PRIMARY HYPEROXALURIA AND KIDNEY TRANSPLANTATION

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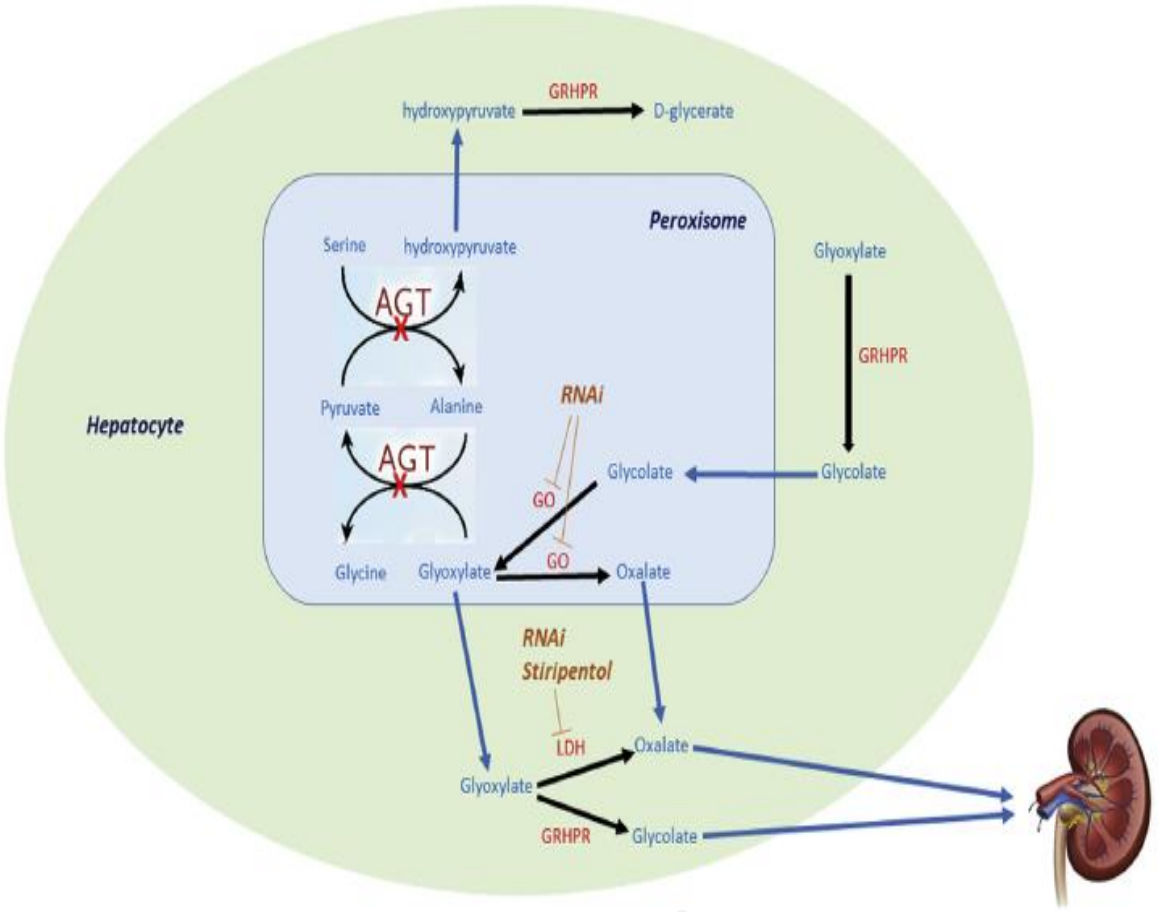
Introduction

- ✓Primary hyperoxaluria type 1 (PH1) is the most common and severe form of PH
- ✓Previous transplant strategies to treat ESRD include liver–kidney transplantation, combined or sequential (liver first and then kidney).
- ✓Many innovative drugs are currently tested to treat the metabolic defect and could avoid liver transplantation
- ✓These promising drugs will modify our approach in the management of PH1 patients with ESRD.

- ✓**Glyoxylate** accumulates as a result of AGT deficiency and is converted to **oxalate** by hepatic lactat dehydrogenase (LDH) and GO
- ✓And to **glycolate** by glyoxylate reductase-hydroxypyruvate reductase (GRHPR).



PREVIOUS TRANSPLANT STRATEGIES FOR PH1 PATIENTS

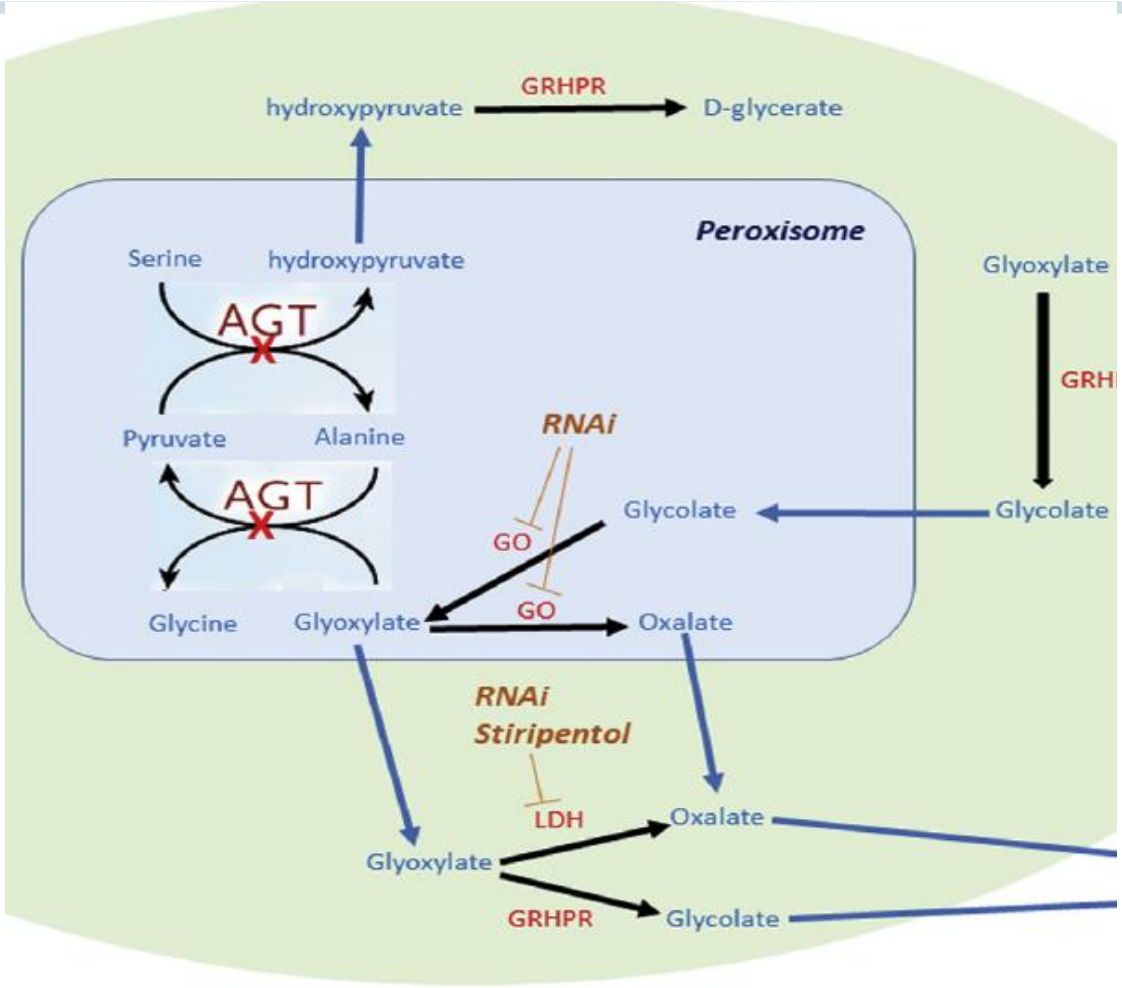
GFR<30CC/min/1.73m2	• dual liver–kidney transplantation is currently proposed
CKD stage 4	• early combined liver–kidney transplantation is preferred when systemic storage is assumed to be quite limited (early after a patient's eGFR declines to below 30 ml/min per 1.73 m2)
CKD stage 5 or chronic dialysis	• when systemic oxalosis is more intense, sequential transplantation can be another option: first the liver followed by hemodialysis to decrease systemic oxalate storage and then the kidney

