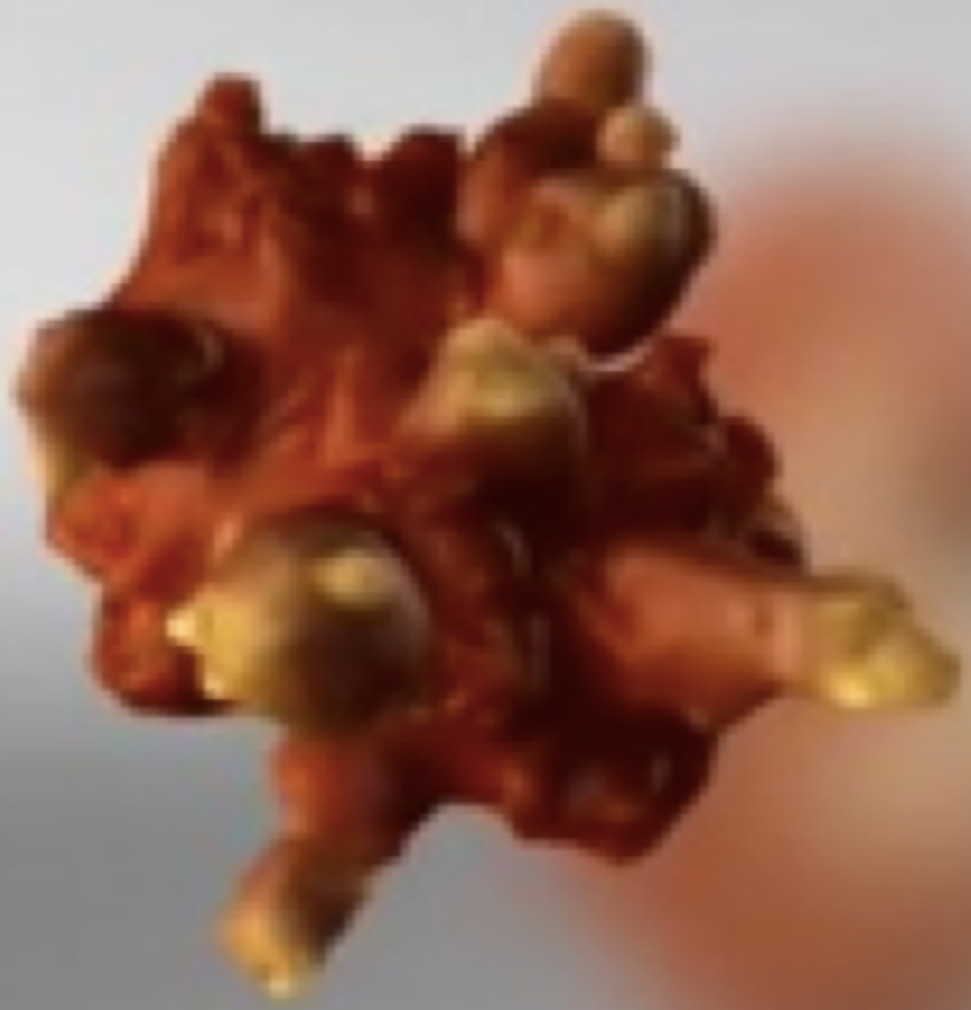
Primary Hyperoxaluria: more than a stone disease



European Reference Network
for rare or low prevalence complex diseases
Network Kidney Diseases (ERKNet)

Jaap Groothoff
Paediatric Nephrologist
Academic Medical Centre
Amsterdam, Netherlands

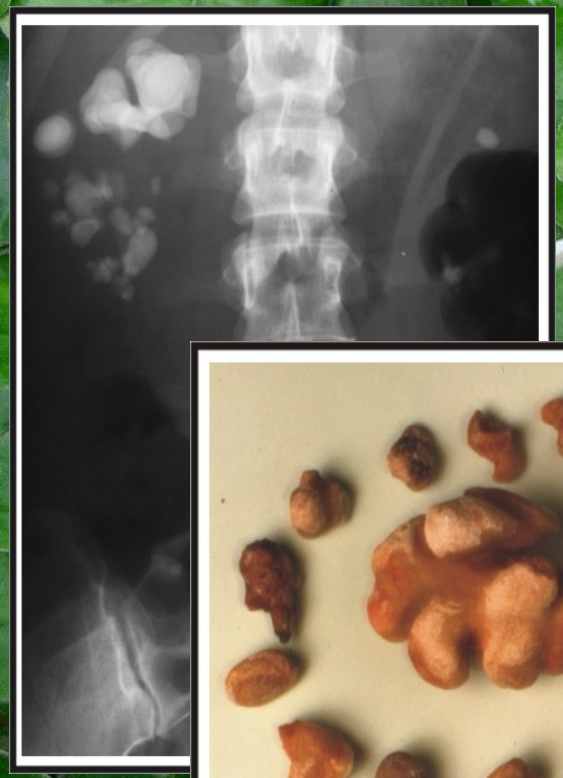
disclosure

- Grants from Alnylam and Dicerna for stable isotope studies

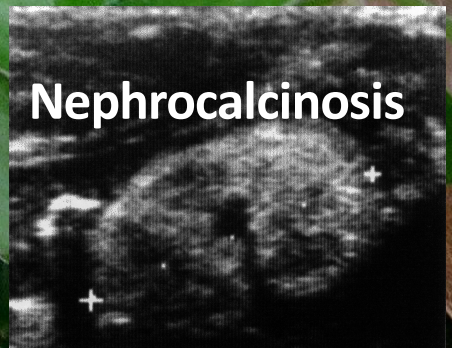
Oxalate: dianion that easily precipitates with Ca^{2+}

Source:

- **wood sorrel (oxalis)**
- Rhubarb
- Spinach
- Chocolate
- Nuts
- Beets
- Buck wheat
- Black pepper
- Black tea

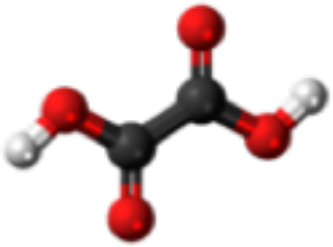


Urolithiasis

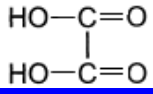


Nephrocalcinosis

Origin of oxalate



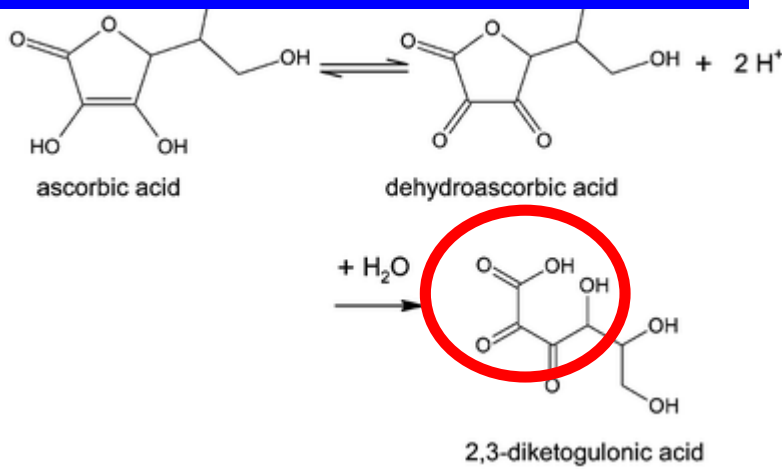
- Diet
- Synthesis by metabolism:
  - Sugars (fructose, glycerol, etc.)

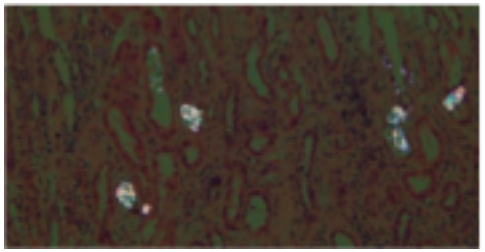


56 y male: ARF (S-creat 400 mcmol/l) due to oxalate-TIN (U-oxalate 1.1 mmol/d) after 16 8-oz glasses of **iced tea** daily (4 liter).

Fahd Syed N Engl J Med 2015; 372:1377-1378

- Dietary uptake increased by fat malbsorption





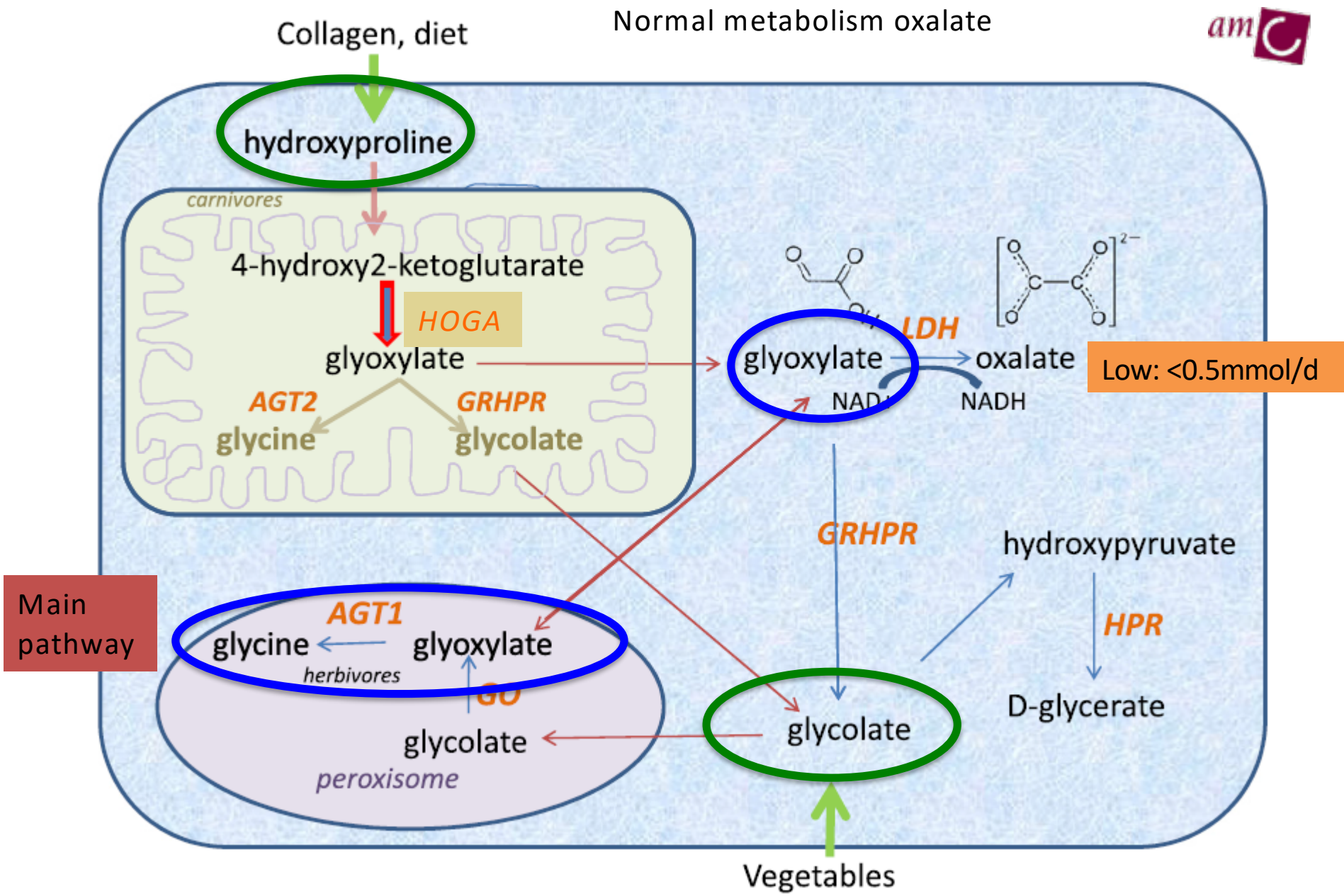
Potent inhibitors of calcium oxalate crystals

