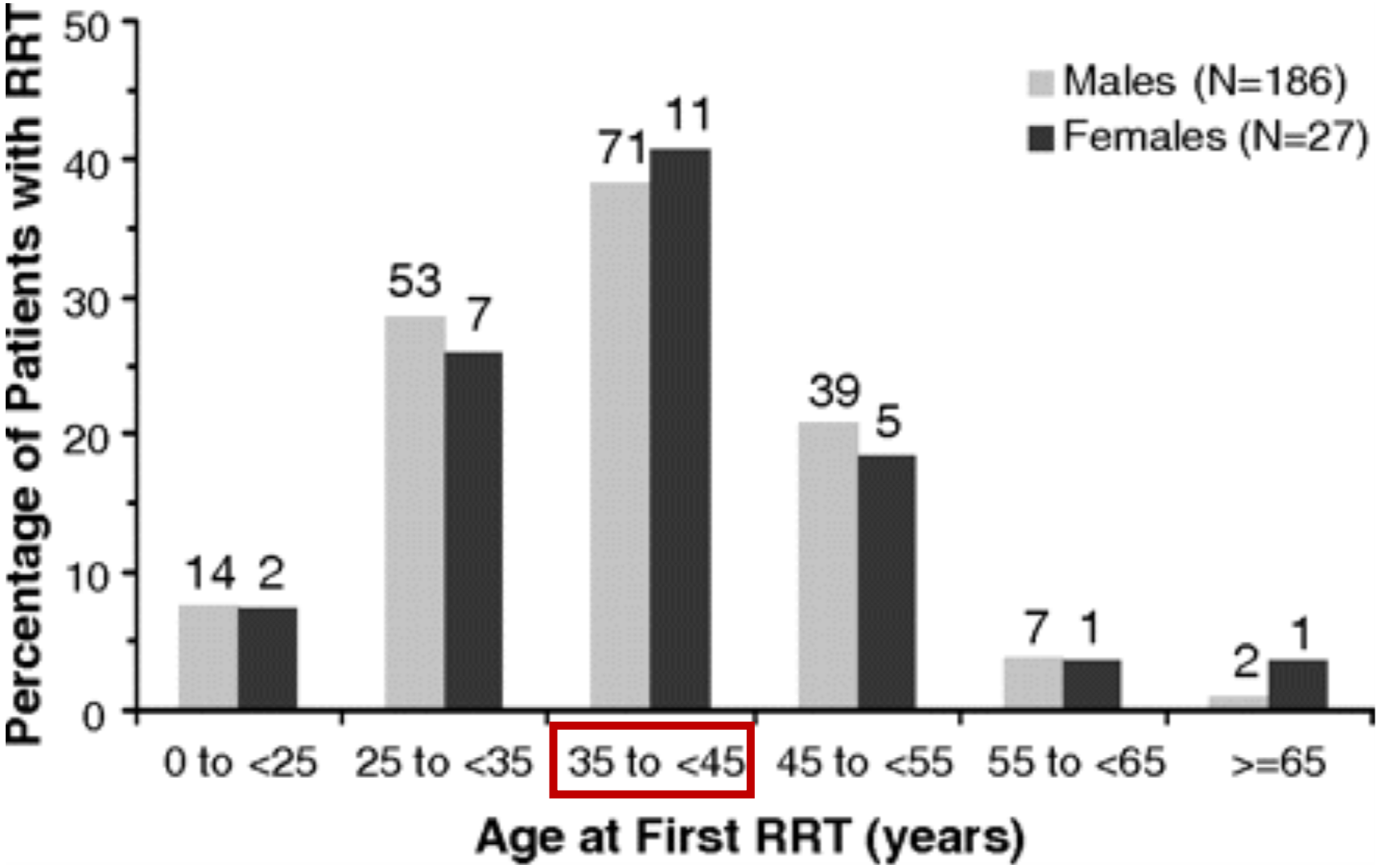
4.3 In a patient on haemodialysis, and when ERT is deemed indicated, we recommend administering the ERT during a haemodialysis session. (1A)

