HYPOXIA INDUCIBLE FACTOR-PROLYL HYDROXYLASE INHIBHITORS

DR VILESH VALSALAN

CONSULTANT NEPHROLOGIST AND TRANSPLANT PHYSICIAN

ACADEMIC CORDINATOR – EXTRA CORPOREAL NEPHROLOGY GROUP [ECNG]

INTRODUCTION

- Under normal oxygen conditions, **prolyl hydroxylase enzymes** degrade HIF (hypoxia-inducible factor).

HIF-PHIs inhibit these enzymes → stabilize HIF → activate transcription of:

Erythropoietin (EPO) (mainly in kidney & liver)

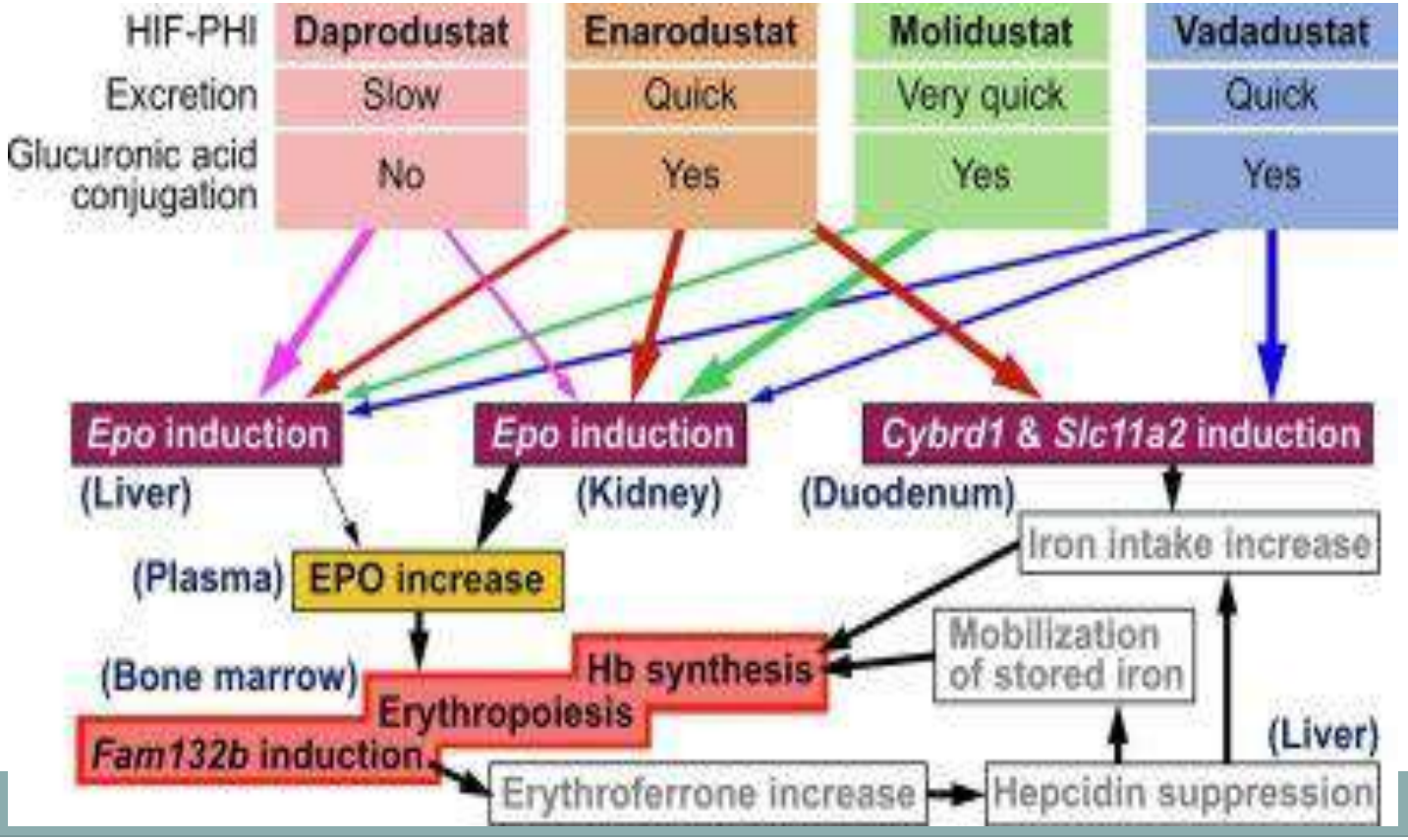
Transferrin

DMT1

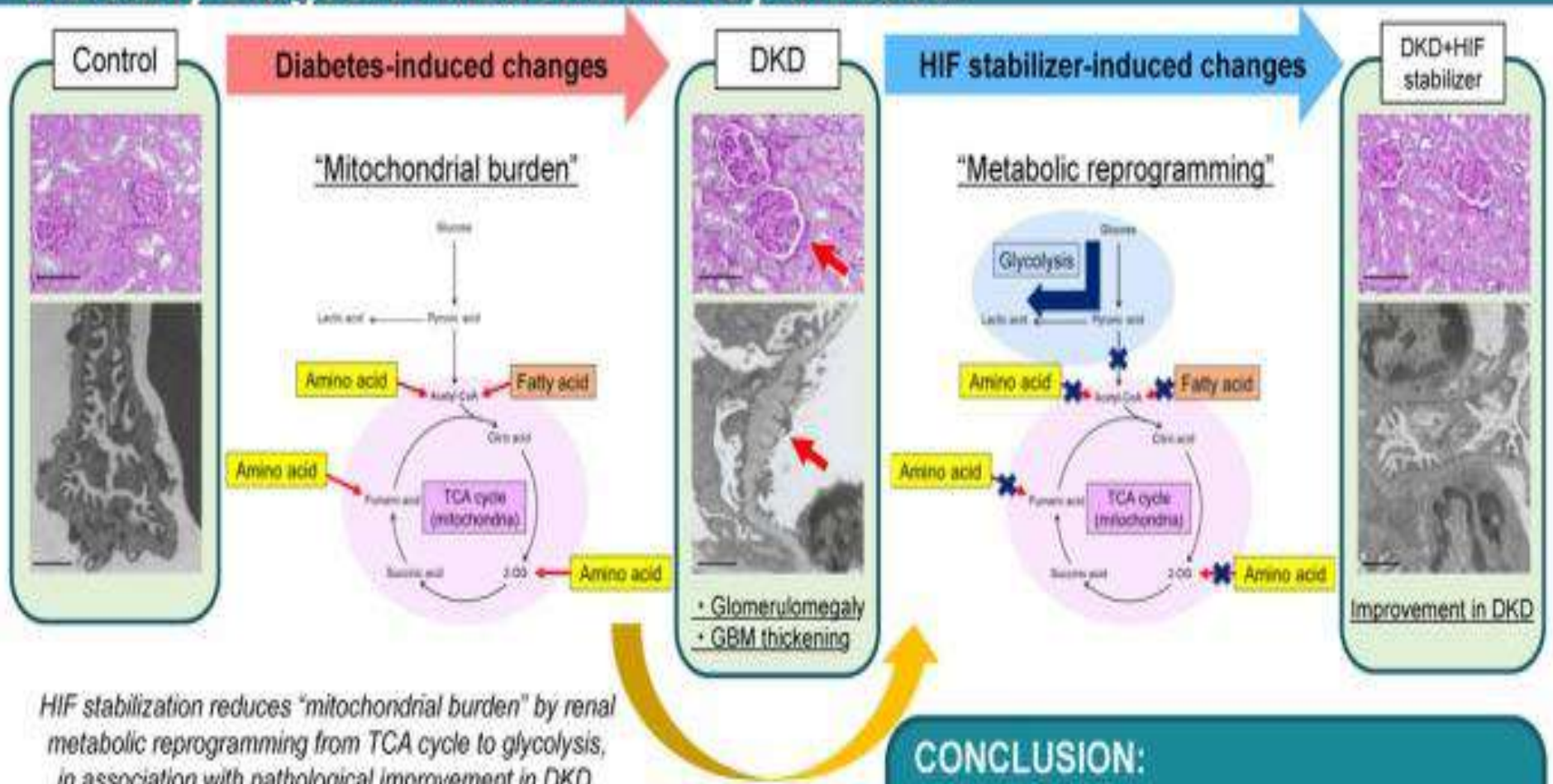
↓ **Hepcidin** (improves iron availability)

- Mobilises iron and may reduce IV iron needs.
- Works better in ESA hyporesponsive states.

- HIF-PHIs induce renal and hepatic Epo gene expression in a drug-specific manner.
- The kidney outperforms the liver in HIF-PHI-inducible EPO production.
- HIF-PHIs directly induce duodenal gene expression related to iron intake.



The oral hypoxia-inducible factor prolyl hydroxylase inhibitor enarodustat counteracts alterations in renal energy metabolism in the early stages of diabetic kidney disease.



HIF stabilization reduces "mitochondrial burden" by renal metabolic reprogramming from TCA cycle to glycolysis, in association with pathological improvement in DKD.

CONCLUSION:

HIF stabilization counteracts renal energy metabolism alterations occurring in the early stages of diabetic kidney disease.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Hasegawa et al., 2019

DOSAGE

- **Dialysis-dependent (DD) patients** - 100 mg administered thrice weekly post dialysis.