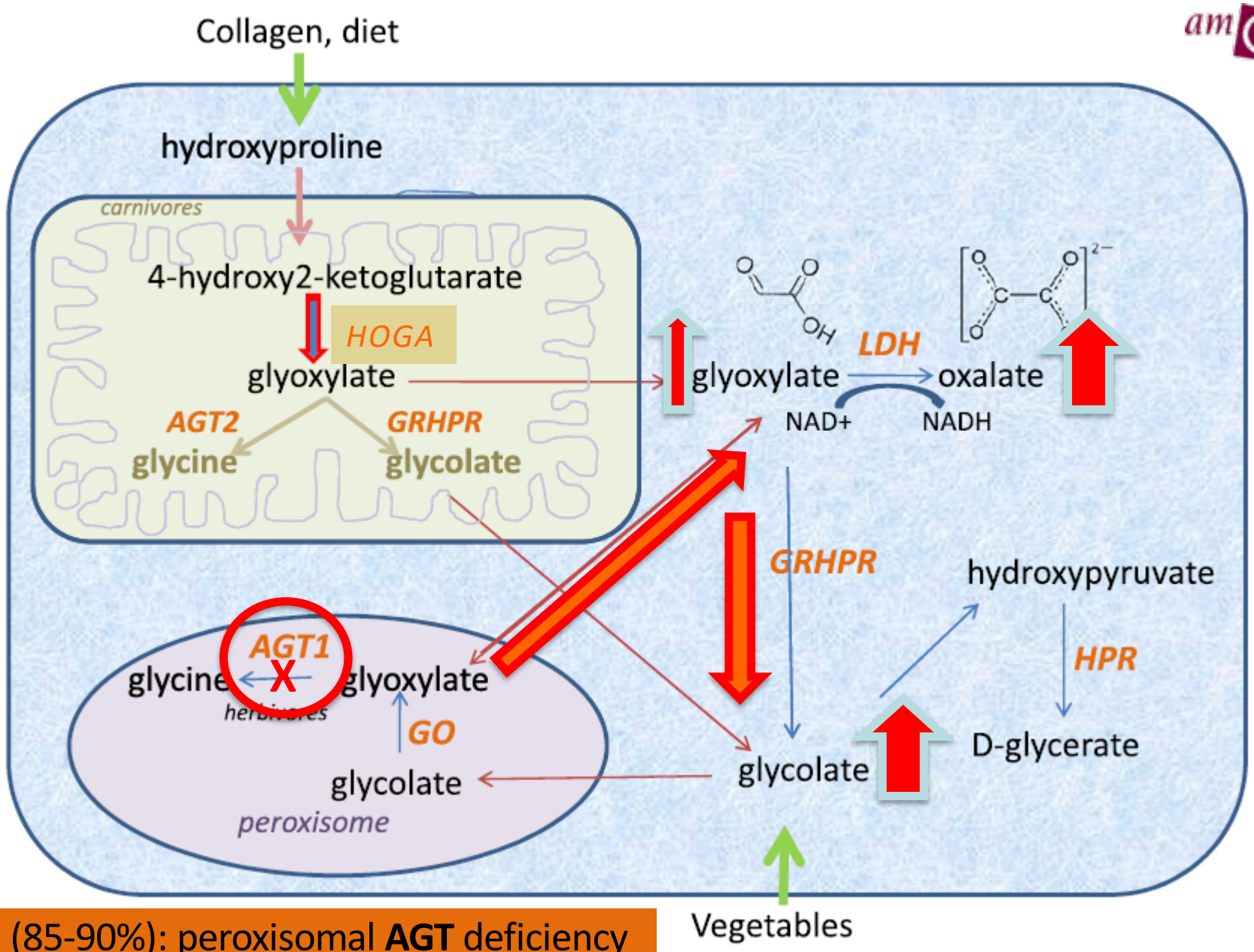
- 1. Citrate:
  - Competition with oxalate in calcium binding- > soluble complex
  - Citrate **protects** cells from oxalate **crystal induced injury** by preventing lipid peroxidation

- 2. Magnesium (over 500 times more soluble than CaOx)
  - Less suitable as therapy (diarrhea, high doses)

Byer K, Khan SR J Urol. 2005 Feb;173(2):640-6.

Normal metabolism oxalate





PH 1: (85-90%): peroxisomal **AGT** deficiency

-> biomarker: **high glycolate**

PH1-> mutations cause AGT deficiency because

1. Protein is not produced

2. Protein is producted , but inactive

3. Protein is producted, but unstable:

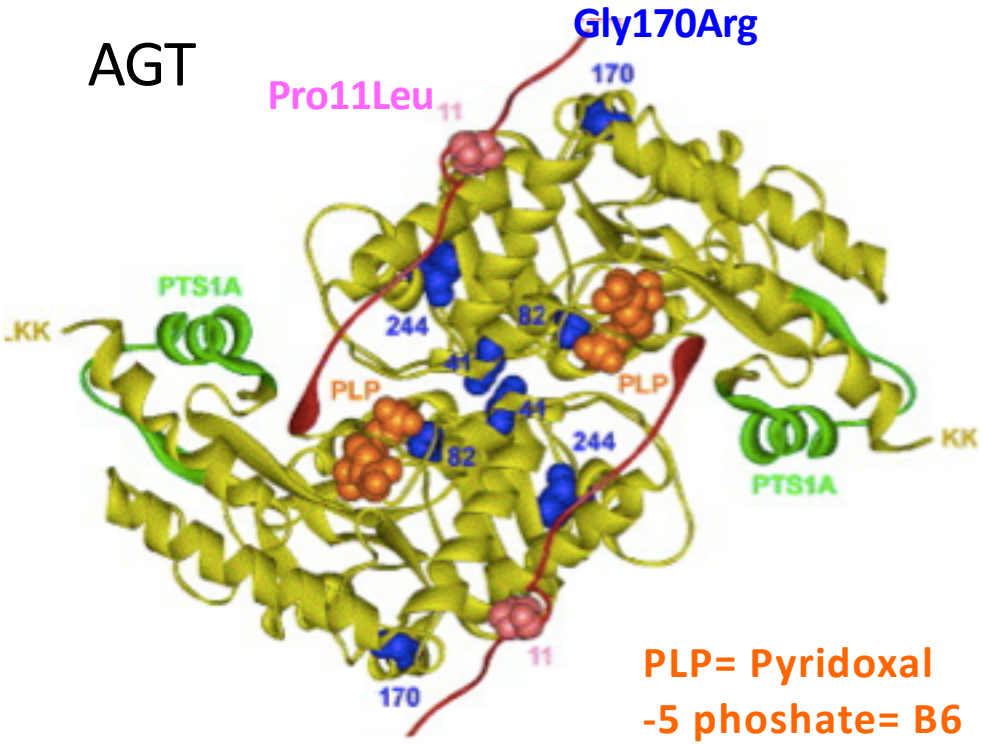
   3a. Degrades rapidly

   3b. Aggregates rapidly

   3c. Located in the wrong organel:
   Mitochondrial ‘mistargeting’

Mistargeting mutations in PH1

AGT



PLP= Pyridoxal
-5 phoshate= B6

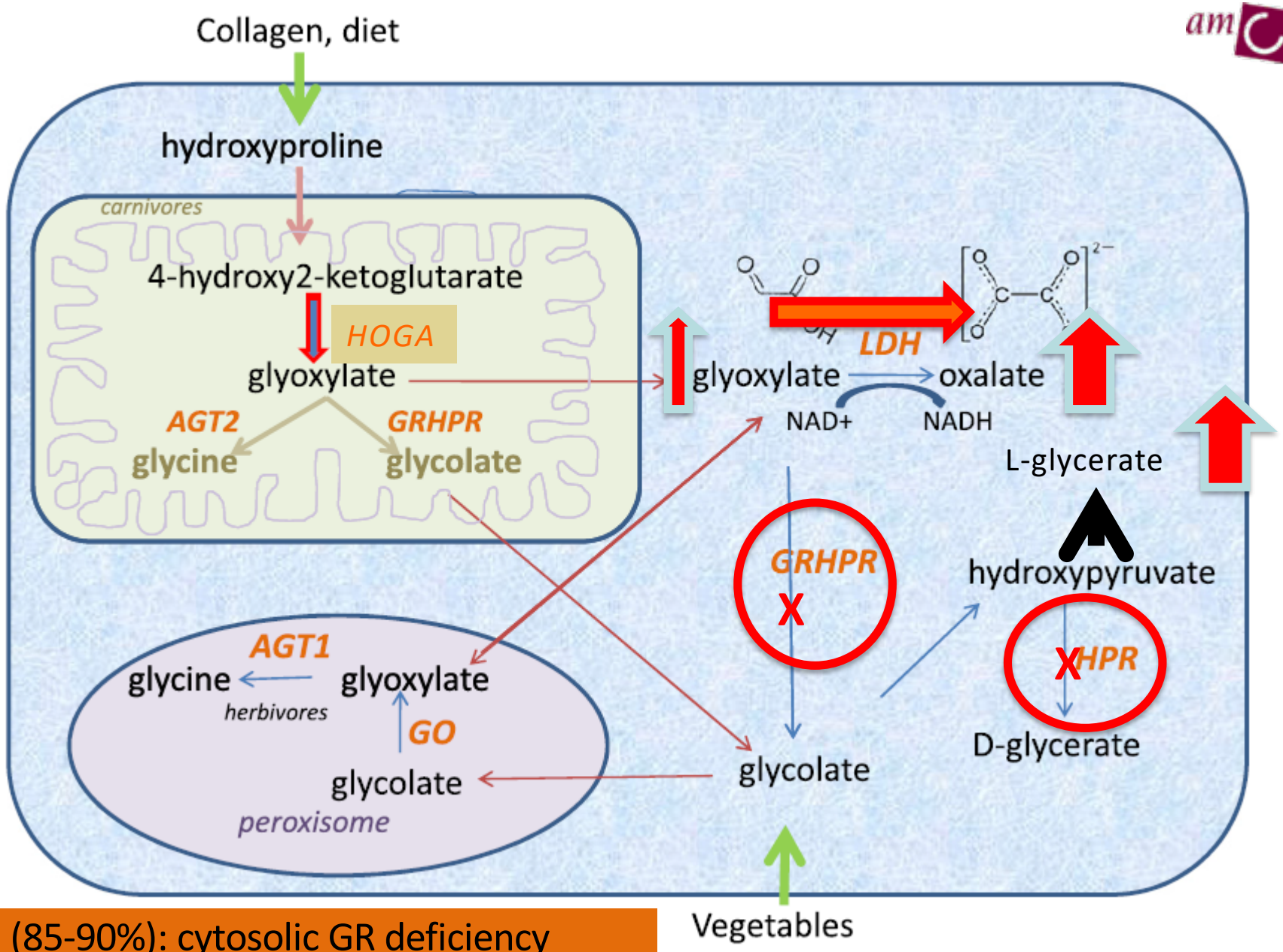
Gly170Arg (+Pro11Leu polymorphism)-> peroxisome-to-mitochondrion **mistargeting by unfolding -> impaired dimerization**:

(partly) reversed by Vit B6 => lowering/normalisation oxalate on B6 therapy:

30% PH1 EU patients

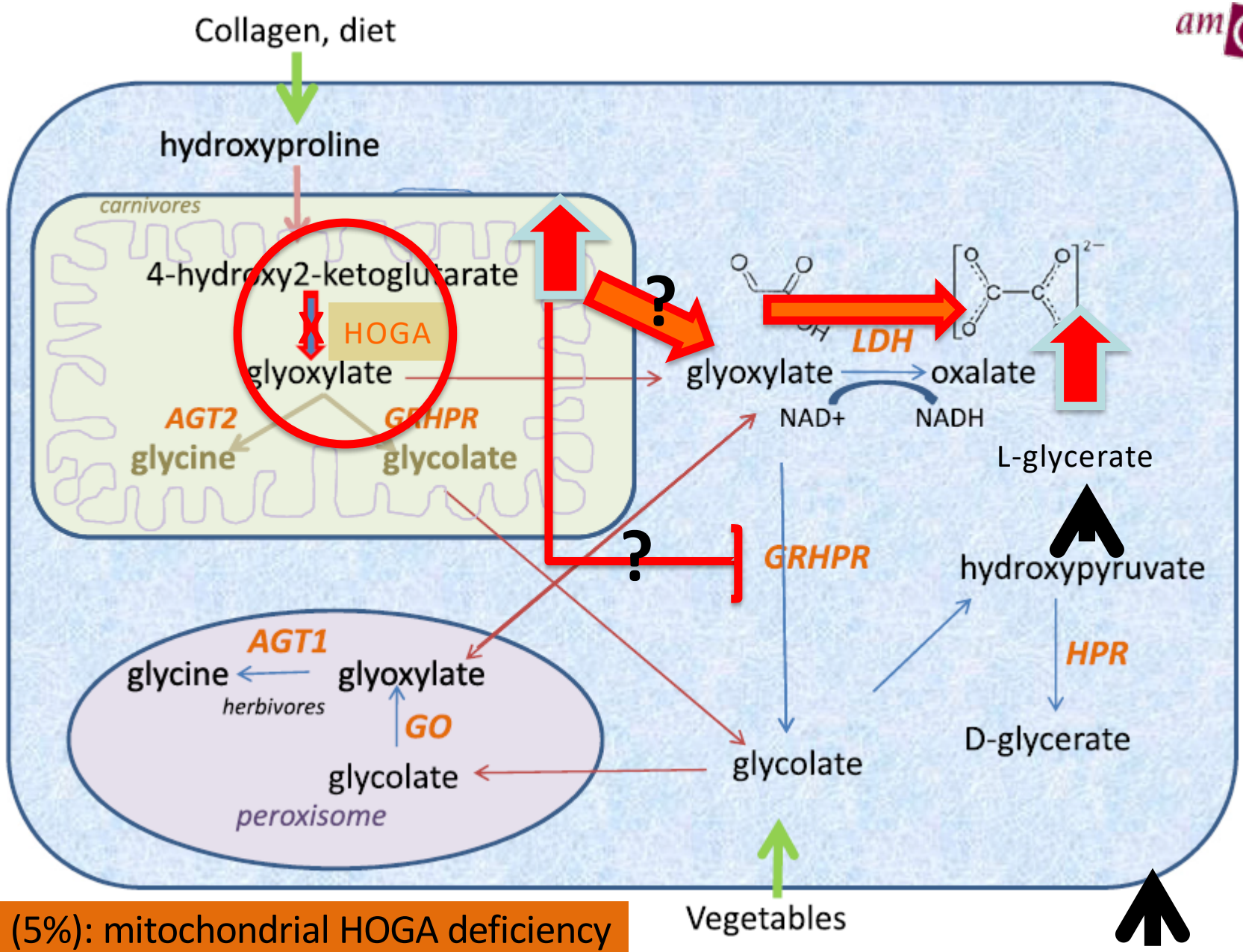
Fargue S, BBA) - Molecular Basis of Disease 1832, Issue 10, 2013, Pages 1776-1783
Danpure C, Molecular Cell Research 1763, Issue 12, 2006, Pages 1776-1784

Hoyer-Kuhn Vitamin B6 in Primary Hyperoxaluria CJASN. 2014 Mar 7; 9(3): 468–477.



PH 2: (85-90%): cytosolic GR deficiency

-> biomarker: **high L-glycerate**

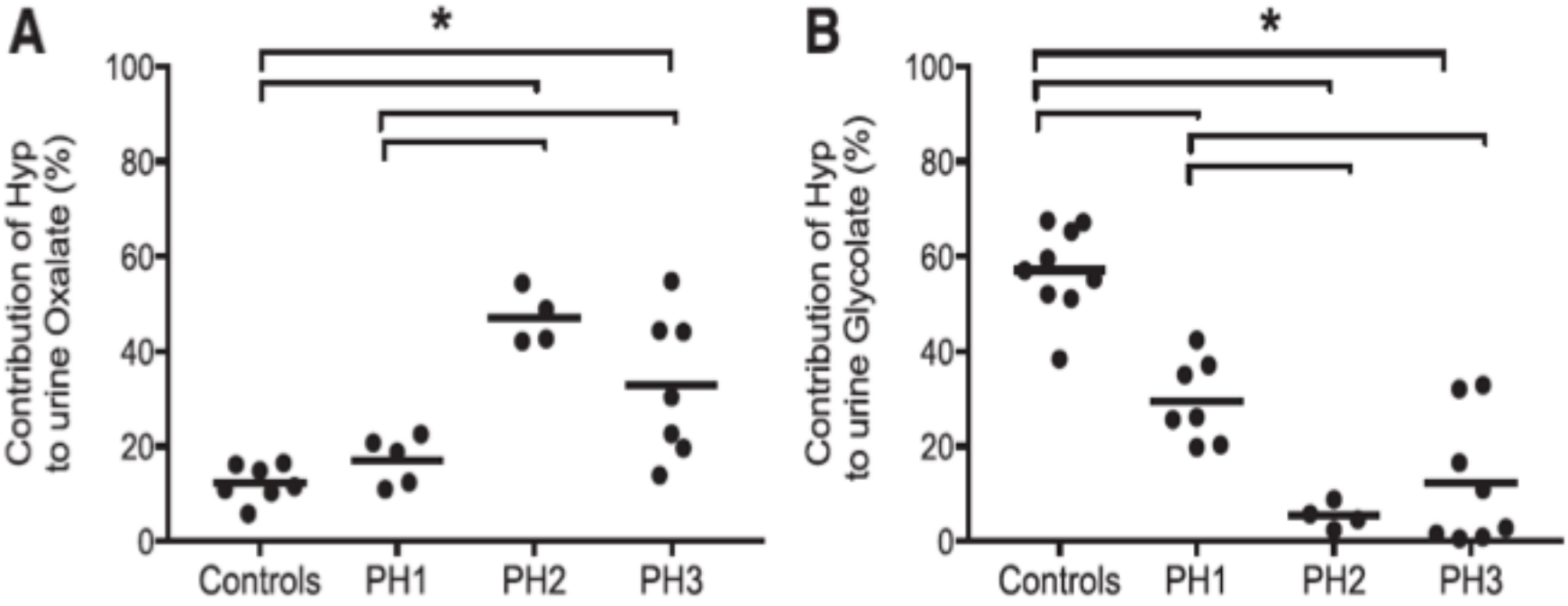


PH 3: (5%): mitochondrial HOGA deficiency

-> biomarker: **high HOG***

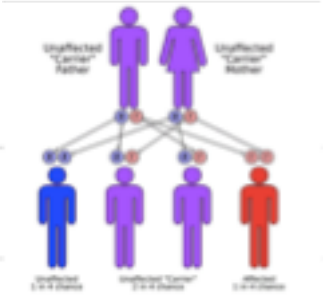
*4 hydroxy-2 oxo (keto)-glutarate

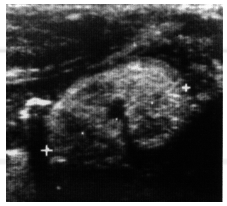
Similar high contribution hydroxyproline in PH 2 & PH3

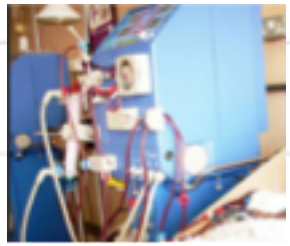


Fargue et al al J Am Soc Nephrol 29, 2018.

Symptoms at time of diagnosis (data Oxaleurope database)

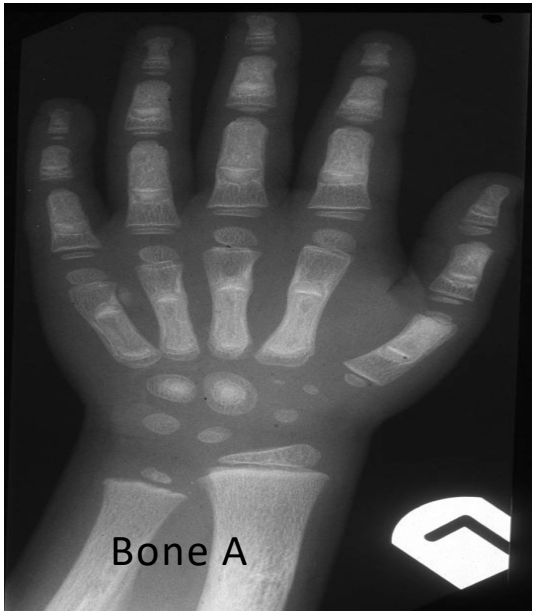


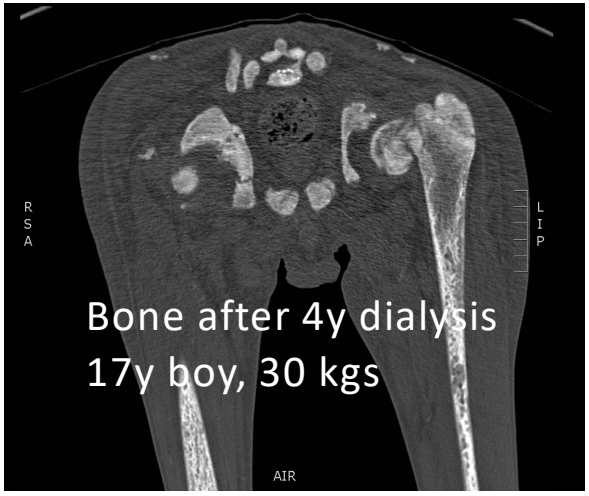




Comorbidity A and other patients

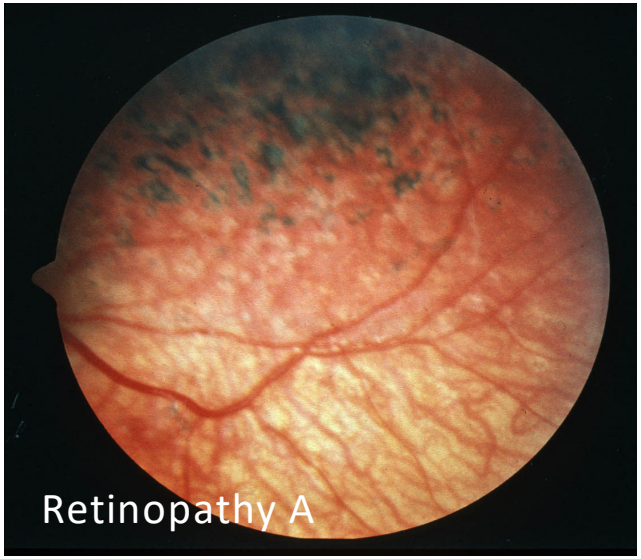
- Multiple fractures (26x)
- impaired vision, retinopathy
- Growth retardation, final height 155 cm
- Hearing loss
- Retarded mental development