LIMITATIONS OF CURRENT STRATEGIES

Main issue is liver TX

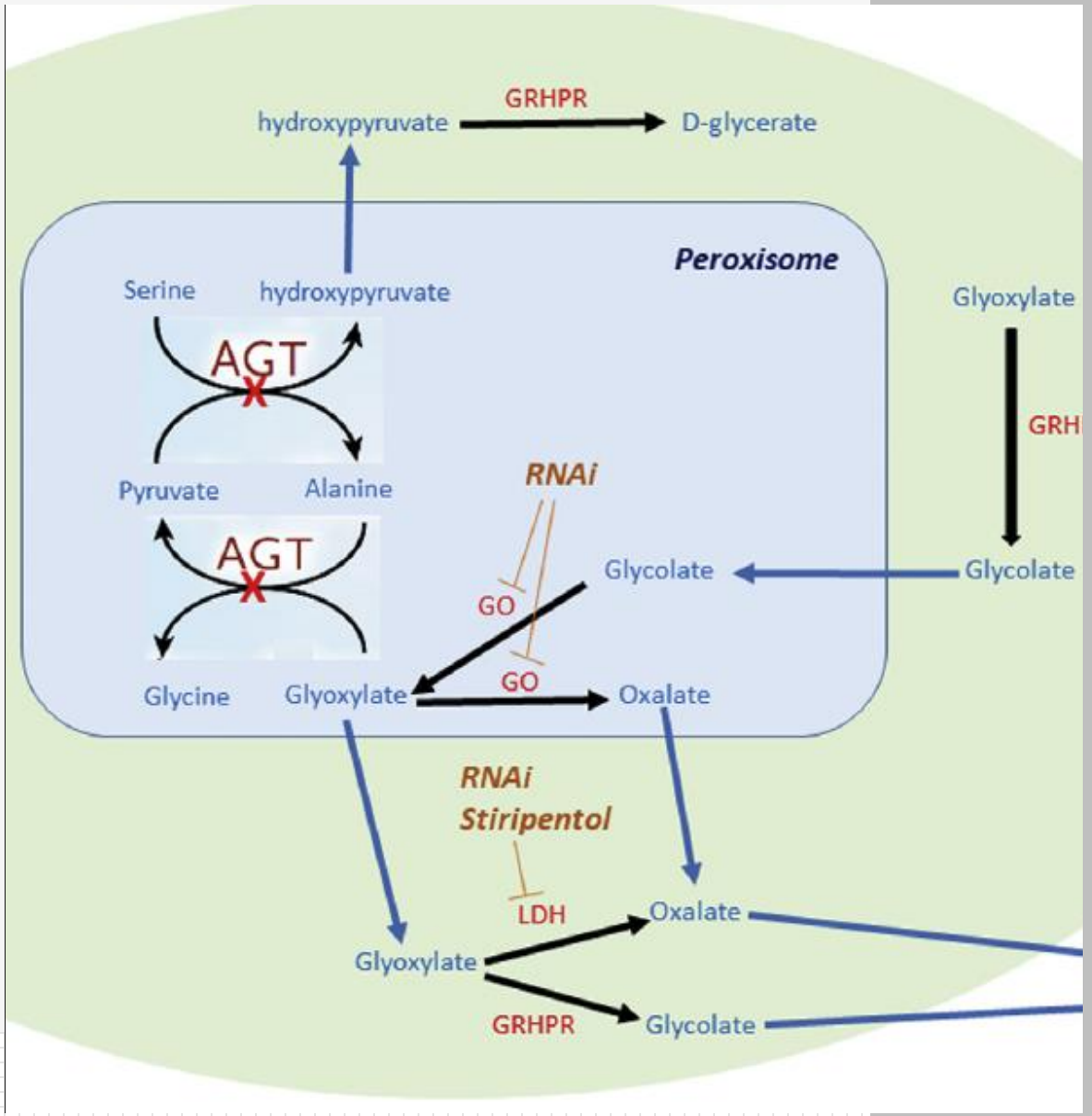
Organ shortage = Increase in systemic storage and oxalosis	Morbidity and mortality of liver transplantation	1-, 5-, and 10-year patient survival 86%, 80%, and 69% = Not optimal in young population

RNA Interference Drugs



- ✓small interfering RNAs (siRNAs) allows targeted depletion of mRNA molecules encoding the goal protein
- ✓One key enzyme in the hepatic oxalate synthesis is glycolate oxidase (GO)
- ✓**Lumasiran** reduced urinary oxalate (UOx) concentration up to 50% after a single dose in the genetic mouse model of PH1 and up to 98% after multiple doses in a rat model