4.4 We recommend kidney transplantation as a valuable option in patients who are eligible for this intervention. (Ungraded statement)

4.5 After renal transplantation, we do not suggest ERT for renal indications, but it can be continued for non-renal indications. (Ungraded statement)

Terryn, Nephrol Dial Transplant. 2

Age at first renal replacement therapy



Ortiz, Nephrol Dial Transplant. 2

Criteria to stop or not start ERT

riteria	Class of recommend
mpliance > 50% of infusions	Class I
to attend regularly (according to local guidelines) at FU visits	Class I
ent life threatening or severe infusion reactions that do not respond to prophylaxis, e.g. anaphylaxis	Class I
request	Class I
age renal disease, without an option for renal transplantation, in combination with advanced heart failure class IV)	Class IIA
age FD or other comorbidities with a life expectancy of < 1 year	Class IIB
cognitive decline of any cause	Class IIB
response for 1 year when the sole indication for ERT is neuropathic pain while receiving maximum tive care*	Class IIB
a for not starting ERT	**Class of recommend**
ced cardiac disease with extensive fibrosis [37] if cardiac disease is the sole treatment indication†	Class I
age renal disease, without an option for renal transplantation, in combination with advanced heart failure class IV)	Class IIA
age FD or other comorbidities with a life expectancy of < 1 year	Class IIB
cognitive decline of any cause	Class IIB

Biegstraaten *et al. Orphanet Journal of Rare Diseases* (201

eening, diagnosis, and management of patients h Fabry disease: conclusions from a "Kidney ease: Improving Global Outcomes" (KDIGO) ntroversies Conference

ael Schiffmann[1], Derralynn A. Hughes[2], Gabor E. Linthorst[3], Alberto Ortiz[4], Einar Svarstad[5,6], l G. Warnock[7], Michael L. West[8] and Christoph Wanner[9]; for Conference Participants[10]

te of Metabolic Disease, Baylor Research Institute, Dallas, Texas, USA; [2]Department of Haematology, Royal Free London NH ation Trust, & University College London, UK; [3]Department of Endocrinology and Metabolism, Academic Medical Center, dam, Netherlands; [4]Unidad de Dialisis, IIS-Fundacion Jimenez Diaz/UAM, IRSIN, Madrid, Spain; [5]Department of Clinical Medi ity of Bergen, Bergen, Norway; [6]Department of Medicine, Haukeland University Hospital, Bergen, Norway; [7]Division of Nephrol ment of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA; [8]Department of Medicine, Dalhousie ity, Halifax, Canada; and [9]Department of Medicine, Division of Nephrology, University Hospital of Würzburg, Würzburg, Germ

Limits

o scientific evidence as to the optimal age of ERT initiation.

o uniform guidelines, and conditions and age to start ERT differ in variou

ountries.

evelopment of signs or symptoms related to FD is an indication to start E

ne benefits of early treatment, before irreversible tissue injury occurs,

hould be balanced against the burden of biweekly infusions in very young

dividuals.

ack of agreement on cessation criteria.

Kidney International (2017) **91,** 284

Knowledge gaps and research recommendations

Determine when to start treatment in asymptomatic or pauci-

ymptomatic patients, females, with non-classic disease

Obtain expanded information on the natural history of FD in classi

emale patients and non-classic FD patients, and the effects of ERT

hese groups

stablish criteria and biomarkers for dose individualization

nefropatia in corso di malattia di derson-Fabry: nuove raccomandazioni sulla gnosi, il follow up e la terapia

Mignani[1], Maurizio Gallieni[2], Sandro Feriozzi[3], Antonio Pisani[4], Nicola Marziliano[5], Amelia Morrone[6]

SSIBILE CONSIDERARE UN EVENTUALE AUMENTO DELLA POSOLOGIA DELL'AGALSIDASI, NEL RISPETTO DELLE DEI FARMACI

so di peggioramento della funzione renale (riduzione di e-GFR > 3 mL/min/anno)

