



Real-world experiences with the use of HIF-PH inhibitors

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COI disclosure

presenter: Masaomi Nangaku

I have the following relationships to disclose.

Potential Financial Conflicts of Interest

(1)Employment: No

(2)Stock ownership or options: No

(3)Patent royalties/licensing fees: No

(4)Honoraria and advisory fees: Kyowa-Kirin, Astellas, Astra Zeneca, GSK, Daiichi-Sankyo, Tanabe-Mitsubishi, Chugai, Torii, JT, Novo Nordisk, BI

(5)Research funding: Kyowa-Hakko-Kirin, Daiichi-Sankyo, Astellas, Ono, Tanabe-Mitsubishi, JT, Chugai, Bayer, Torii, Takeda

THE NOBEL PRIZE
IN PHYSIOLOGY OR MEDICINE 2019



William G.
Kaelin Jr.

Sir Peter J.
Ratcliffe

Gregg L.
Semenza

“for their discoveries of how cells sense
and adapt to oxygen availability”

THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET

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Hypoxia Inducible Factor- Prolyl Hydroxylase Inhibitor (HIF-PHi)

Approval

Roxadustat

Sept 2019

Daprodustat

June 2020

Vadadustat

June 2020

Enarodustat

Sept 2020

Molidustat

Jan 2021

Currently available in Japan

Case Study :

How to transition patients from ESAs to HIF-PH inhibitors?

Is pairing with iron important?

Twenty-five years ago, diagnosed with hypertension and managed on medication (ARB and Ca blocker) and lifestyle changes

Five years ago, referred to our hospital due to kidney dysfunction (eGFR 31) and proteinuria

Four years ago, darbepoietin was started and Hb level was maintained at about 9 g/dL with 60 µg/month of darbepoietin

Darbepoietin was changed to daprodustat (4mg per day)

Patient information

| | |
|-----------------|---------------------------------------|
| Sex | Male |
| Age | 63 |
| BP | 146/88 mmHg |
| Hb | 9.3 g/dL |
| Ferritin | 138 ng/mL |
| TSAT | 36% |
| eGFR | 13.4 mL/min/1.73 m² |

Twenty-five years ago, diagnosed with hypertension and managed on medication (ARB and Ca blocker) and lifestyle changes

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| | Before conversion | Week 2 | Week 4 | Week 6 | Week 10 | Week 12 |
|-----------------|--------------------------|---------------|---------------|---------------|----------------|----------------|
| Hb | 9.3 | 9.9 | 10.2 | 10.4 | 9.8 | 10.3 |
| Ferritin | 138 | | | | | 12 |
| TSAT | 36 | | | | | 11 |

Twenty-five years ago, diagnosed with hypertension and managed on medication (ARB and Ca blocker) and lifestyle changes

Five years ago, referred to our hospital due to kidney dysfunction (eGFR 31) and proteinuria

Four years ago, darbepoietin was started and Hb level was maintained at about 9 g/dL with 60 µg/month of darbepoietin

Darbepoietin was changed to daprodustat (4mg per day), followed by iron deficiency, and iron supplementation was started.

Patient information

| | |
|----------|---------------------------------|
| Sex | Male |
| Age | 63 |
| BP | 146/88 mmHg |
| Hb | 9.3 g/dL |
| Ferritin | 138 ng/mL |
| TSAT | 36% |
| eGFR | 13.4 mL/min/1.73 m ² |

| | Before conversion | Week 2 | Week 4 | Week 6 | Week 10 | Week 12 | Week 16 |
|----------|-------------------|--------|--------|--------|---------|---------|---------|
| Hb | 9.3 | 9.9 | 10.2 | 10.4 | 9.8 | 10.3 | 10.6 |
| Ferritin | 138 | | | | | 12 | 39 |
| TSAT | 36 | | | | | 11 | 50 |

Case Study :

How to transition patients from ESAs to HIF-PH inhibitors?

Is pairing with iron important?