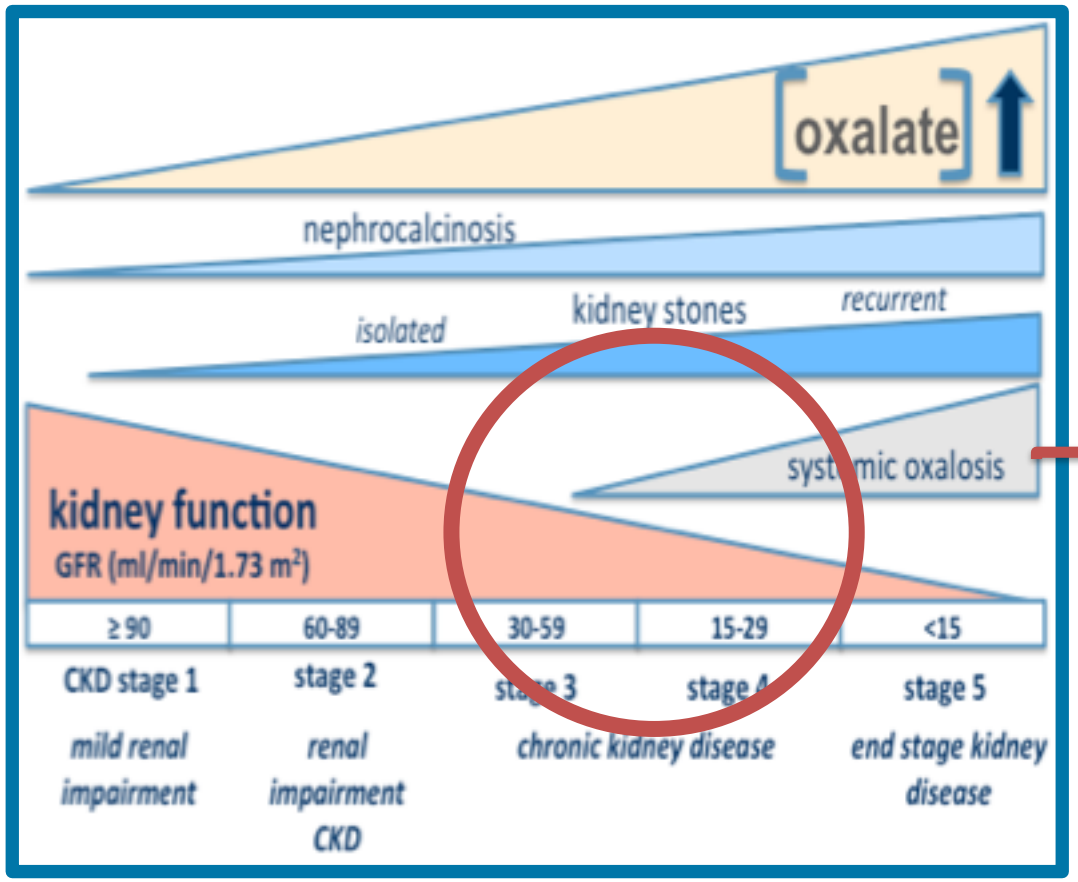




Bone after 4y dialysis
17y boy, 30 kgs


Skin ulcer with oxalate in 17y boy

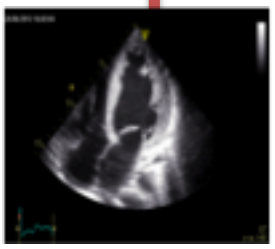

Retinopathy A



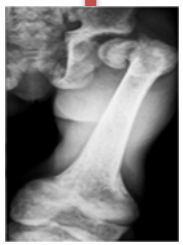
Clinical Threshold(s)?

- eGFR < 40 ml/min/1.73m^2
- Plasma Oxalate > 30 µmol/L

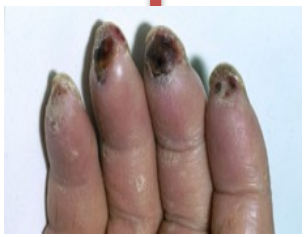
Systemic oxalosis



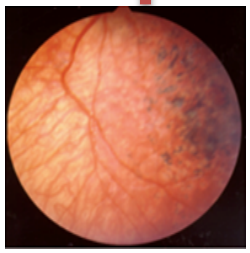
Heart



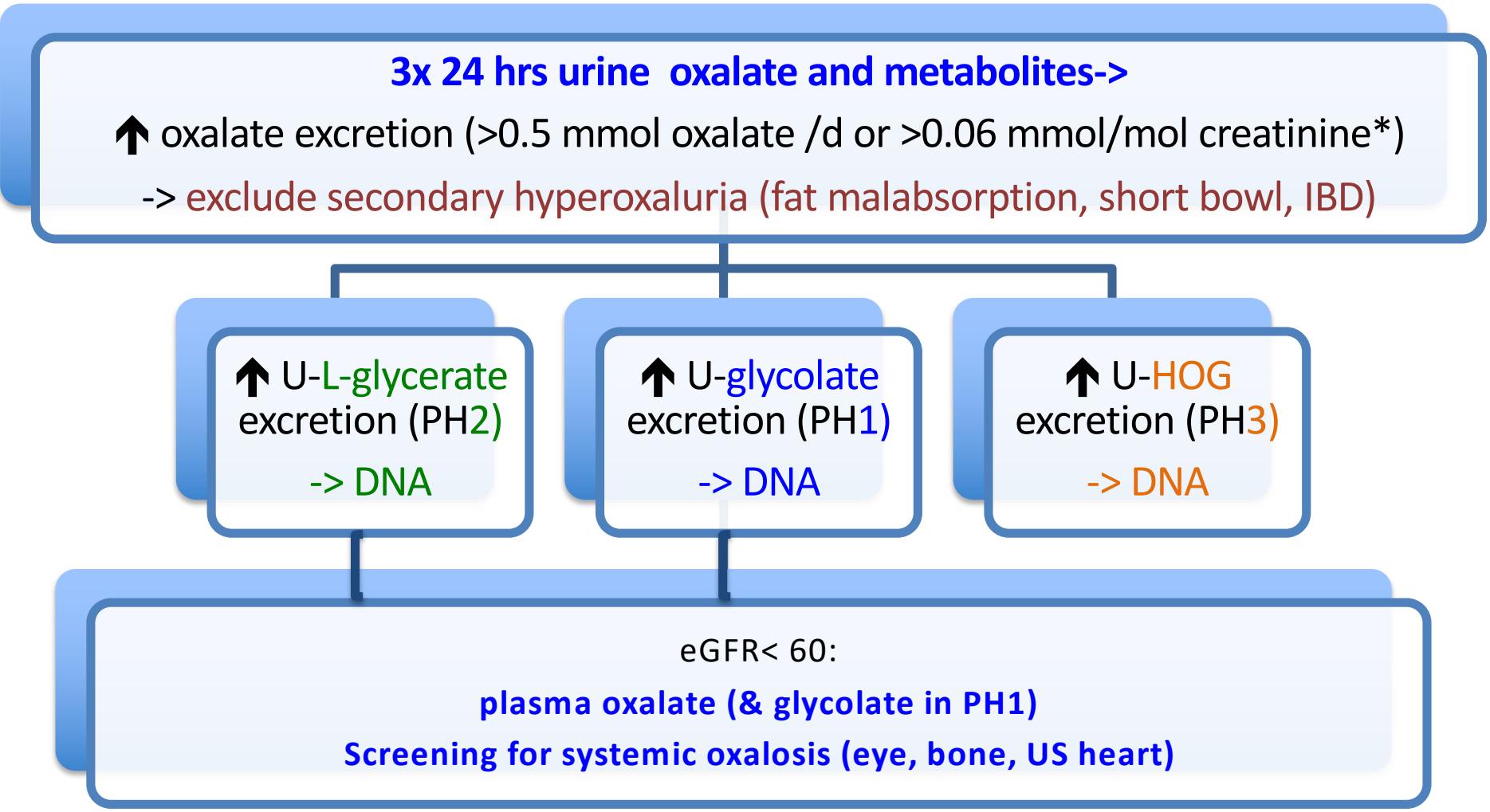
Bone



Vascular/Skin



Eye



* reference levels higher for children age 0-6 years

Cochat et al. Nephrol Dial Transplant (2012) 27: 1729-1736

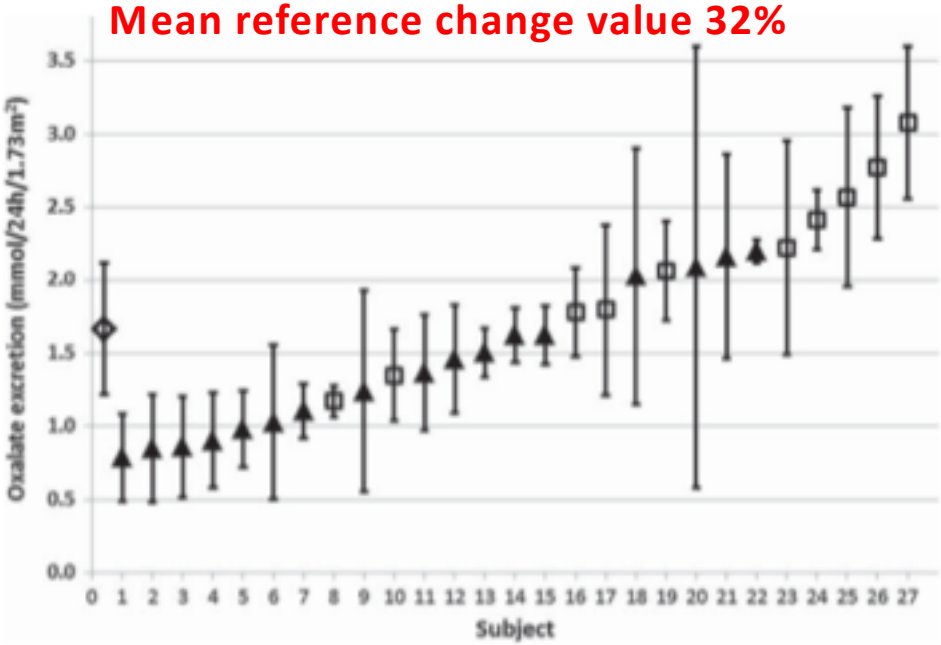
Pitfalls diagnostics

- High variability oxalate excretion
- Easy precipitation calcium-oxalate -> under detection
- Conversion ascorbic acid into oxalate -> over detection

-> at least 3 consecutive 24 hrs urine collection

Range of U oxalate in 27 PH1 patients

Mean reference change value 32%



Clifford-Mobley et al,
Urolithiasis (2016), 44: 333-337

PH1 -> classical theory

Assumption of 3 clinical phenotypes:

1. infantile form: 100% renal failure & systemic oxalosis

2. juvenile form: urolithiasis, nephrocalcinosis & 50% renal failure

3. late onset disease: mild, occasionally stone passage (Mrs A?)