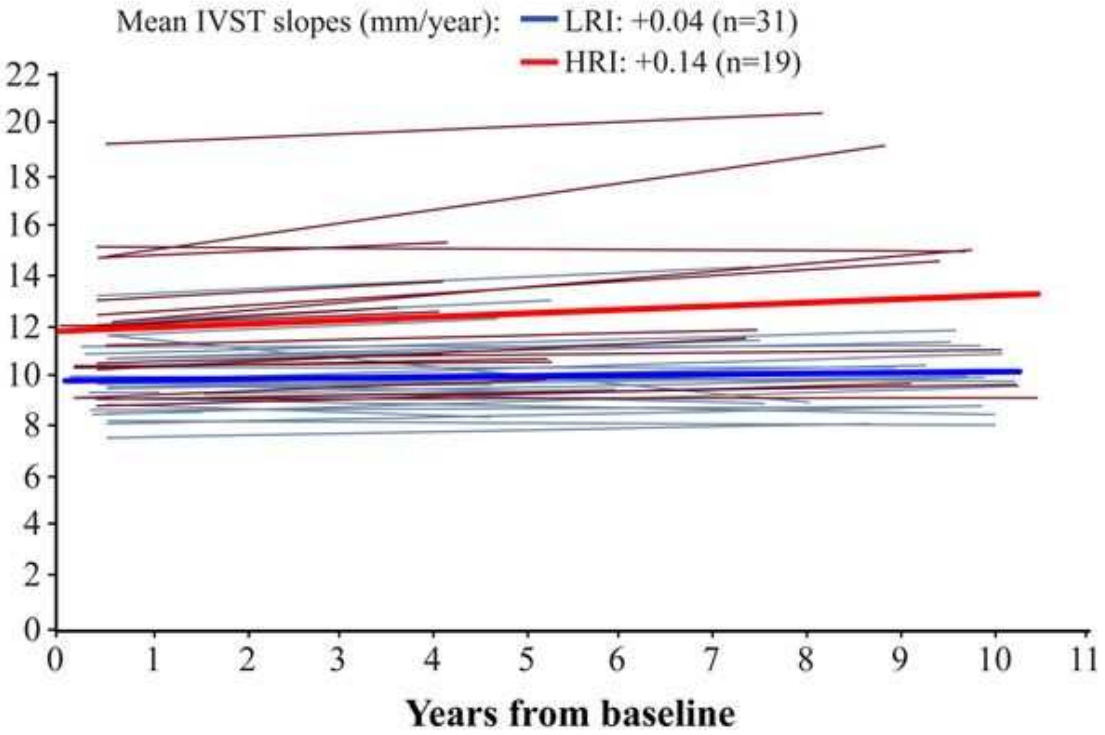
so di ripresa della sintomatologia soggettiva (NON RENALE)