Starting dose of enarodustat

non-dialysis dependent CKD

2 mg/day

dialysis dependent CKD

4 mg/day

Starting dose of daprodustat

non-dialysis dependent CKD

ESA naïve: 4 mg/day in case $Hb < 9$, 2 mg/day in case $Hb \geq 9$

ESA conversion: 4 mg/day

dialysis dependent CKD

4 mg/day

Starting dose of roxadustat

ESA naïve: 50 mg

ESA conversion: 70 mg or 100 mg

| EPO (IU/wk) | darbepoietin (µg/wk) | Epoetin beta-pegol (µg/wk) | roxadustat |
|-------------|----------------------|----------------------------|------------|
| <4500 | <20 | ≤100 | 70 mg |
| ≥4500 | ≥20 | >100 | 100 mg |

Starting dose of vadadustat

300 mg/day

Starting dose of molidustat

non-dialysis dependent CKD

ESA naïve: 25mg/day

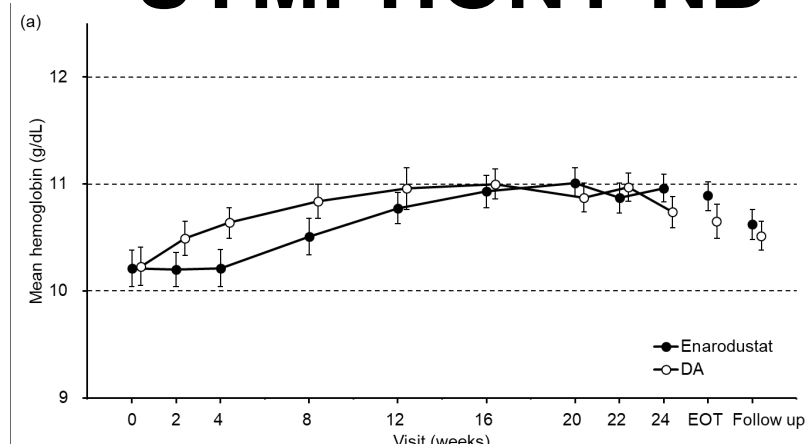
ESA conversion: 25 or 50mg/day

| EPO (IU) once/wk | EPO (IU) once/2 wks | darbepoietin (µg) once /2wks | darbepoietin (µg) once /4wks | Epoetin beta- pegol (µg) once/4wks | Molidustat |
|---------------------|------------------------|------------------------------------|------------------------------------|--|------------|
| ≤1500 | ≤3000 | ≤15 | ≤30 | ≤25 | 25 mg |
| >1500 | >3000 | >15 | >30 | >25 | 50 mg |

dialysis dependent CKD
75mg/day

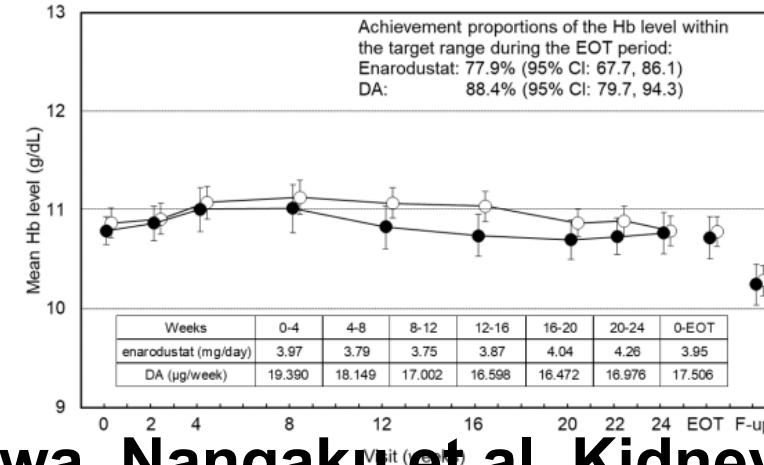
phase 3 of enarodustat in Japanese patients