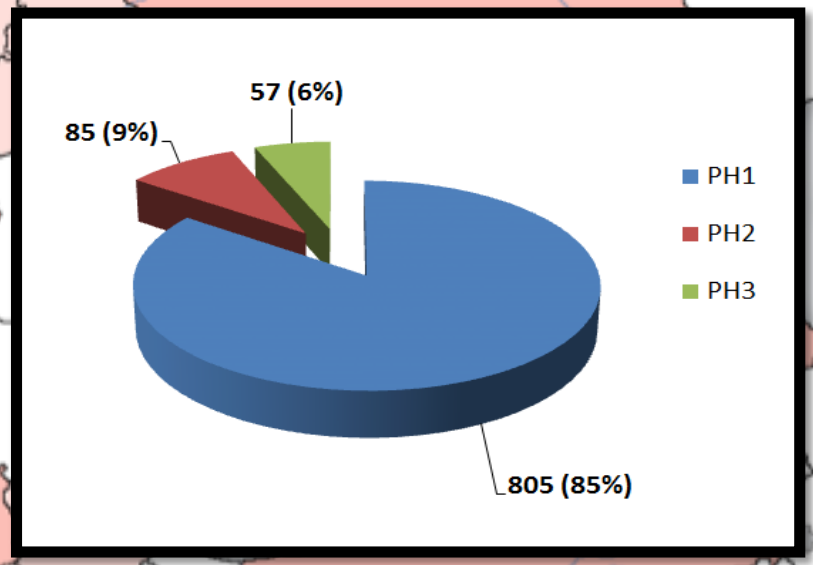
Estimated prevalence rate (per 10^6)

The Netherlands	- 5.42
UK	- 2.84
France	- 2.32
Germany	- 1.62
Italy	- 1.55

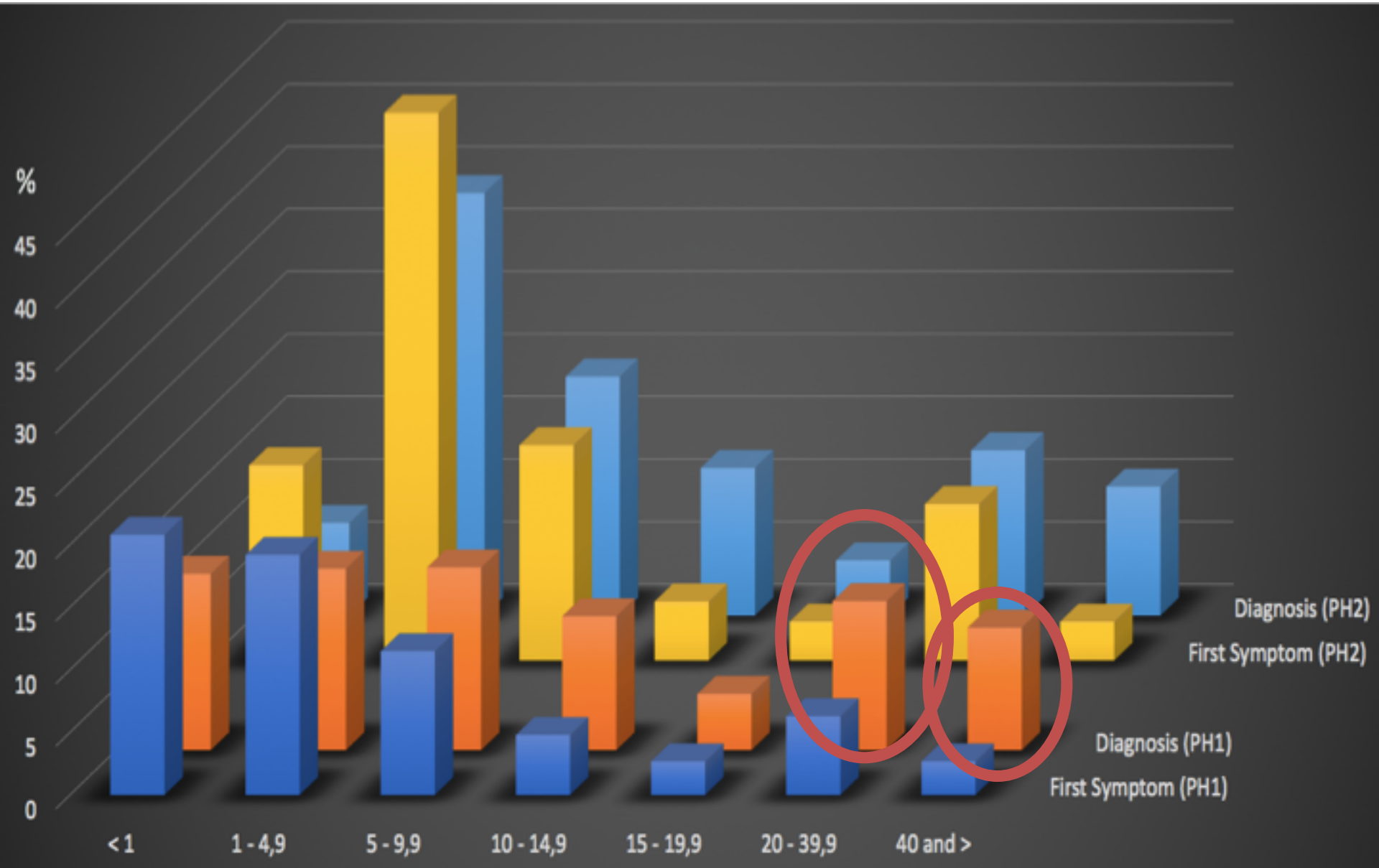
OXAIL EUROPE

2018

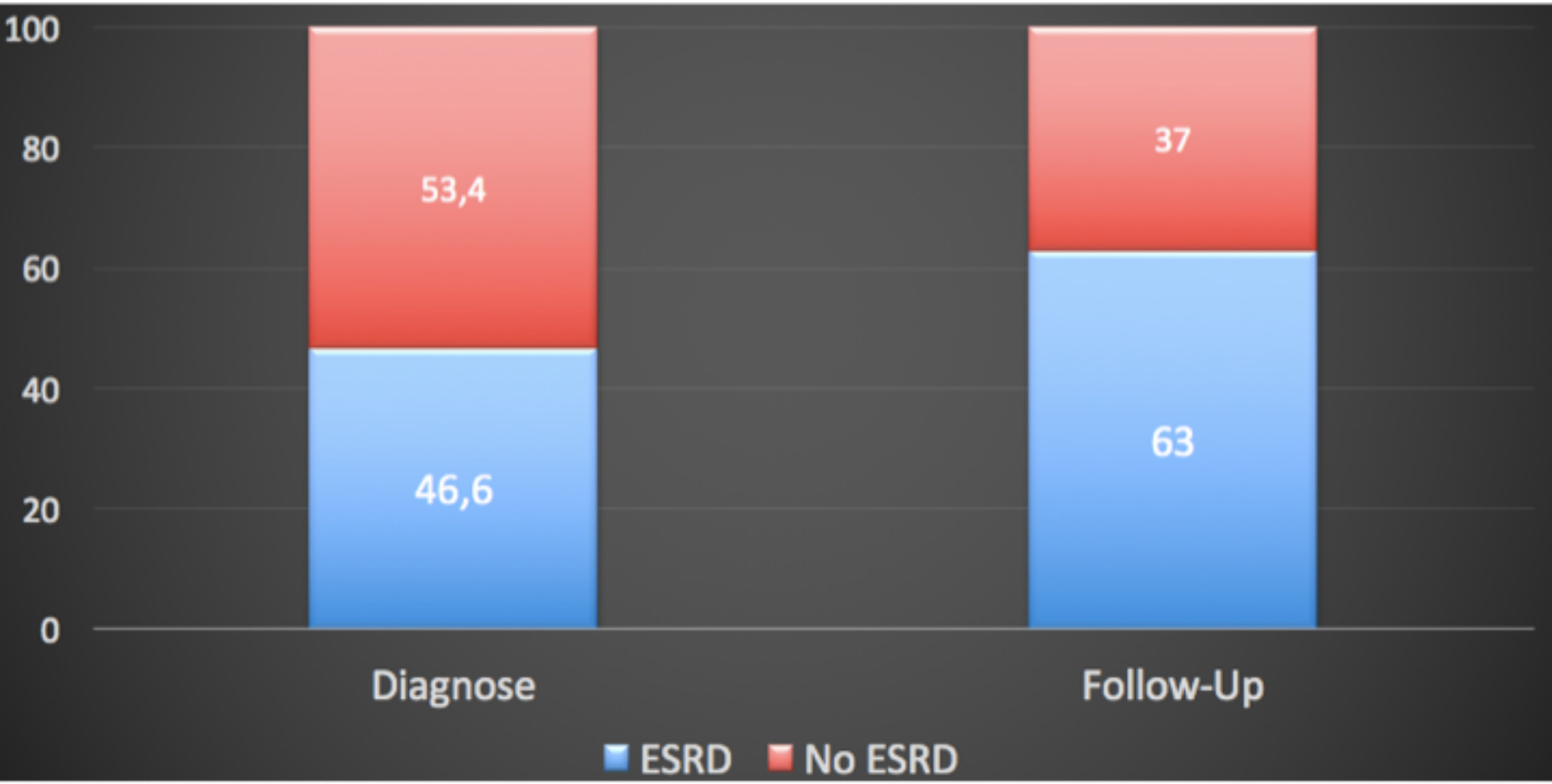
- **>1200 PH Patients**
- **21 Countries**



Age at time of symptoms & diagnosis



ESRD in PH1

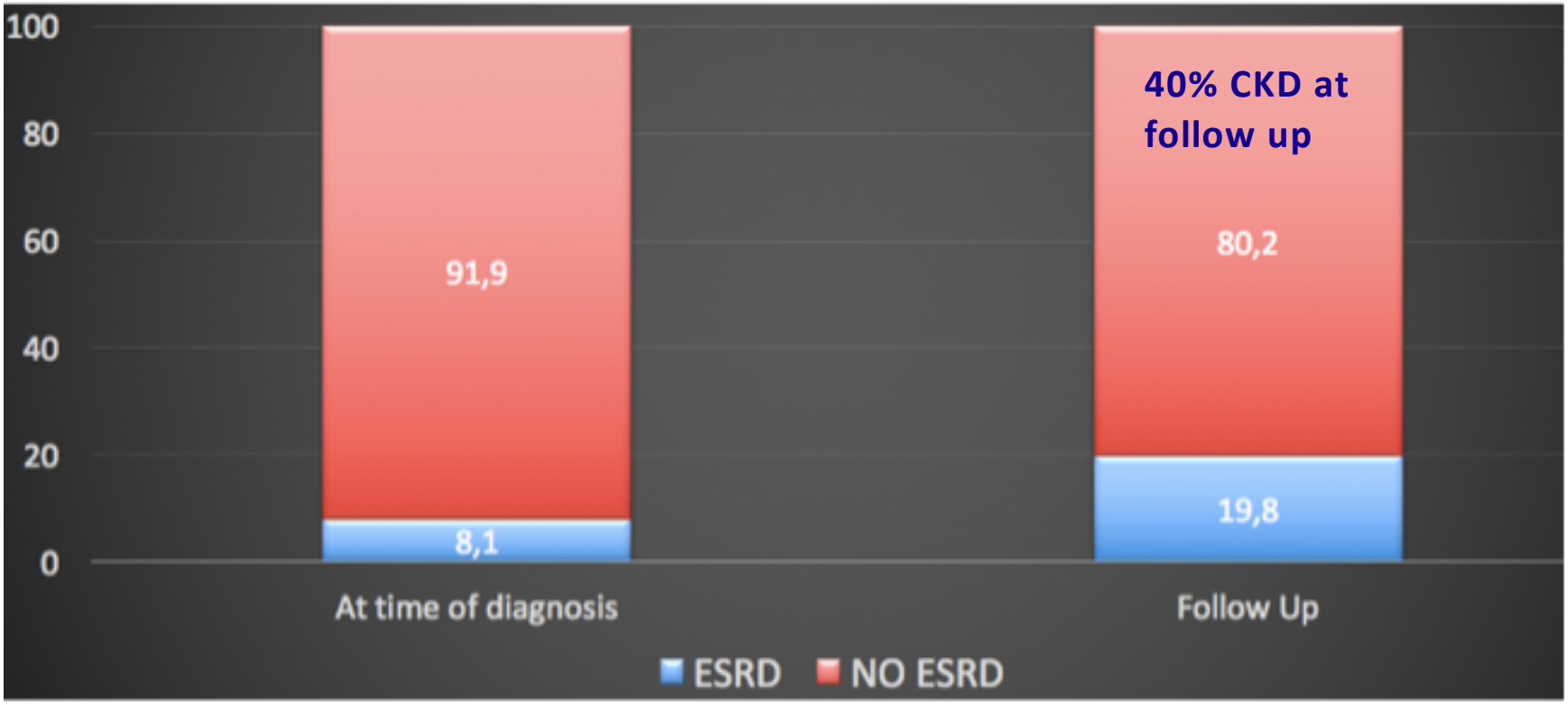


ESRD at time of diagnosis

< 18 years (34.3 %)