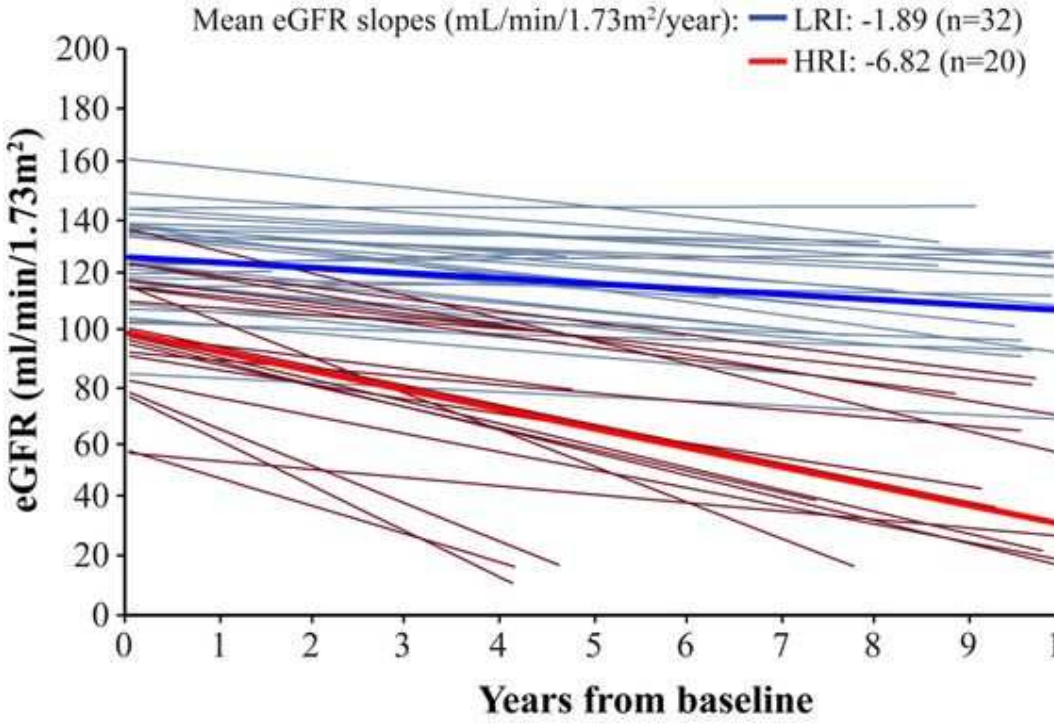
Mignani et al, G Ital Nefrol 2

L ARTICLE

ear outcome of enzyme replacement therapy agalsidase beta in patients with Fabry disease

ue P Germain,[1] Joel Charrow,[2] Robert J Desnick,[3] Nathalie Guffon,[4] mpf,[5] Robin H Lachmann,[6] Roberta Lemay,[5] Gabor E Linthorst,[7] Packman,[8] C Ronald Scott,[9] Stephen Waldek,[10] David G Warnock,[11] Veinreb,[12] William R Wilcox[13]





Dominique P Germain et al. J Med Genet 2015;52:353

ry STabilization indEX (FASTEX): an innovative tool he assessment of clinical stabilization in Fabry ase