SYMPHONY-ND



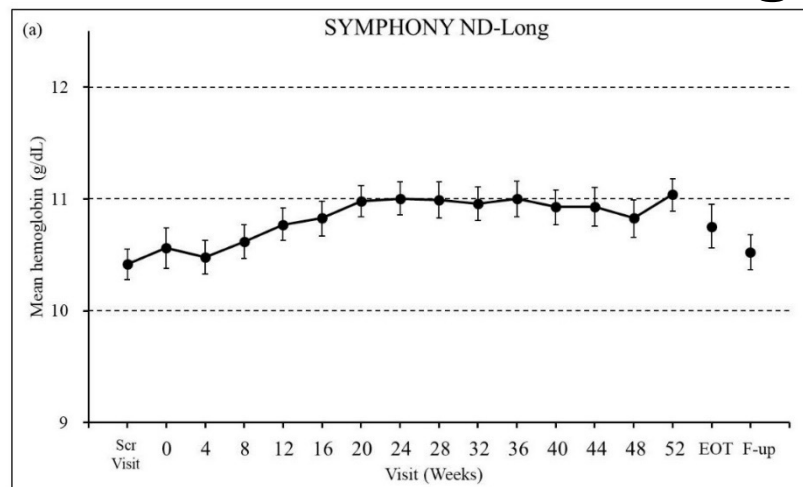
Akizawa, Nangaku et al. KI Rep 2021

SYMPHONY-HD



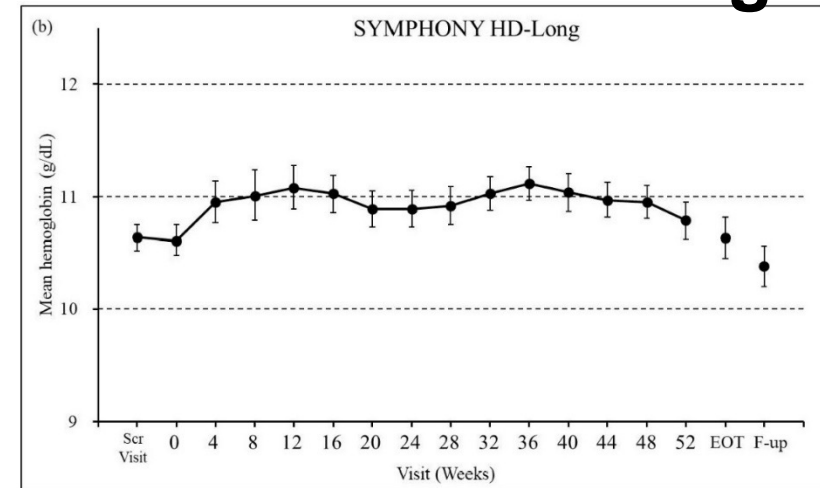
Akizawa, Nangaku et al. Kidney Dis 2021

SYMPHONY-ND Long



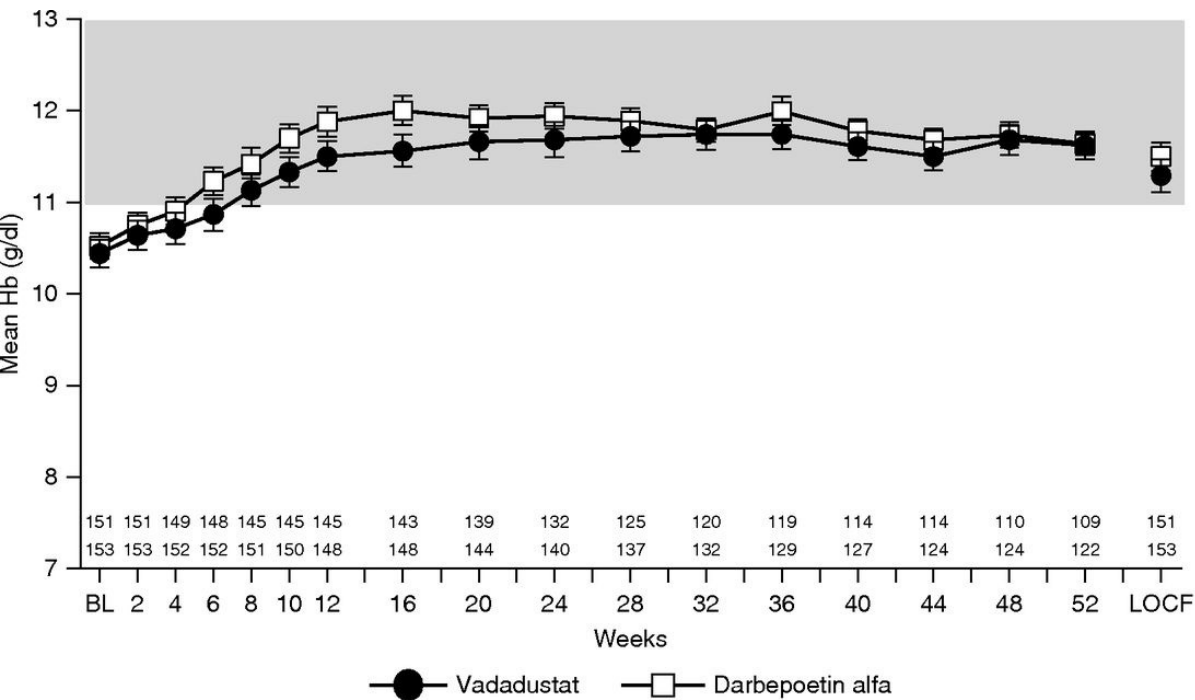
Akizawa, Nangaku et al. Ther Apher Dial 2021