> 18 years (73.9%)

Renal impairment – PH2



- Age at time of ESRD (Median 42,67, r 23,50 – 74,83)

Unpublished data Oxaleuroped atabase

therapeutic strategies to date

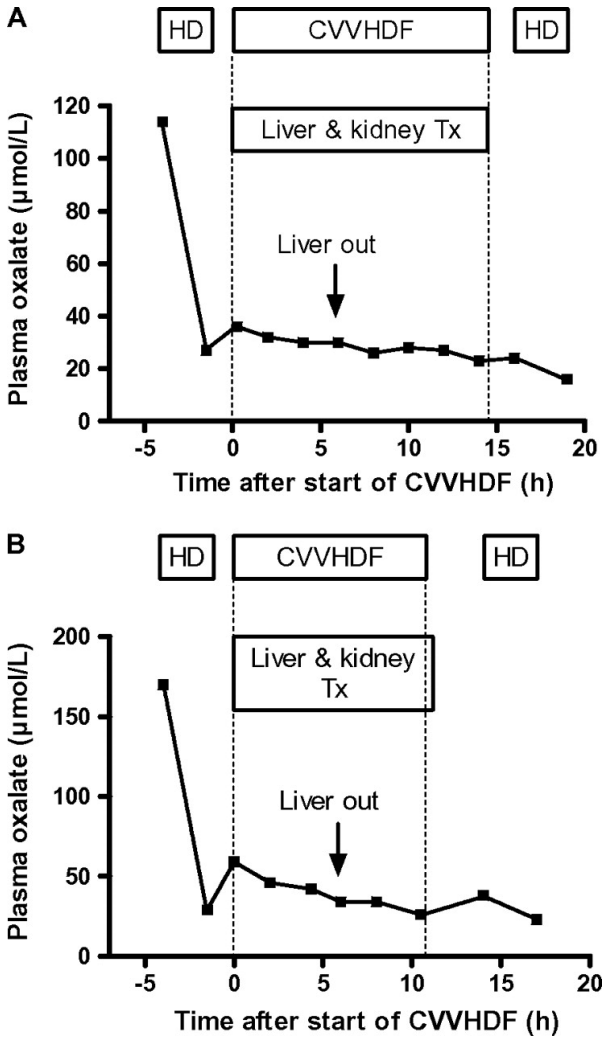
All patients:

- **Water: 3 liters/m²/day**
- Potassium citrate 0.5 mmol/kg/d
- B6 (5-20 mg/kg/d) for some PH1 subtypes

- eGFR< 40 -> recommendation **liver tx or combined liver-kidney tx**
- Dialysis -> recommendation liver tx, later k-tx **(sequential liver-kidney-tx)**
- Dialysis & B6+- > consider **only kidney-tx**

Cochat et al. Nephrol Dial Transplant (2012) 27: 1729-1736

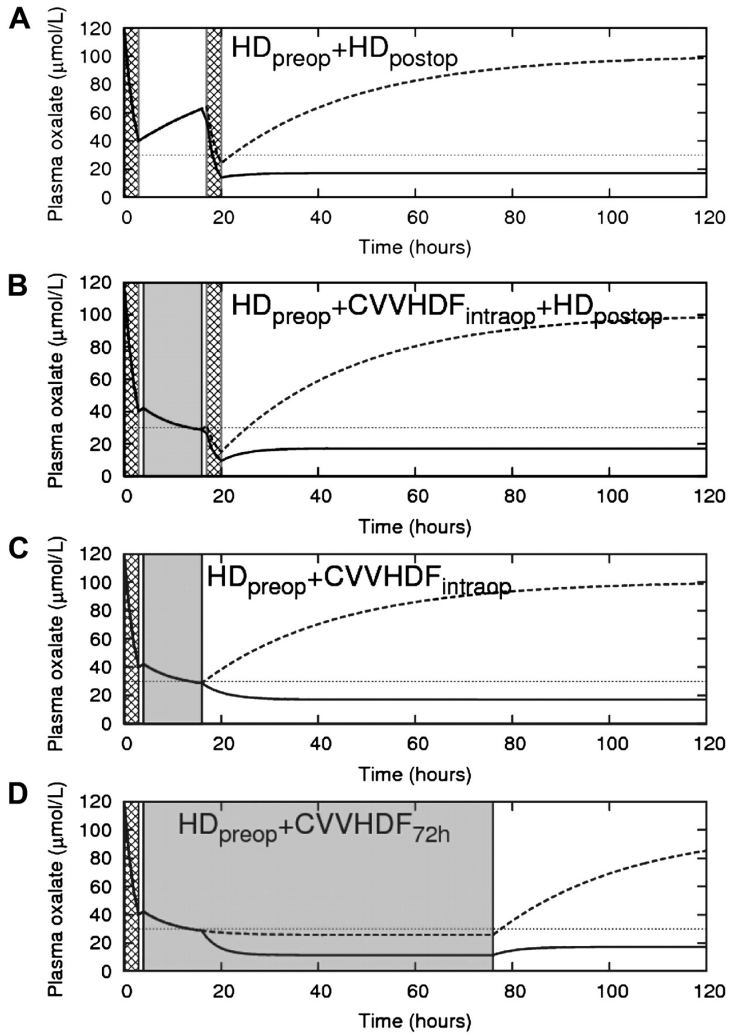
(A) Plasma oxalate levels during pre-operative HD, intra-operative CVVHDF and post-operative HD in Patient 1 (A) and 2 (B).



Casper F.M. Franssen et al. NDT Plus 2011;4:113-116

CKJ CLINICAL KIDNEY JOURNAL

Plasma oxalate levels for different dialysis strategies.



solid line -> p-oxalate levels in case of immediate renal tx function

dotted line -> p-oxalate levels in case of absent renal tx function

Casper F.M. Franssen et al. NDT Plus 2011;4:113-116

CKJ CLINICAL KIDNEY JOURNAL


Waiting for
better
times…

New therapies

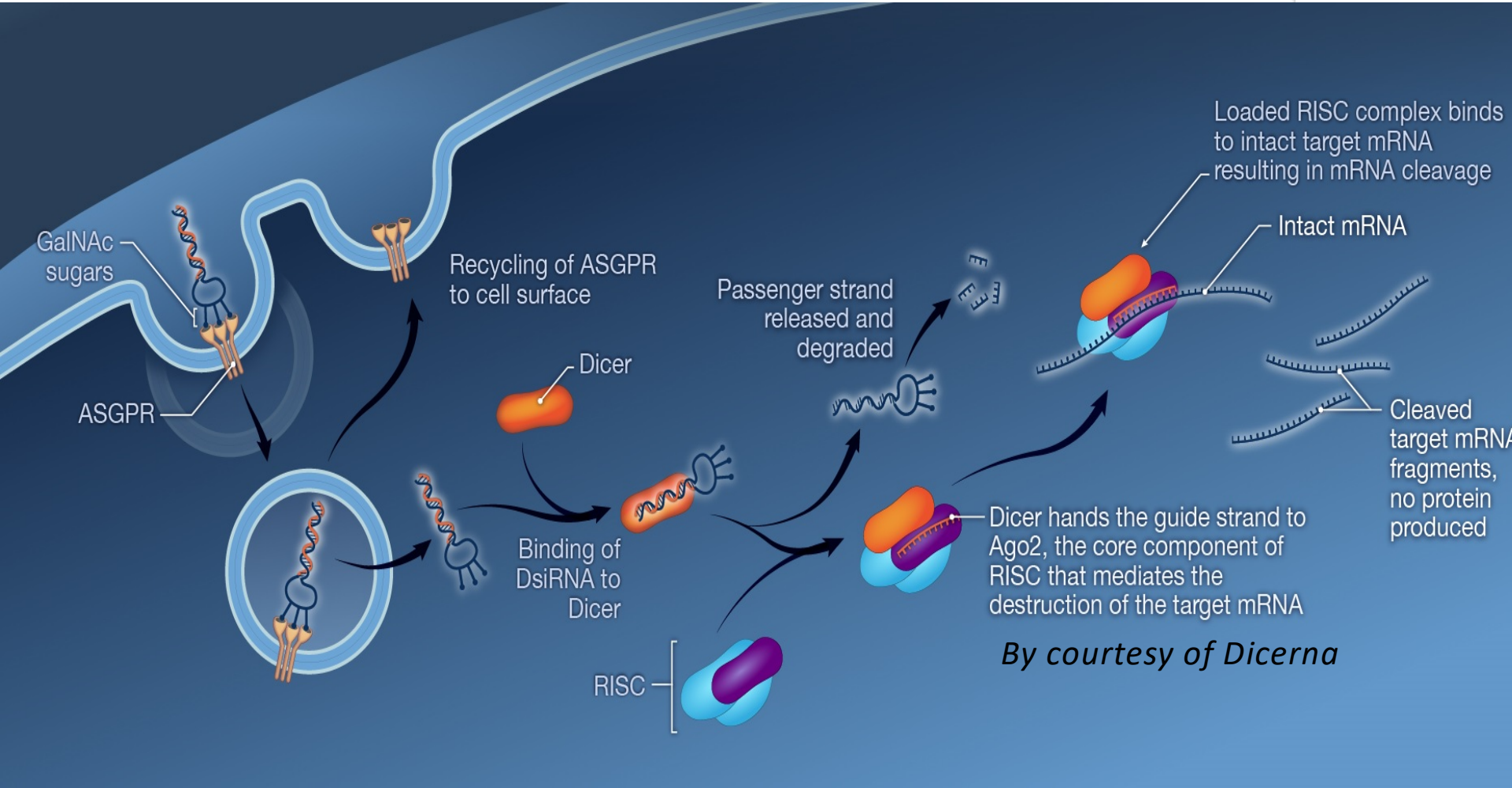
- **Substrate reduction therapy**
  - Prevention oxalate production by inhibition precursor
  - Method: RNA-interference -> inhibition protein production
  - 2 ongoing phase2/3 trials: Dicerna & Alnylam