ckj OXFORD
Leading European

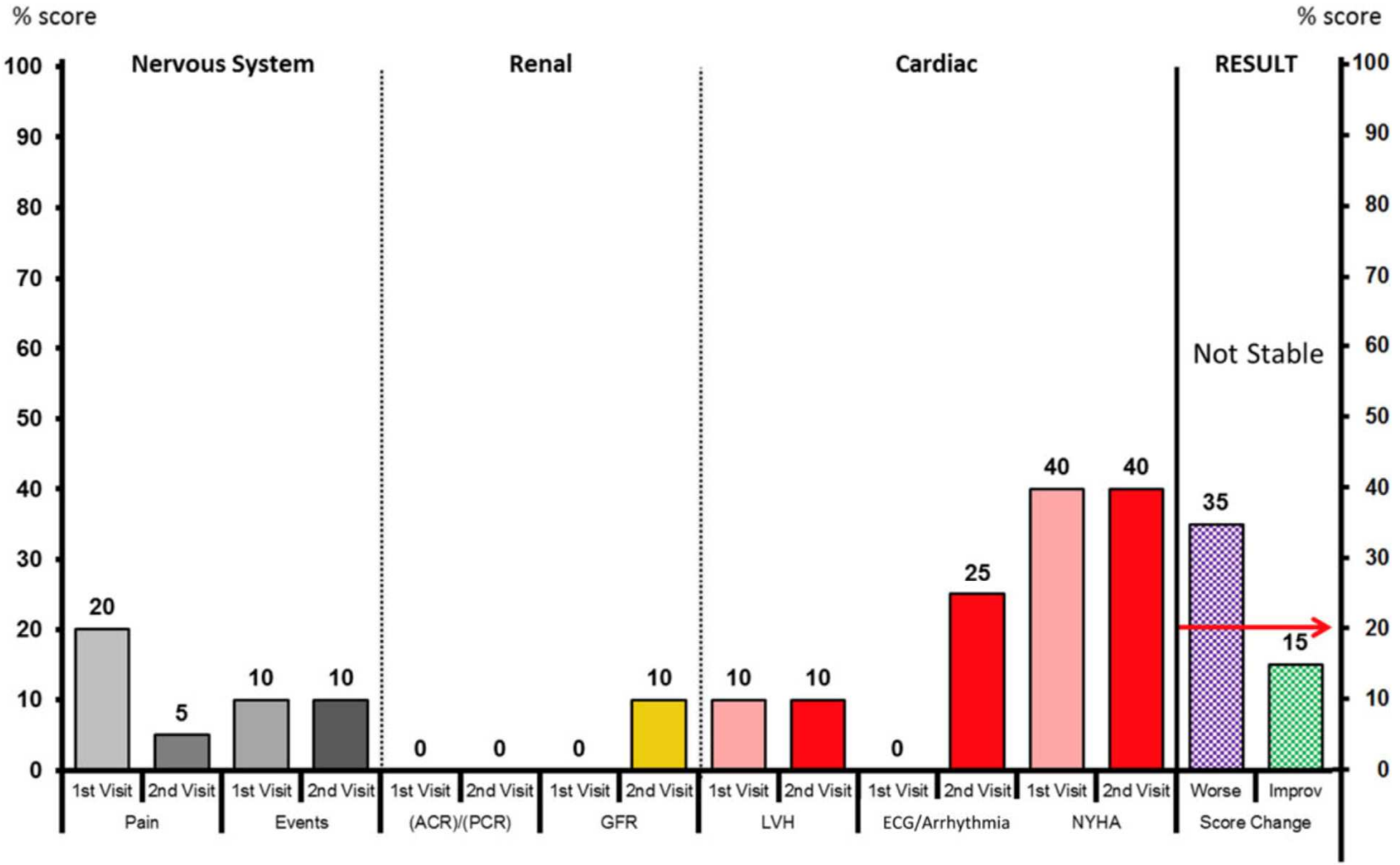
Nervous system score			
Score	Pain	Score	Events
0	None	0	None
1	Mild without treatment	1	Hyperintensity of white matter
2	Moderate without treatment	2	TIA
3	Present and controlled with therapy	3	ischaemic or haemorrhagic
4	Present and not controlled with therapy	4	Recurrent TIA or stroke

Renal system score			
Score	Albuminuria (ACR)/proteinuria (PCR)	Score	eGFR
0	ACR <22 mg/g (or <2.5 mg/mmol)	0	<135 mL/min >90 mL/min
1	ACR 22–299 mg/g (or 2.5–29 g/mmol)	1	>135 mL/min (Hyper filtration)
2	PCR >300 ≤ 499 mg/g	2	<90–≥60 mL/min
3	PCR >500 ≤ 799 mg/g	3	≤59–≥30 mL/min
4	PCR >800 mg/g	4	≤29 mL/min

Cardiac system score					
Score	LVH	Score	ECG/arrhythmia	Score	NYHA
0	No LVH	0	None	0	
1	Diastolic dysfunction	1	Short PQ, ST alteration	1	I
2	Mild LVH (11.5–13.5 mm)	2	LVH on ECG	2	II
3	Moderate LVH (>13.5–15 mm) or Fibrosis MRI	3	AVB, PSVT, AF, NSVT, bradycardia	3	III
4	Severe LVH (>15 mm)	4	PM, ICD	4	IV

Mignani et al, Clin Kid Journal 2

ry STabilization indEX (FASTEX): an innovative tool he assessment of clinical stabilization in Fabry ase



Mignani et al, Clin Kid Journal 2

Knowledge gaps and research recommendations

Therapeutic regimens

tablish criteria and biomarkers for dose individualization

aluate combination therapy: substrate synthesis reduction

mbined with ERT or with a pharmacological chaperone

Kidney International (2017) **91,** 284

nefropatia in corso di malattia di derson-Fabry: nuove raccomandazioni sulla gnosi, il follow up e la terapia