SYMPHONY-HD Long



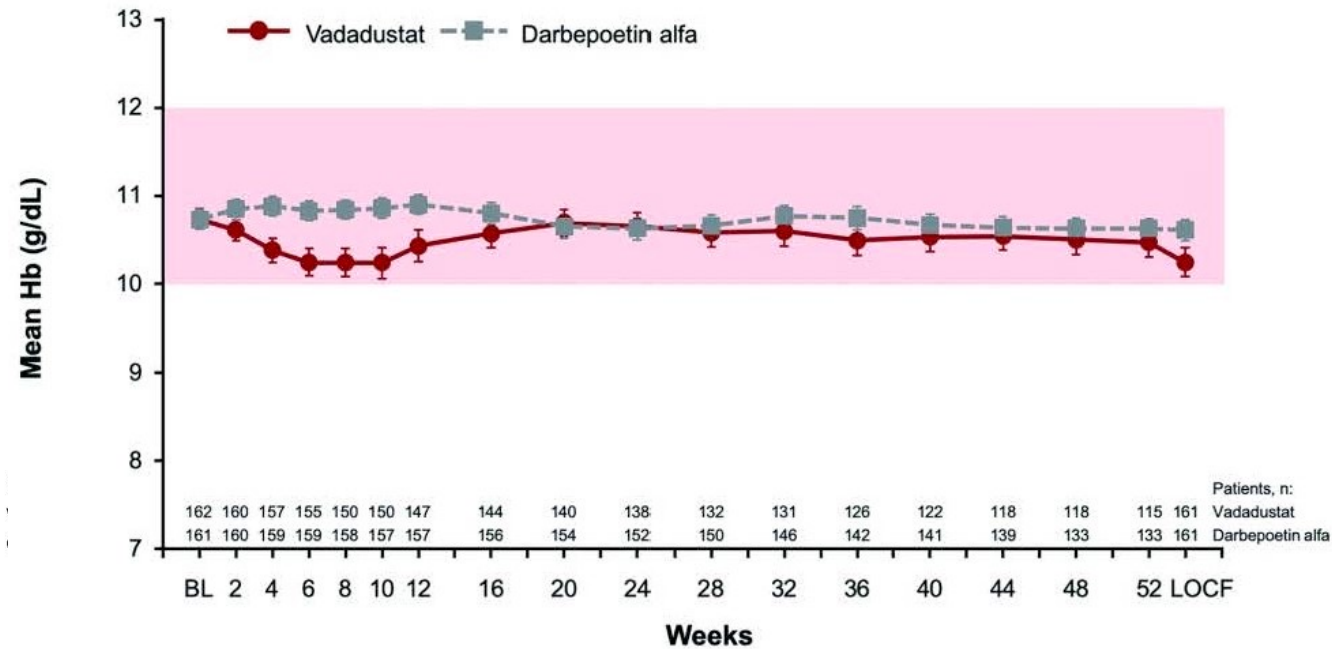
phase 3 of vadadustat in Japanese patients