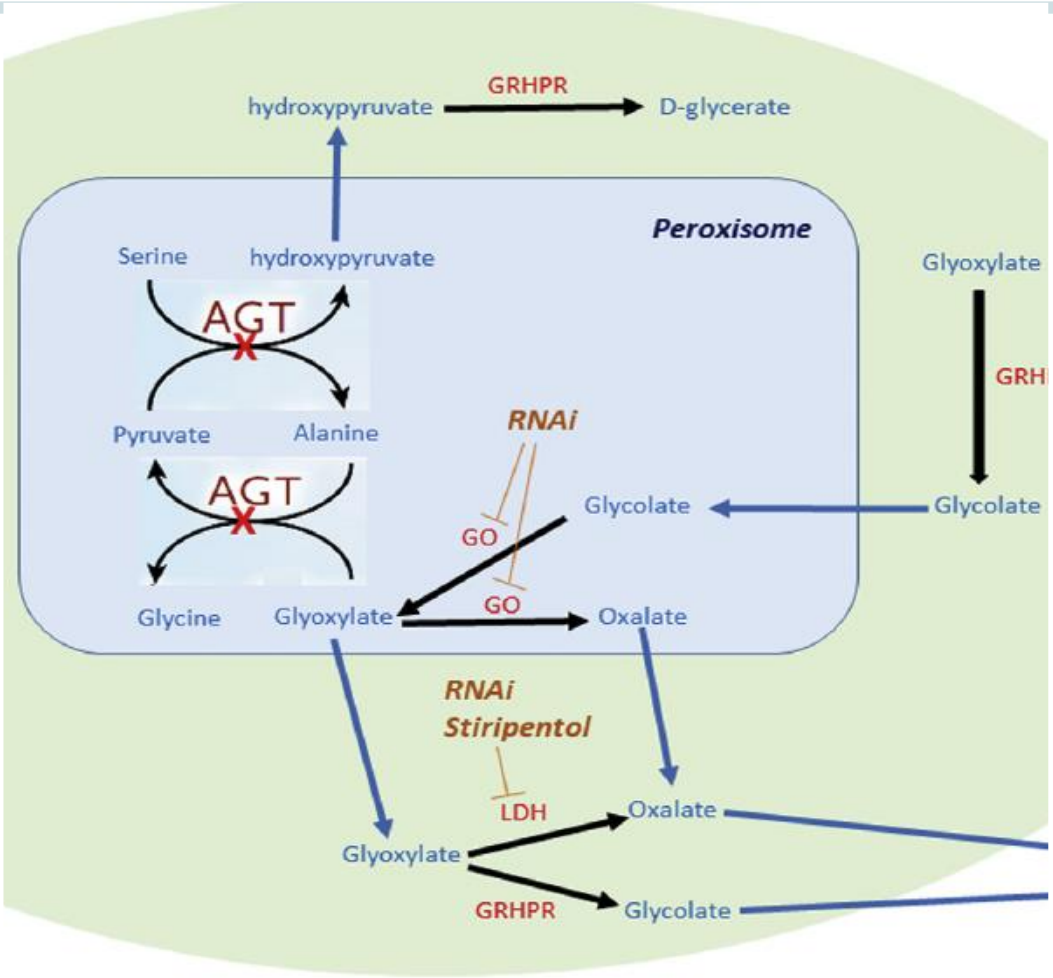
Innovative treatment	Drug name	Phase II-III clinical trials ongoing
RNA interference targeting glycolate oxidase	Lumasiran	Illuminate A (phase III) *NCT03681184* Main inclusion criteria: age ≥ 6 yr, eGFR ≥30 ml/min Preliminary results: 65.4% reduction of 24-h urinary oxalate at month 6; no serious adverse event reported[18] Estimated completion date: May 2024 Illuminate B (phase III) *NCT03905694* Main inclusion criteria: age ≤ 5 yr, preserved kidney function Preliminary results: NA Estimated completion date: September 2024 Illuminate C (phase III) *NCT04152200* Main inclusion criteria: all ages, eGFR ≤45 ml/min (including chronic dialysis) Preliminary results: NA Estimated completion date: August 2025



Nedosiran

✓Nedosiran, an RNAi targeting hepatic LDHA (1 of the genes encoding for hepatic lactate dehydrogenase [LDH], responsible for the final conversion of glyoxylate to oxalate)

stiripentol



- ✓LDH Type 5 Inhibitors
- ✓antiepileptic drugs to treat seizures in Dravet syndrome.
- ✓It resulted in rapid decrease in urinary oxalate excretion in a 17-year-old girl with normal kidney function but failed to decrease plasma oxalate in a 17 month-old patient with dialysis-dependent PH1

The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023
Homa Hotel, Tehran

Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope

TEHRAN 2023

- ✓We recommend that liver transplantation is combined with kidney transplantation in patients with PH1 and advanced disease (eGFR <30 ml/min/1.73 m2) who do not respond to pyridoxine and have no access to RNAi therapy

- ✓The strategy for either sequentially or simultaneously performed liver and kidney transplantation should be decided based on the clinical situation and the preference of the local surgeon

- ✓Isolated kidney transplantation should be considered in patients with PH1 and stage 5D CKD who are homozygous for pyridoxine-responsive mutations

- All patients aged **<18 years** with kidney stones or nephrocalcinosis and **eGFR >30** ml/min/1.73 m²
- All patients aged **>18 years** with recurrent (>2) kidney stone episodes or nephrocalcinosis and **eGFR >30** ml/min/1.73 m²

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- At least **two urine oxalate assessments**, preferably from 24 h urine collection
- Oxalate-to-creatinine ratio spot urine in small children

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Hyperoxaluria

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- Genetic assessment for PH
- Exclude enteric cause of hyperoxaluria
- Urine hyperoxaluria metabolites, if available
- Start VB6, citrate, hyperhydration

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PH1
- VB6 fully or partially responsive: continue VB6, measure response, consider RNAi if urine oxalate is not normalized
- VB6 non-responsive: RNAi therapy indicated

All patients with **eGFR <30** ml/min/1.73 m² and nephrocalcinosis or kidney stones

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Plasma oxalate assessment (plasma glycolate levels if available)

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Hyperoxalaemia, corrected for GFR

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- Urgent genetic assessment for PH
- Exclude enteric disease
- Start VB6
- Consider intensified dialysis, based on plasma oxalate level
- Consider starting RNAi therapy

↓

PH1
- VB6 non-responsive mutation: RNAi therapy indicated
- VB6 responsive mutation: consider RNAi therapy, based on plasma oxalate level