Mignani[1], Maurizio Gallieni[2], Sandro Feriozzi[3], Antonio Pisani[4], Nicola Marziliano[5], Amelia Morrone[6]

NDO UNA FORMULAZIONE DI AGALSIDASI PUÒ ESSERE CONVERTITA CON L'ALTRA

esenza di intolleranza ad una delle due formulazioni nonostante un'adeguata premedicazione e la riduzione della velocità di infu
e del farmaco

so di reazione allergica ad una delle due formulazioni considerando la possibilità di una cross-reazione e praticando comunque
adeguata premedicazione

esenza di una ripresa della sintomatologia soggettiva non renale, in particolare di dolore neuropatico

Mignani et al, G Ital Nefrol 2

Therapy of Fabry disease

Support Therapy

Support Therapy of Fabry disease

Cardiac and cerebrovascular disease (Ace-i, Anrticoagulation, antiplatelet agents, etc)

Pulmonary disease

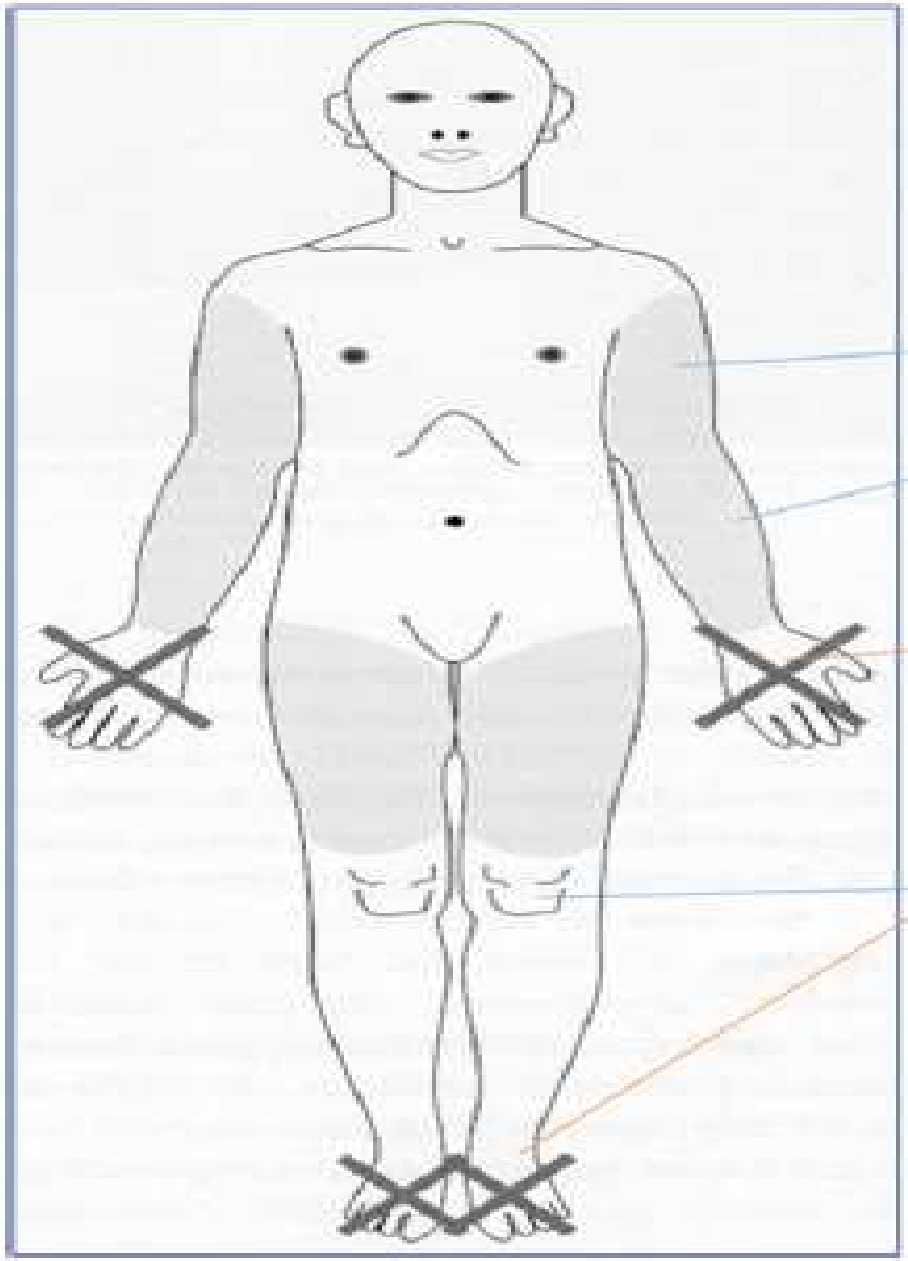
Neuropathic pain (chronic pain and pain crisis)