- **Non dialysis dependent patients (NDD)**
  - erythrocyte stimulating agent (ESA) naive - 100 mg three times weekly,
  - switching from an ESA -100, 125 or 150 mg thrice weekly, depending on the previous dose of ESA (epoetin, darbepoetin or methoxy polyethylene glycol-epoetin beta).

- **Maintenance dose** - based on haemoglobin levels assessed every 4 weeks, with a maximum dosage of 150 mg three times weekly

ESAs Compared to HIF-PHIs

	ESAs	HIF-PHIs
MOA	• Stimulate RBC production	• HIF stimulates EPO production & erythropoiesis, improves iron uptake • HIF-PHI prevents HIF degradation
Benefits	• Raise Hb, reduced need for RBC transfusion • Improved HRQoL (inconsistent)	• Raise Hb, reduced need for RBC transfusion • Improve HRQoL (?); network meta-analysis: daprodustat associated with reduced fatigue vs roxadustat[1]
Effectiveness	• Same if given in equivalent doses • epoetin and darbepoetin more effective SC	• No head-to-head clinical trials, but network meta-analysis showed no difference[1]
Safety	• HTN • Access thrombosis, thromboembolic events, MACE • Enhance some malignancies	• HTN • Access thrombosis, thromboembolic events, MACE • Enhance malignancies?

Randomized Study of Roxadustat on Efficiency and Safety for Post-transplantation Anemia (PTA) Treatment

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Methods and cohort

- Randomized trial, 2:1
- China, single center
- 150 patients with kidney transplant

	Roxadustat	vs	control
	3 times/wk		usual care
Hb g/dL	10.46±0.44		10.43±0.59
eGFR mL/min1.73 m²	50.19±20.3		53.22±21.09

Results

12 weeks

Primary outcome

	Hemoglobin	ΔHb from baseline >1g/dL	Total iron-binding capacity μmol/L	Adverse events
Control N=38	11.19	45.95%	51.20 ± 8.93	21.05%
Roxadustat N=90	12.20	78.89%	59.93 ± 12.28	16.67%

Hb= hemoglobin, eGFR= estimated glomerular filtration rate

KI REPORTS
Kidney International Reports

Kong W et al, 2024

Visual abstract by:
Cristina Popa, MD
@NephroSeeker

Conclusion: Roxadustat effectively increased Hb in patients with PTA with an adverse event profile comparable to that of the control.

Two Phase 3 Studies on Ophthalmological Effects of Roxadustat versus Darbepoetin

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Methods and Cohorts

Japan
Multicenter

Randomized controlled trials: Darbepoetin alfa (DA) vs roxadustat

Dialysis-dependent (DD) patients (N=302)

Non-dialysis-dependent (NDD) patients (N=262)

Interventions

Darbepoetin alfa

Once every 2 weeks (N=152)

Maximum duration for 24 weeks. Dose titrated to target Hb 10-12 g/dL

Randomized (1:1)

Roxadustat

Thrice weekly (N=150)

Maximum duration for 24 weeks. Dose titrated to target Hb 10-12 g/dL

Results

New or worsening retinal hemorrhage compared to baseline (baseline = with/without retinal hemorrhage)

	DA	Roxadustat	95% CI
DD	36.6% (53/145)	32.4% (46/142)	-15.1% to 6.8%
NDD	39.8% (51/128)	31.4% (38/121)	-20.3% to 3.4%

New retinal hemorrhage compared to baseline (baseline = absent retinal hemorrhage)

	DA	Roxadustat	95% CI
DD	25% (24/96)	19.1% (18/94)	-17.6% to 5.9%
NDD	25% (18/72)	12.9% (8/62)	-25.1% to 0.9%

Conclusion: In these studies, roxadustat, compared to DA, was not associated with an increased risk of adverse ophthalmological events in these cohorts.

KI REPORTS
Kidney International Reports

Sepah YJ et al, 2022

Visual abstract by:
Mythri Shankar, MD, DNB
@nephromythri

ASCEND-D Trial

Study Design

Population: CKD on Dialysis (n≈2964)
Intervention: Oral Daprodustat
Comparator: Injectable ESA

Co-Primary Endpoints:
- Hemoglobin Non-Inferiority
- MACE Non-Inferiority

Efficacy (Hemoglobin)

Hb Change:
Daprodustat: +0.28 g/dL
ESA: +0.10 g/dL

Result: Non-Inferior
Target Hb maintained (10–11.5 g/dL)

Cardiovascular Safety (MACE)

Events:
Daprodustat: 25.2%
ESA: 26.7%

Hazard Ratio: 0.93
(95% CI 0.81–1.07)
Met Non-Inferiority

Key Takeaways

✓ Oral alternative to ESA
✓ Effective Hb maintenance
✓ Comparable CV safety
✓ Useful in dialysis anemia management