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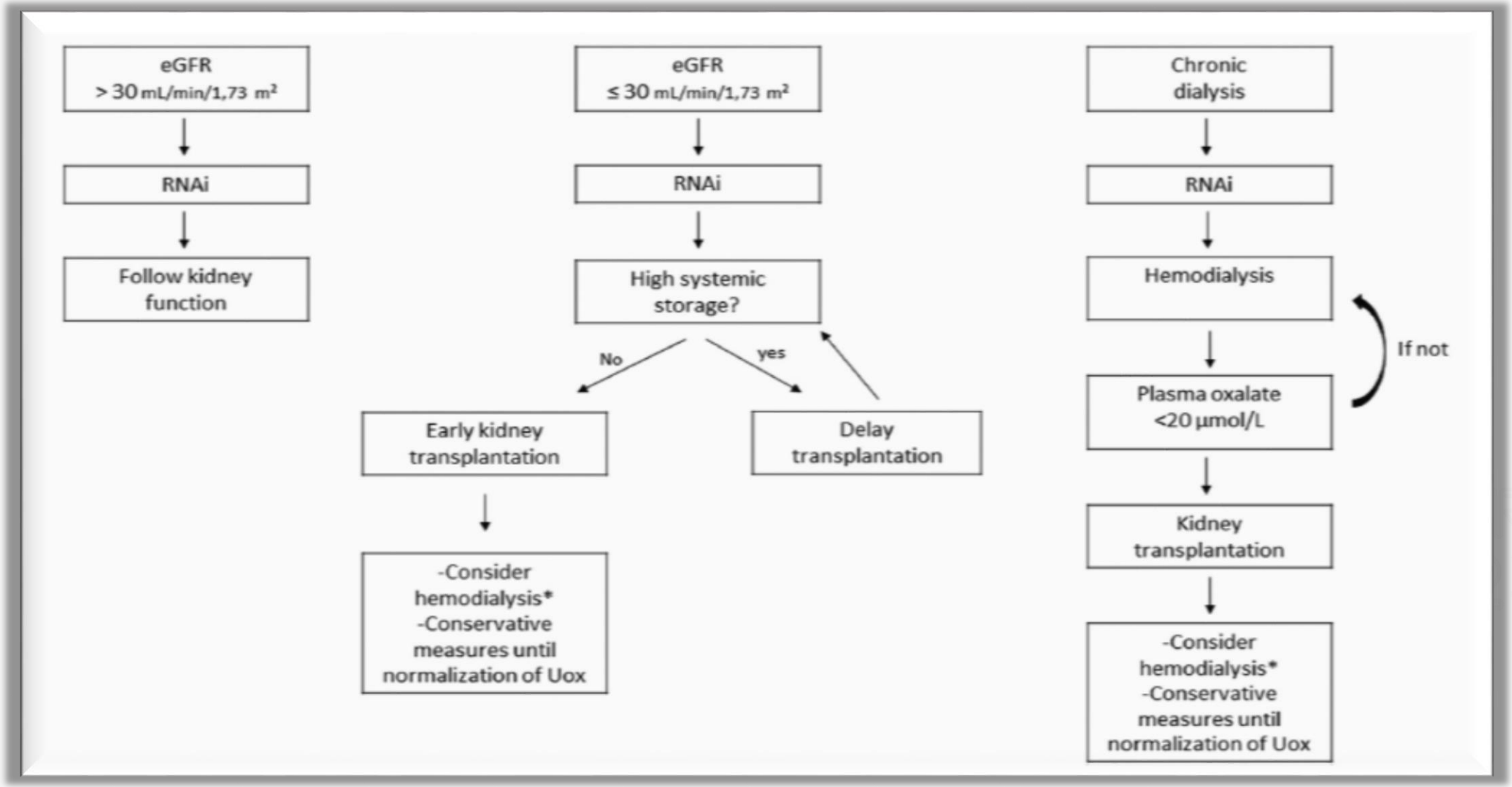
Consider isolated kidney transplantation, based on plasma oxalate response to VB6 and/or RNAi therapy; otherwise consider combined liver–kidney transplantation

New strategies for management and kidney transplantation in 1HO with CKD in the era of (RNAi) drugs



MANAGEMENT OF PH1 PATIENTS IN THE ERA OF NEW TREATMENTS

- With such emerging therapies, **liver transplantation** will hopefully no longer be required
- **quality of life** will be very much improved
- Removing the burden of liver transplantation will improve **survival of patients**

- it is important to note that the current data about lumasiran suggest that unlike liver transplantation, this drug **does not allow complete normalization** of the endogenous production of oxalate.
- 65% reduction of UOx after 6 months of treatment

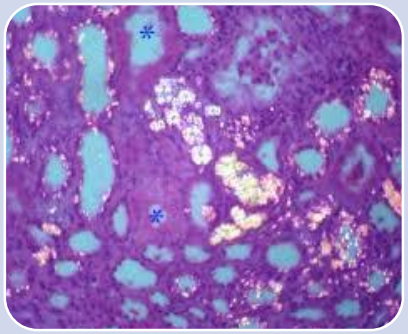
Best Timing for Kidney TX After Correction of the Metabolic Defect

- ✓POx values should be maintained at **<20 mmol/L before considering the kidney transplant** procedure
- ✓this POx value is very difficult to reach in daily clinical practice and also depends on systemic oxalate storage.
- ✓Non-PH1 patients on chronic dialysis often show a POx value > 20 mmol/L,suggesting that this target value might be too low
- ✓Intensive hemodialysis strategies were used (daily sessions of [high-flux] hemodialysis, nocturnal hemodialysis, or, mainly in small children, a combination of hemodialysis and nocturnal peritoneal dialysis1) to maintain POx **during interdialysis sessions below 30–45 mmol/L,**

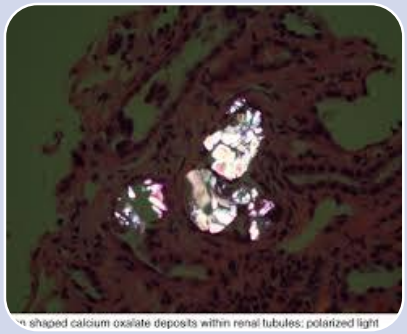
Pox and Uox levels after CLKT

- ✓Although POx levels dropped rapidly, UOx levels dropped slowly and progressively (with a median slope of 0.35 mmol/24 h per year
- ✓After 3 years, 36% of combined kidney–liver recipients still had hyperoxaluria.
- ✓It is essential to closely monitor UOx and POx after kidney transplantation and to continue applying hyperhydration and crystallization inhibitor intake to protect the new kidney allograft from oxalate deposition until normalization of POx and UOx.