Renal disease

Support Therapy of Fabry disease

Neuropathic pain (chronic pain and pain crisis)

Neuropathic pain



J.M. Politei et

Adjuncitive therapy for chronic pain

Agent	Dose range	Cardiac restrictions	Renal restrictions
Carbamazepine [115,116]	250–800 mg/d	May interfere with activity of other drugs (e.g., warfarin)	None
Gabapentin[117]	Slowly titrated from 100 to a max of 2400 mg/d	None	Caution with chronic kidney disease
Phenytoin[118]	300 mg/d	None	None
Pregabalin[89]	75–300 mg/d	None	Caution with chronic kidney disease
Tricyclic antidepressants [119]	25–150 mg/d	Arrhythmias	None
Duloxetine[120]	60–120 mg /d	None	None

Kidney International (2017) **91,** 284

Adjuncitive therapy for pain crisis

Agent	Dose range	Experience in Fabry disease and side effects	Cardiac and renal restrictions
IV lidocaine[12 1]	2–5 mg/kg	Good clinical response	Arrhythmias, no renal restrictions
Tramadol[1 22]	100–400 mg/d	Caution with concomitant use of SSRIs, SNRIs, or TCAs	Caution with chronic kidney disease and epilepsy
Morphine[1 22]	Titration of 30–120 mg every 12 h	Monitor for addiction; constipation	None
Oxycodone [91]	Titration of 20–60 mg every 12 h	Monitor for addiction; constipation	None
Diclofenac [91]	50–150 mg/d	Risk of GI bleeding	Caution with chronic kidney disease

Kidney International (2017) **91,** 284

Support Therapy of Fabry disease

Renal disease

ntiproteinuric therapy and Fabry nephropathy: ctors associated with preserved kidney function uring agalsidase-beta therapy

vid G Warnock,[1] Christie P Thomas,[2] Bojan Vujkovac,[3] Ruth C Campbell,[4] l Charrow,[5] Dawn A Laney,[6] Leslie L Jackson,[1] William R Wilcox,[6] istoph Wanner[7]

J Med Genet 2015;**52**:860–866. doi:10.1136/jmedgenet-2015-1

ntiproteinuric effect of add-on paricalcitol in Fabry sease patients: a prospective observational study

tonio Pisani[1], Massimo Sabbatini[1], Giovanni Duro[2], Paolo Colomba[2] and Eleonora Riccio[1]

hrology, Department of Public Health, University Federico II, Naples, Italy and [2]Institute of Biomedicine and Molecular Immunology MONROY", National Research Council, Palermo, Italy