non-dialysis dependent CKD



Nangaku et al. JASN 2021

HD

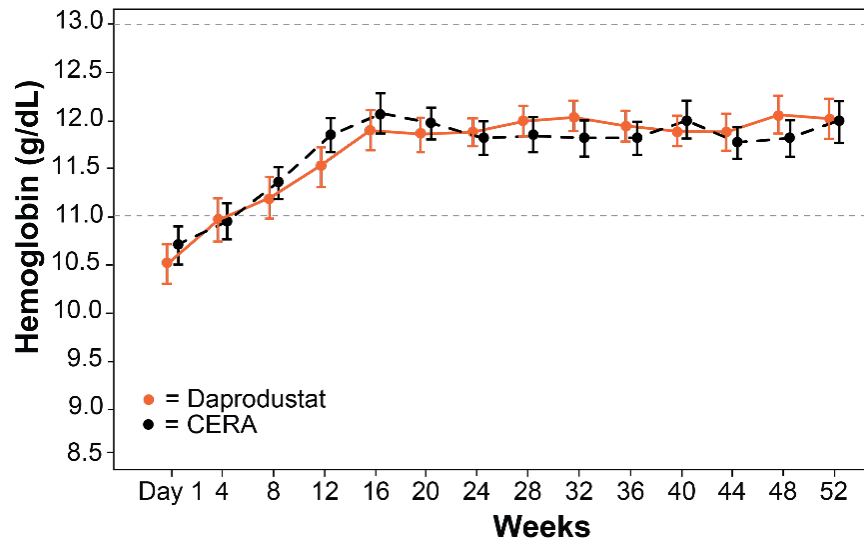


Nangaku et al. NDT 2021

phase 3 of daprodustat in Japanese patients

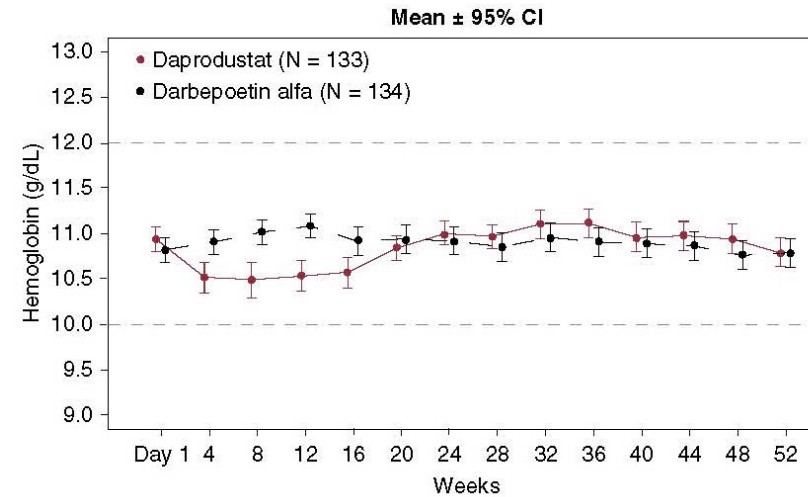
non-dialysis dependent CKD

Plot of Mean Hgb (g/dL) and 95% CIs over Time by Treatment



**Nangaku et al.
Am J Nephrol 2021**

HD

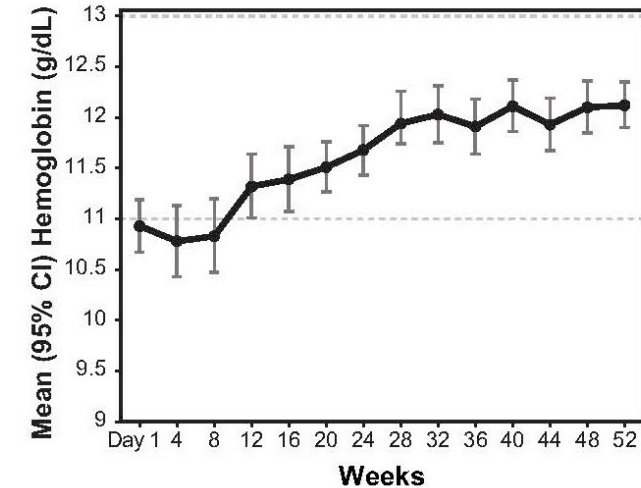


Number of Participants at Visits

| | | | | | | | | | | | | | | |
|------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Daprodustat | 133 | 133 | 127 | 125 | 124 | 123 | 123 | 123 | 122 | 121 | 120 | 117 | 117 | 115 |
| Darbepoetin alfa | 134 | 134 | 132 | 129 | 129 | 129 | 129 | 129 | 127 | 127 | 125 | 125 | 124 | 120 |