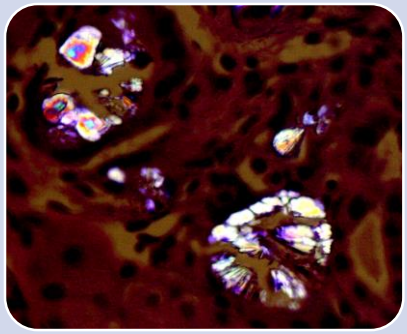
Management With HD after Kidney Transplantation



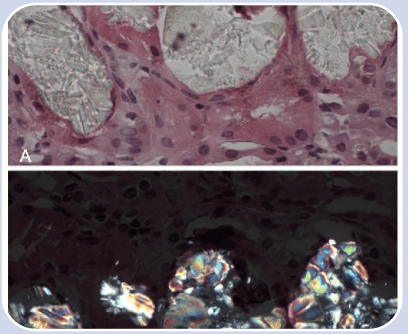
Severe oxalate burden with oliguria



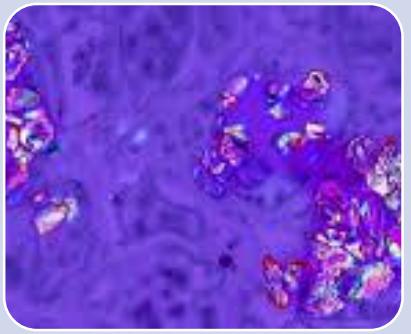
ATN



Delayed graft function



Some teams perform HD in all tx pts

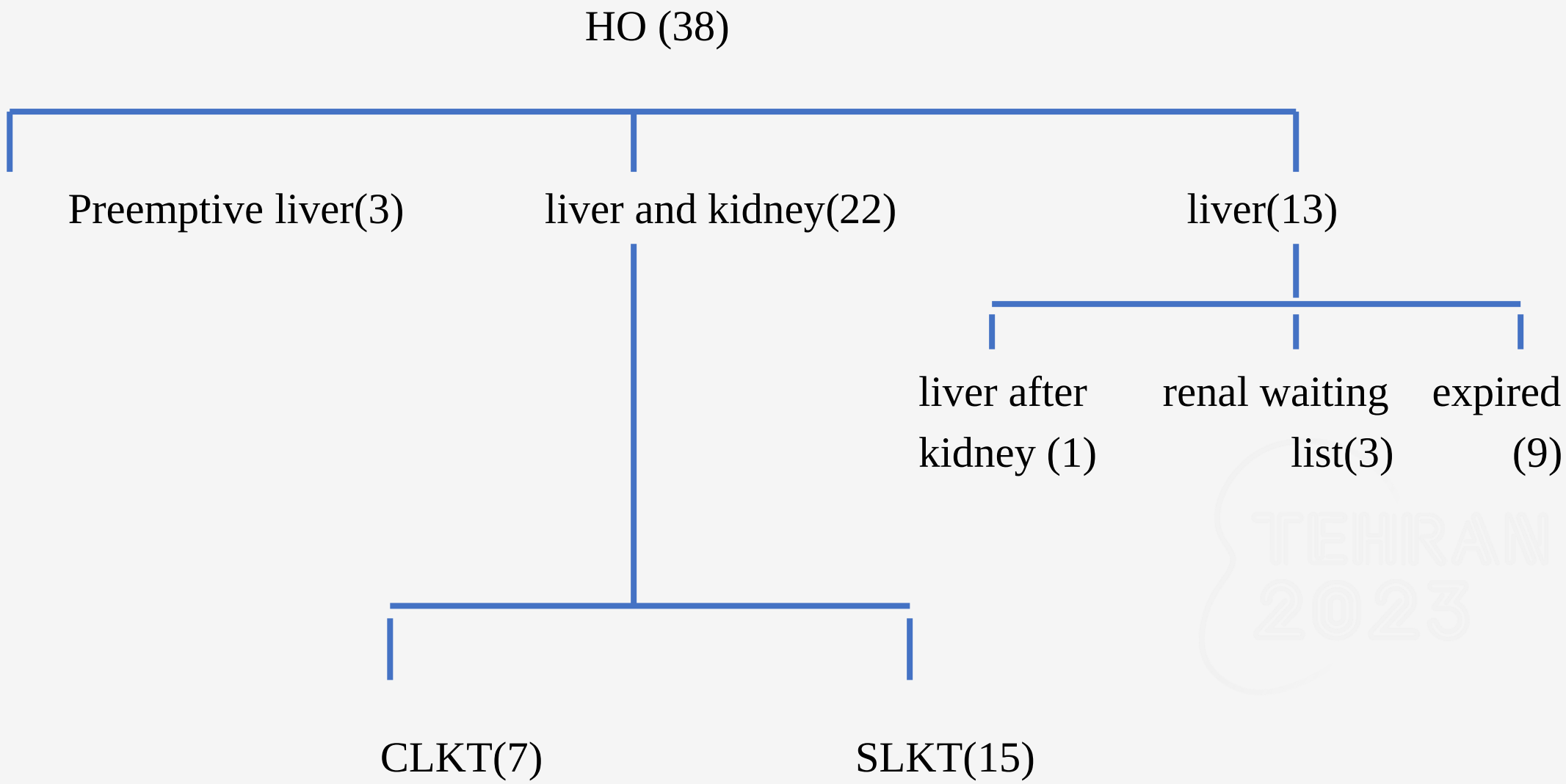


Apply HD until Pox <20 μmol/L.

Native kidney removal

- ✓Native kidneys are target organs of oxalate systemic storage, some centers propose bilateral native kidney removal during transplantation
- ✓The potential usefulness of this procedure is controversial and debatable
- ✓Further prospective studies including larger cohorts are needed to assess the efficacy and safety of such operative procedures