Nephrol Dial Transplant (2015) 30: 661–6

Take Home Messages

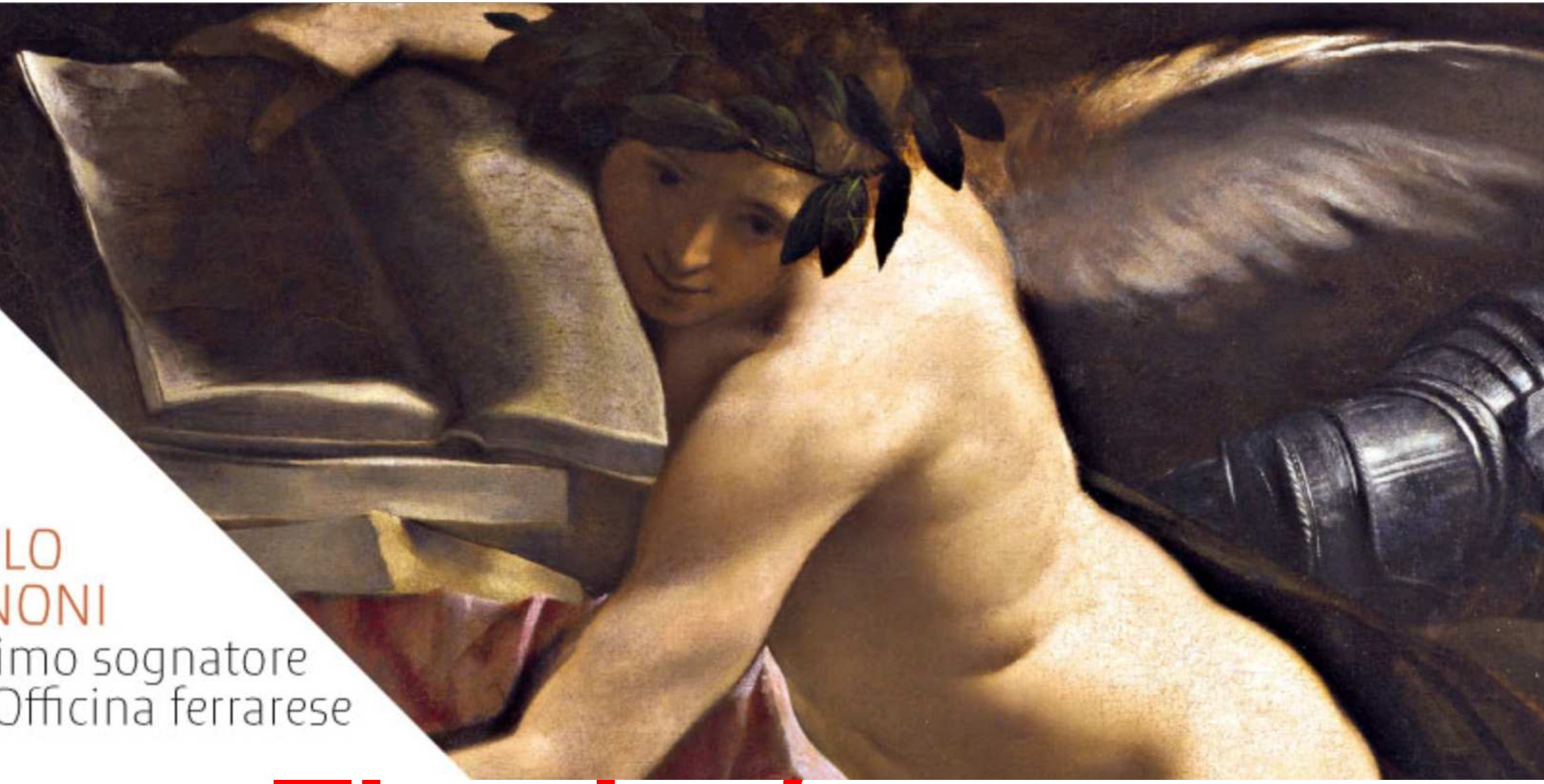
Guidelines are very useful in summarizing current knowledge

on Fabry disease therapy

There are differences in recommendations of therapy initiation

Study comparing both ERT formulations are still underpowered

There are a variety of research questions on Fabry disease



Thanks for your attention