Dicerna pharmaceuticals

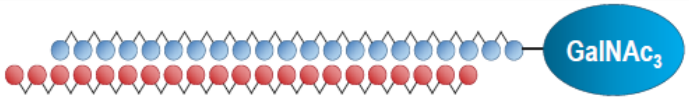
Alnylam PHARMACEUTICALS

RNA interference technique

->ds-RNA→cleaved by dicer →small single fragments (iRNA) → bound to activating elements: RNA Induced Silencing Complex (RISC) formation



N-acetylgalactosamine (GalNAc) sugar ligand conjugates iRNA -> vector of iRNA



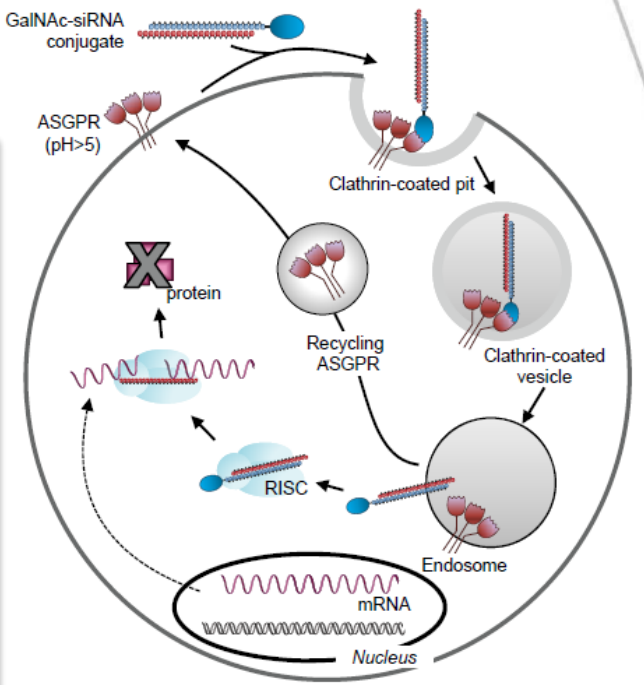
Asialoglycoprotein Receptor (ASAGPR)

- Highly expressed in hepatocytes
- High uptake

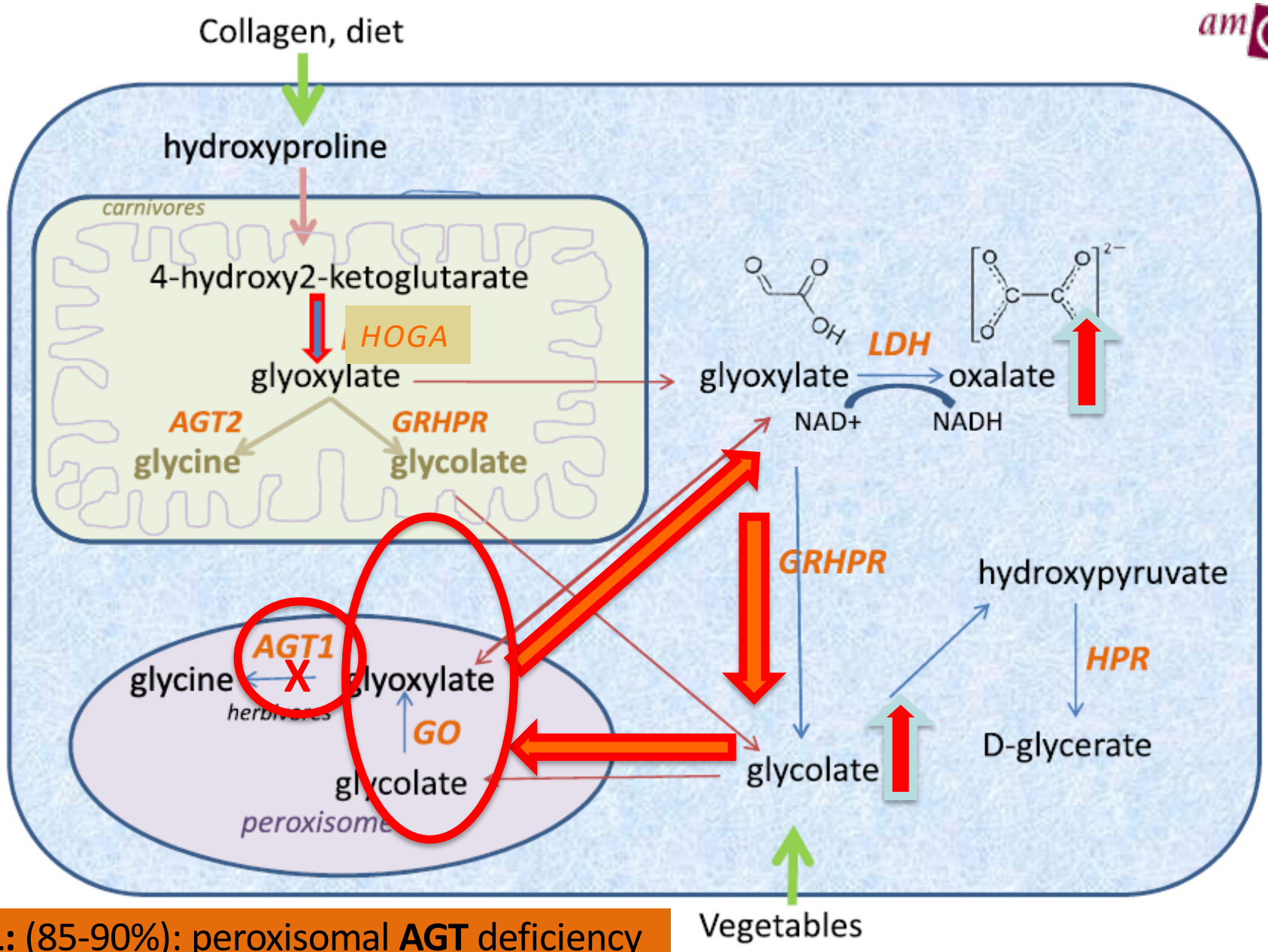
- Efficient delivery to hepatocytes by **s.c. Injection**

- **Liver specific**

- Proof of principle other iRNA drugs



By courtesy of Alnylam

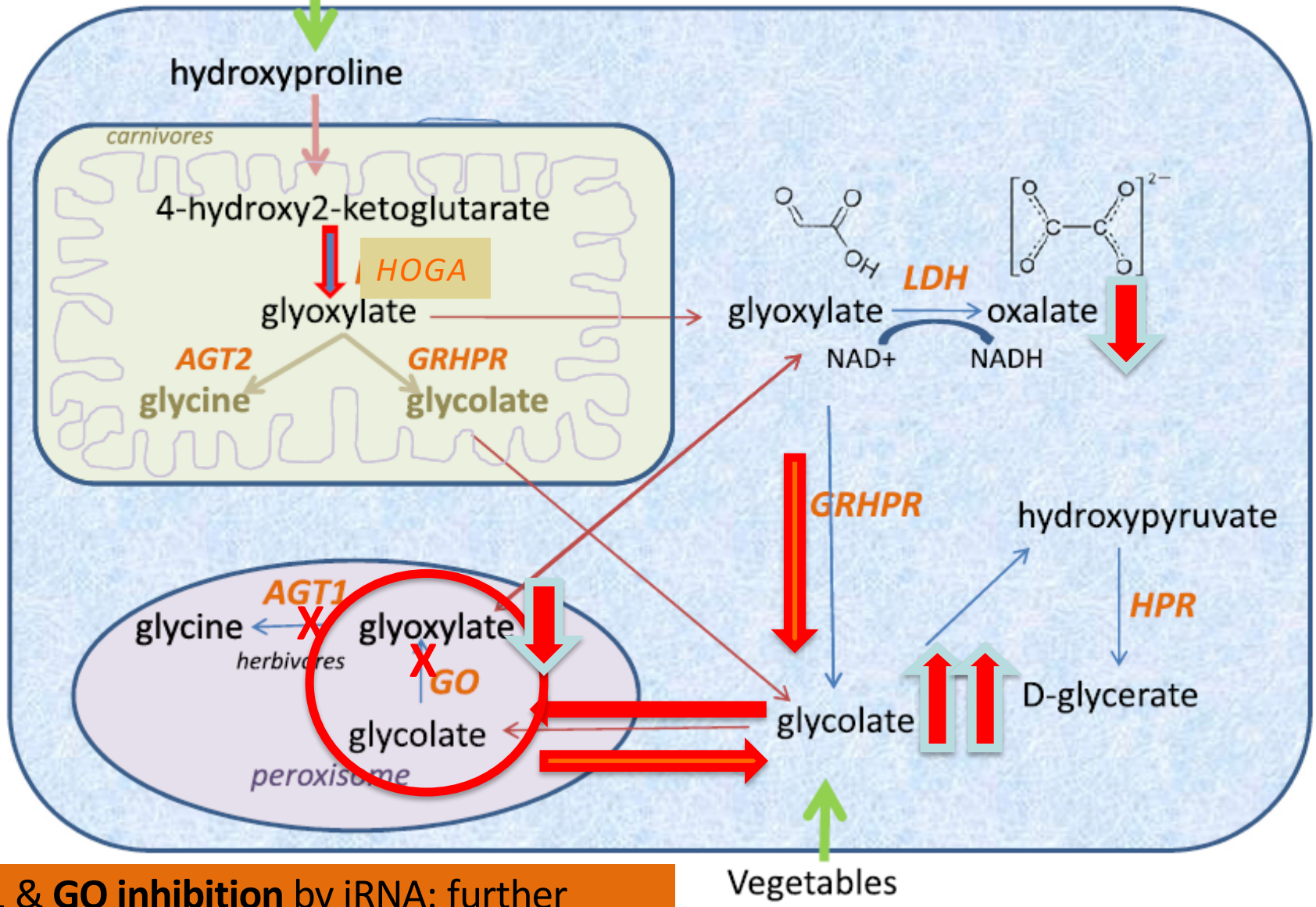


PH 1: (85-90%): peroxisomal **AGT** deficiency

-> biomarker: **high glycolate**

Collagen, diet

Substrate reduction therapy: 1. GO inhibtion



PH 1 & **GO inhibition** by iRNA: further **increase glycolate,** normalisation oxalate

Rare Glycolate oxidase deficiency -> no clinical phenotype

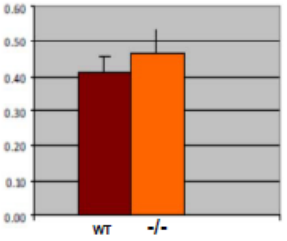
Deficiency well tolerated → increased glycolate excretion

- Single, 8-yr old boy, homozygous GO1 loss-of-function
  (identified by Dr. Yaacov Frishberg)
  - Dramatic increase in urinary glycolate, with normal oxalate
  - Normal sized kidneys - no nephrocalcinosis or nephrolithiasis

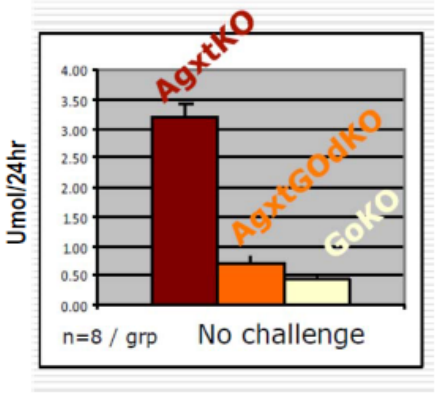
Urinary Glycolate (mmol/mol creatinine)	
normal range	< 90
Case	2000