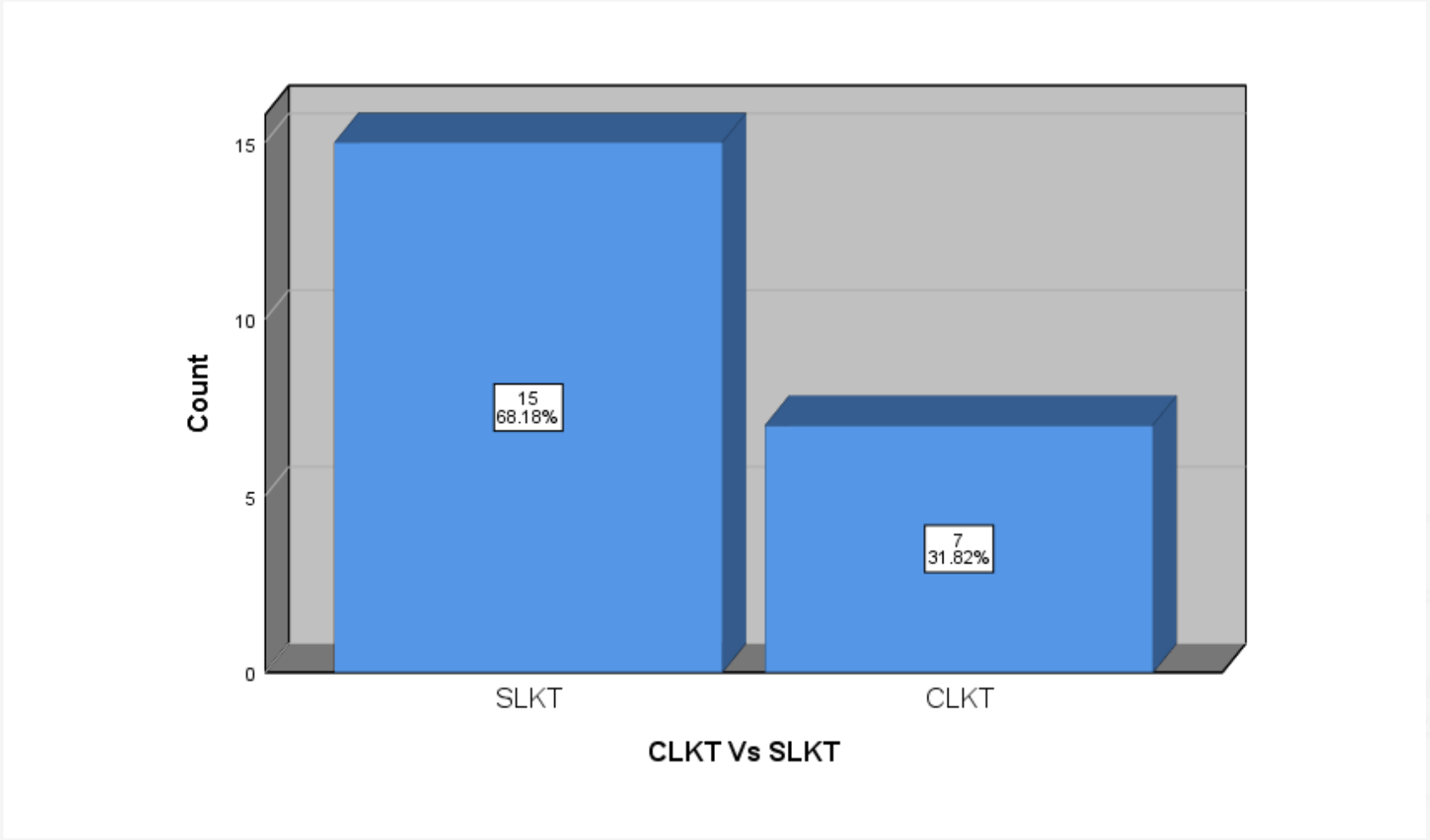
Patients ≤ 20 years old with 1 HO in shiraz tx center



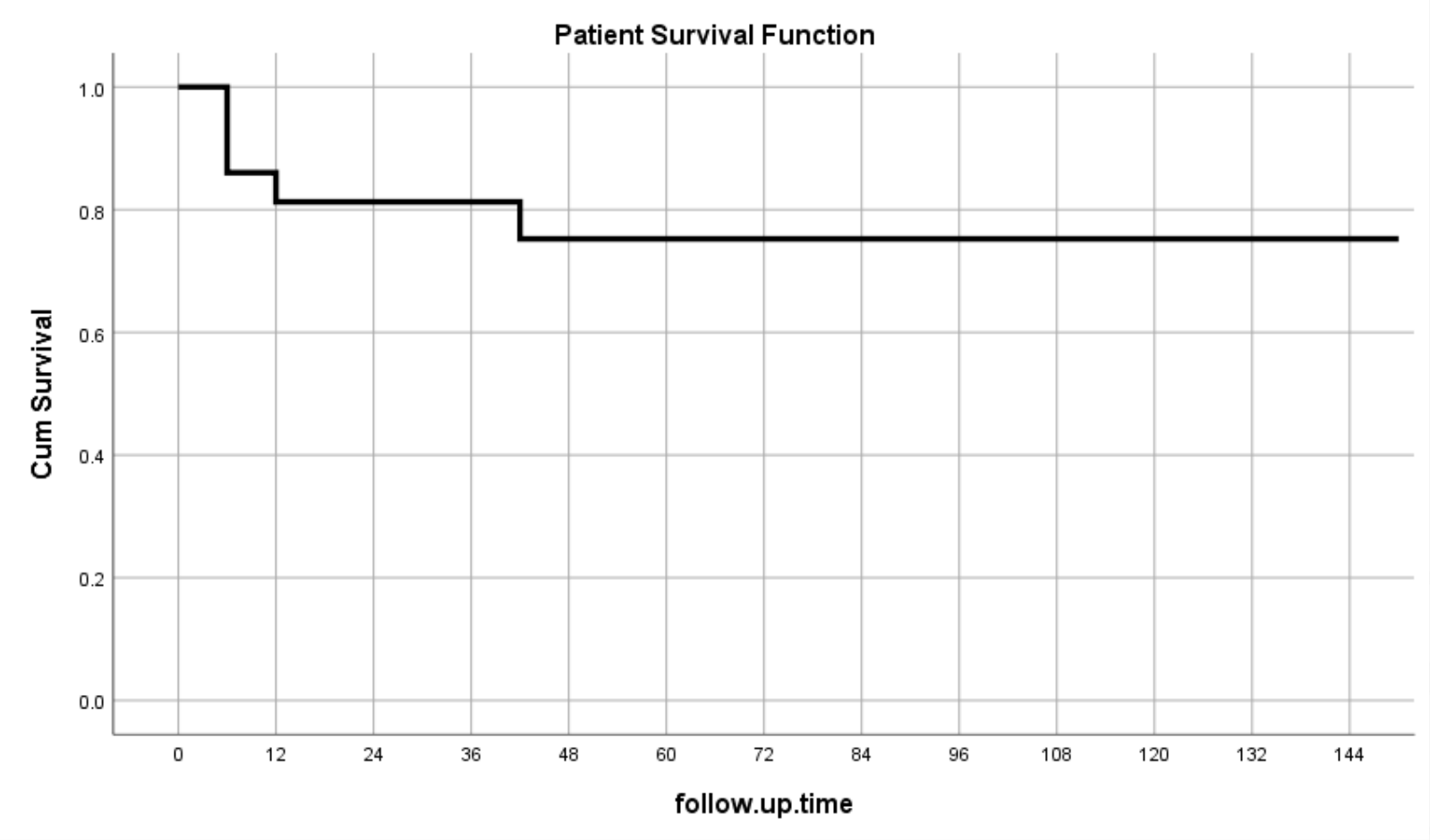
characteristics

- age at TX (yr)	15± 4.64 (5-20) med(16)
- age (yr)	20.47± 7.46 (10-32) med(21)
- gender (M/F)	15/7
- type of TX	
CLKT	7
SLKT	15
PLT	3
LT	13

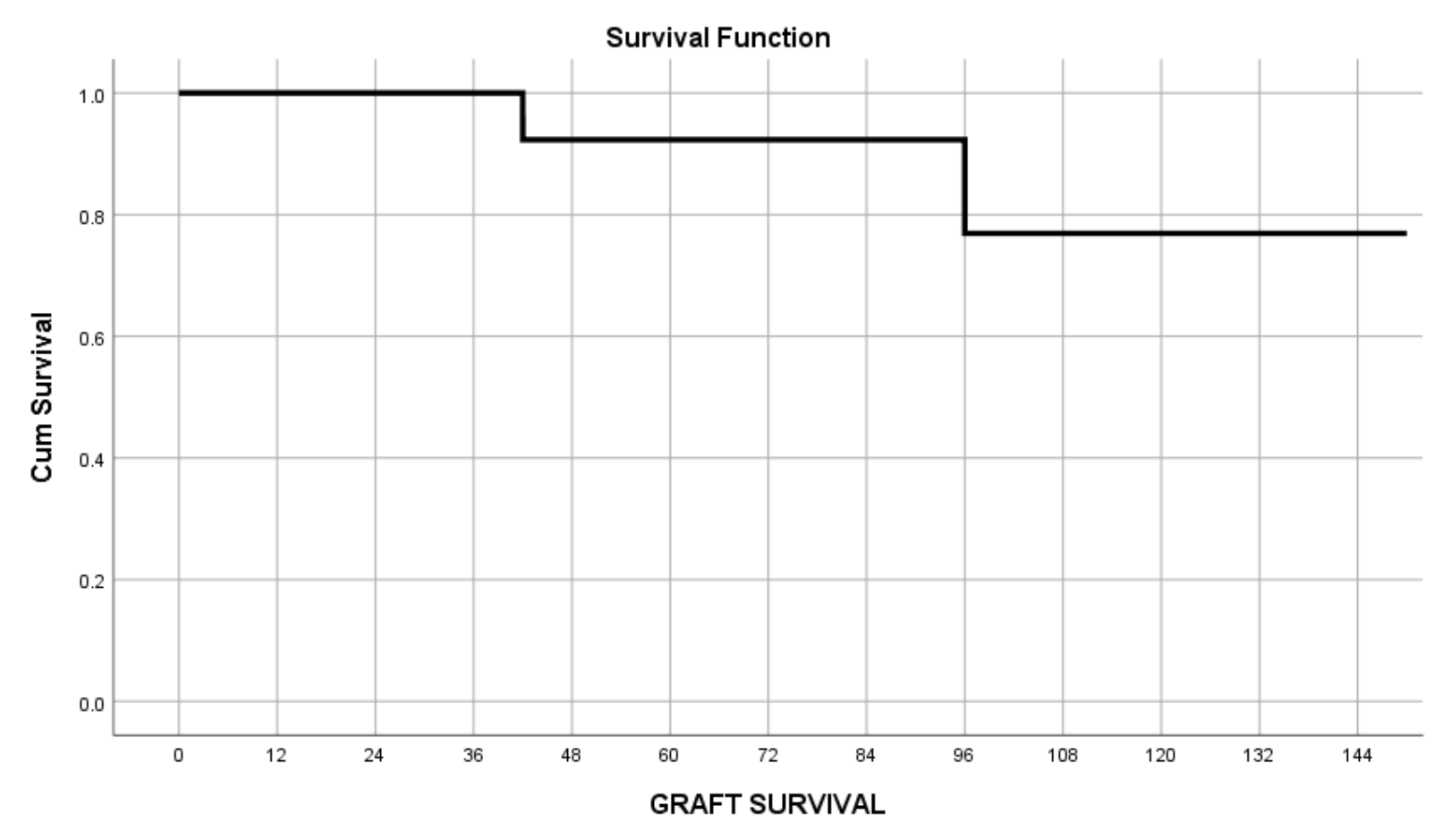
follow up (mo)	58.14±44.91 (5-149) med(50)
CR	1.34±0.45 (0.58-2.3) med (1.30)
GFR	62.76± 15.32 (39-96) med(56)
graft survival(1-5-10 yr)	100% 92% 77%
pt survival (1-5-10 yr)	81% 75% 73%