- GO1 deficient mice are also asymptomatic, normal urinary oxalate
  - Glycolate levels not reported (expect ~20x increase)

Urinary Oxalate



Urinary Oxalate



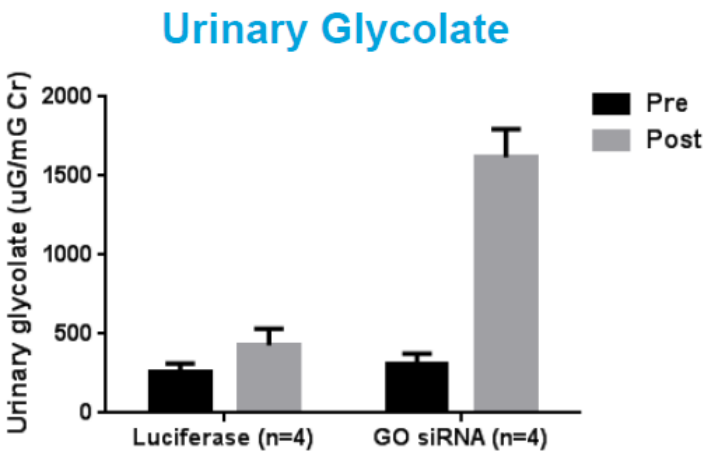
- Breeding GO1 deficient mice with PH1 disease mice (AGT deficient) substantially resolves the UOx levels (Dr. Eduardo Salido)
- Strong validation for the therapeutic premise of glycolate oxidase knockdown

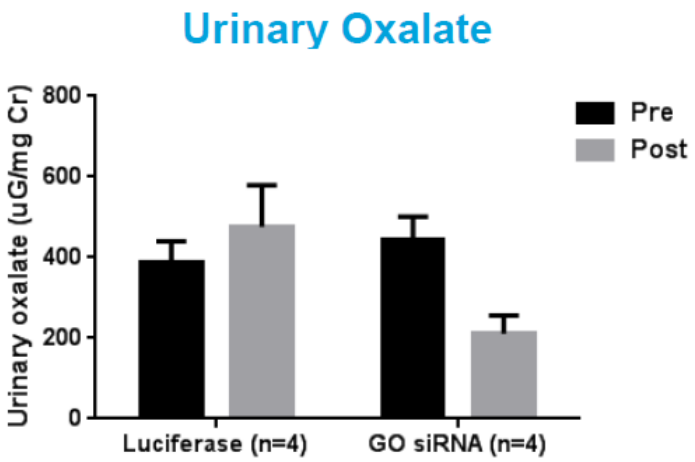
J Med Genet 2014; 51:526-9
11th Annual PH Workshop, June 27-29, 2014, Chicago, IL

By courtesy of Alnylam

GO1 knockdown lowers oxalate in a genetic PH1 mouse model

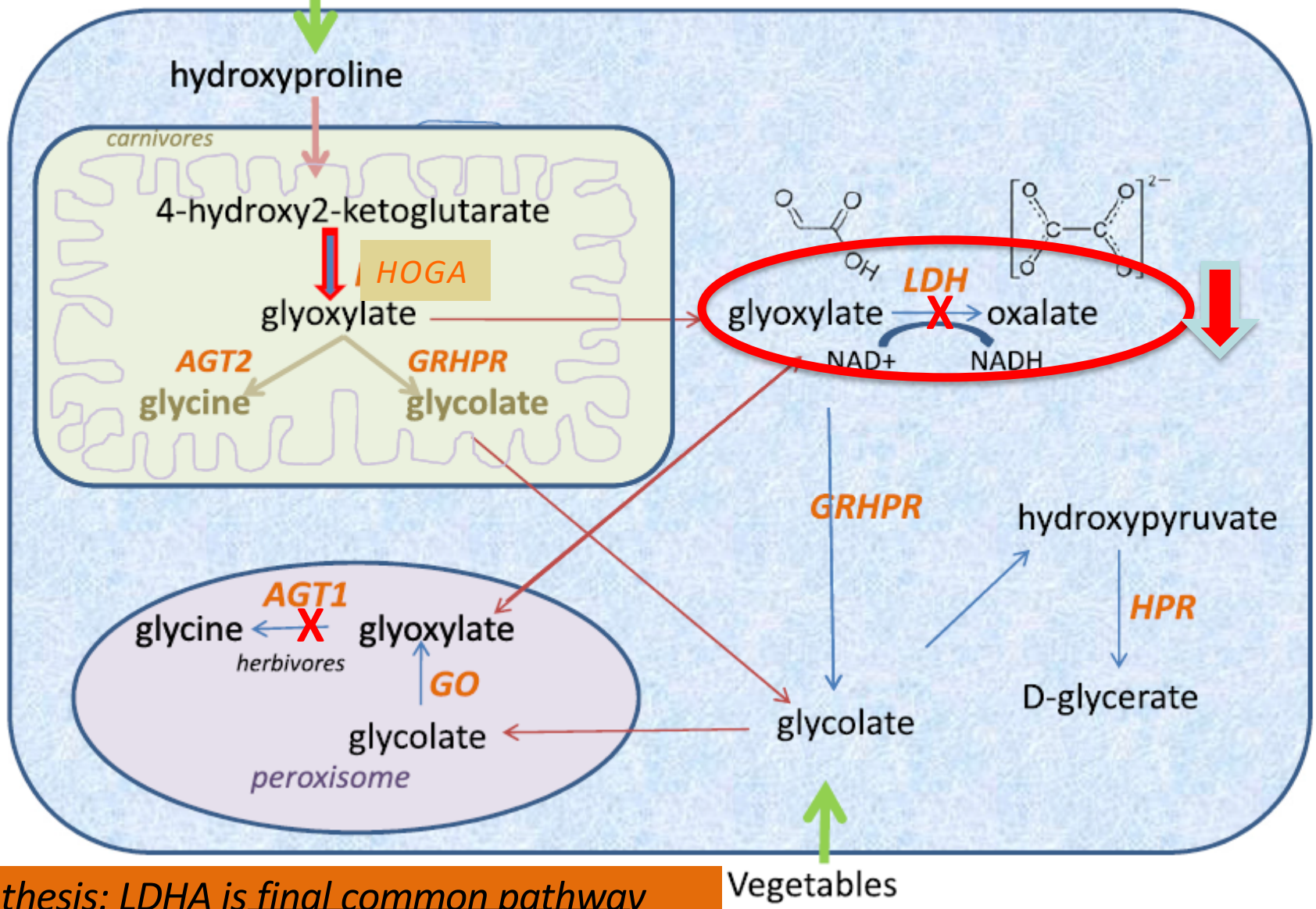
- Glycolate oxidase activity is decreased > 98% following GO1 siRNA treatment of mice with PH1 (mice deficient in AGT)
- As expected, glycolate excretion increases dramatically
- Oxalate levels decrease substantially, confirming the therapeutic hypothesis





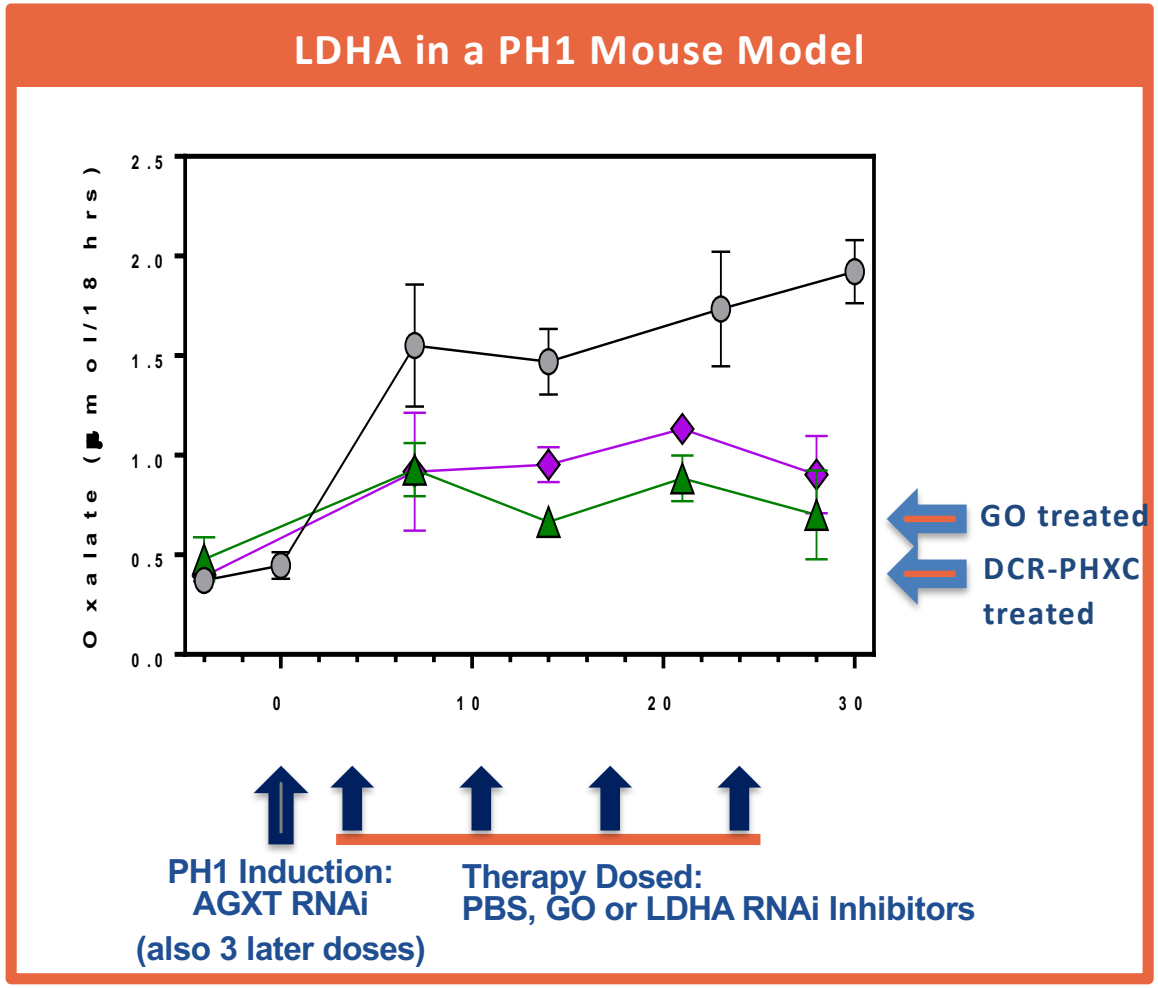
By courtesy of Alnylam

Substrate reduction therapy: 2. LDHA inhibtion



*hypothesis: LDHA is final common pathway glyoxylate conversion to oxalate-> **for all PH?***

LDHA vs GO Inhibition in PH1 Model: Oxalate Suppression



Several reports with LDHA deficient families with no phenotype

By courtesy of Dicerna

Conclusions

- Important under detection of PH
- Promising new therapies emerging
- Careful selection of patients is warranted for new therapies
- Diagnosis can easily be missed due to high variation in oxalate excretion
- Adult diagnosed PH is associated with adverse outcome
- PH1: 2/3 ESRD at follow up, B6+: late onset ESRD
- Primary Hyperoxaluria is not a benign disease, even if 1st symptoms are mild

European Reference Network
for rare or low prevalence complex diseases

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Thank you for your attention

Next Webinar:

June 5th: Gema Ariceta (Barcelona) on Familial hypomagnesemia with hypercalciuria and nephrocalcinosis