Count
15
10
5
0
15
68.18%
7
31.82%
SLKT
CLKT
CLKT Vs SLKT

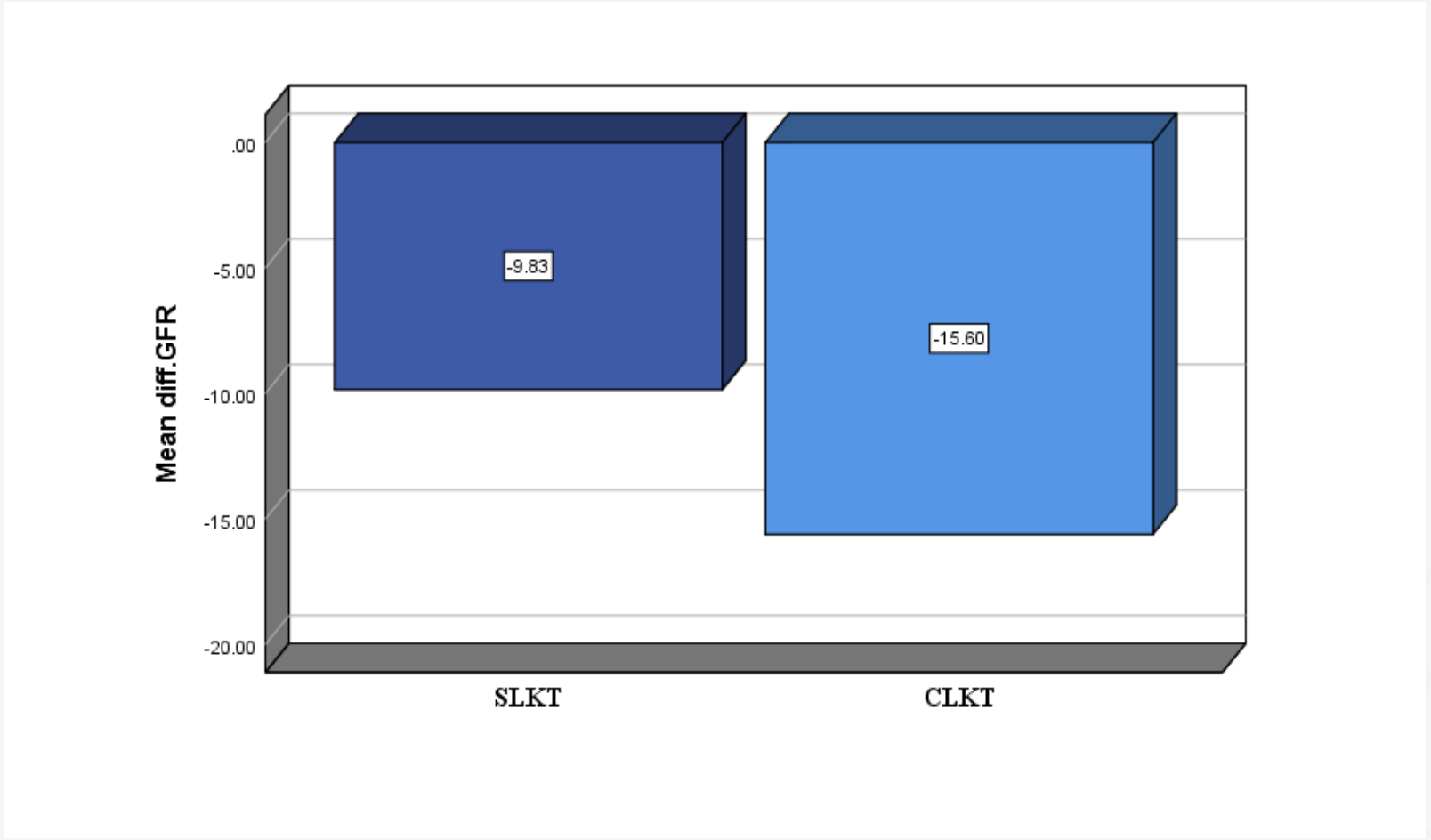
PATIENT SURVIVAL



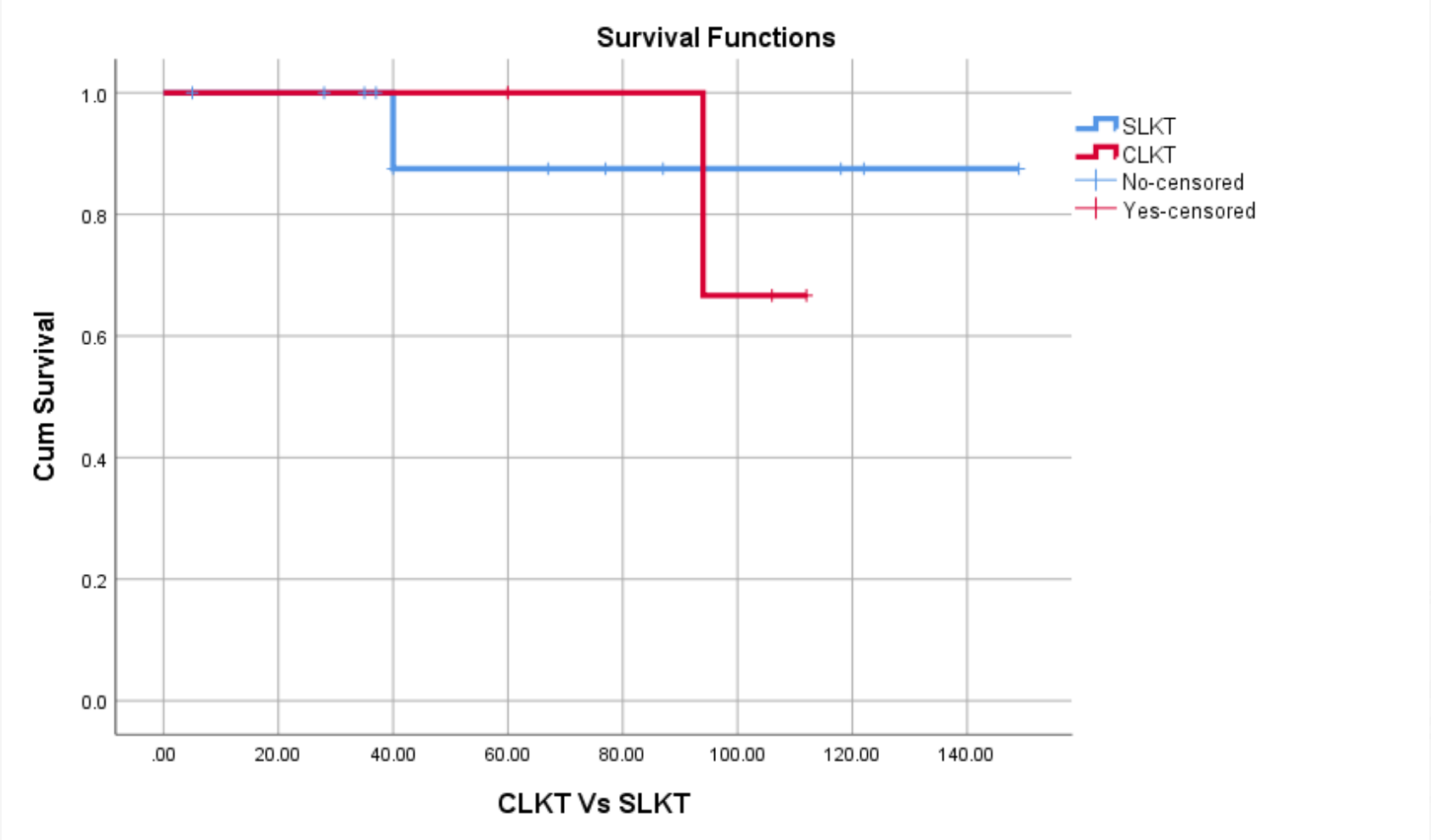
GRAFT SURVIVAL



CLKT Vs SLKT



GRAFT SURVIVAL (CLKT Vs SLKT)



CONCLUSION

- ✓The management of kidney transplant candidates and recipients will be profoundly modified in the near future
- ✓Liver transplantation will no longer be necessary to treat the liver metabolic defect associated with PH1
- ✓Developing better tools to evaluate the systemic oxalate burden will help delineate the best timing for kidney transplantation to avoid oxalate deposition