**Akizawa, Nangaku et al.
CJASN 2020**

PD

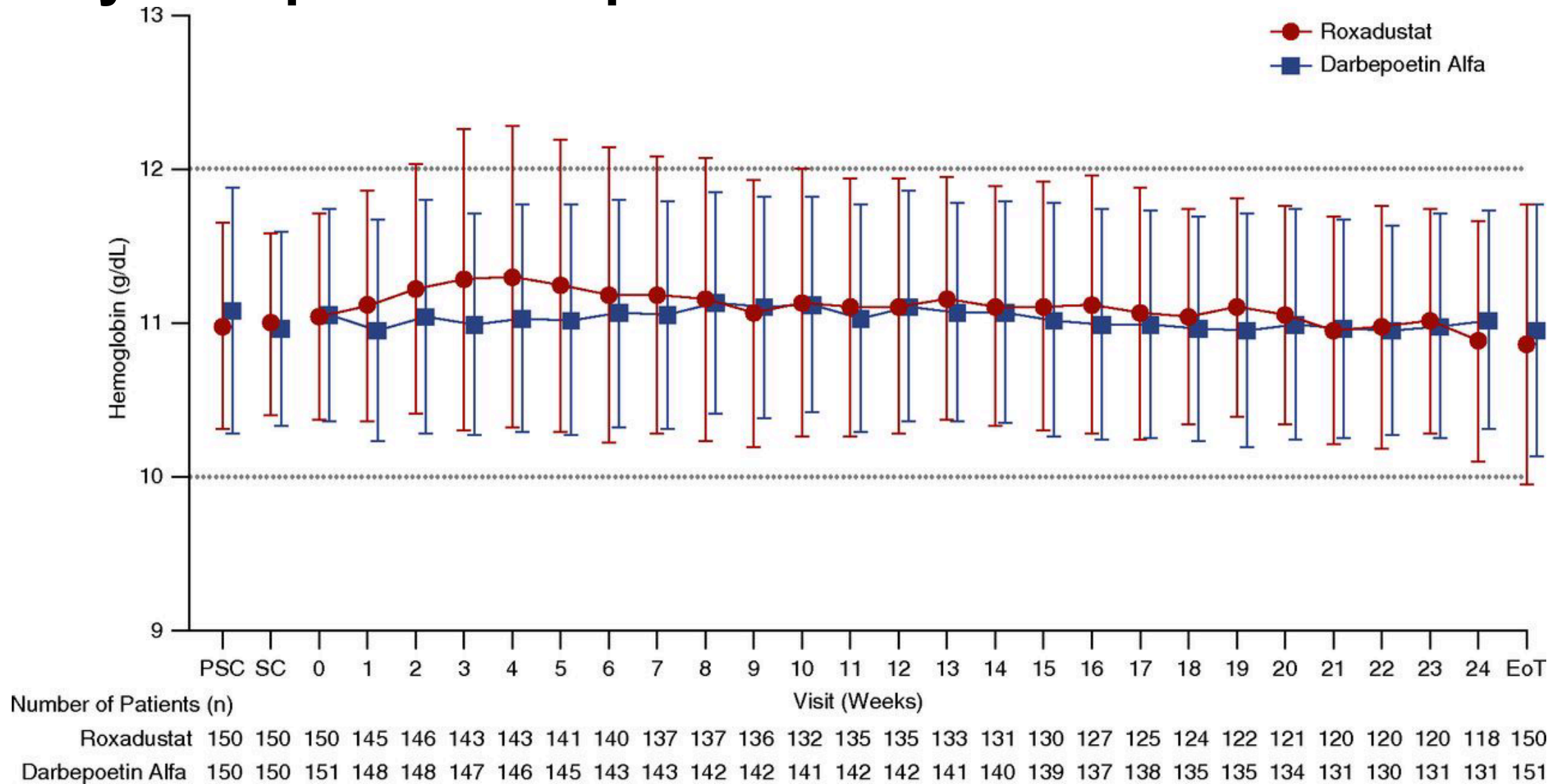


Number of Participants at Visits

| | | | | | | | | | | | | | |
|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 52 | 52 | 51 | 49 | 48 | 47 | 46 | 45 | 42 | 42 | 42 | 41 | 41 | 41 |
|----|----|----|----|----|----|----|----|----|----|----|----|----|----|

**Kanai, Nangaku et al.
Ther Apher Dial 2021**

Phase 3, randomized, double-blind, active-comparator study of Japanese HD patients



Case Study :

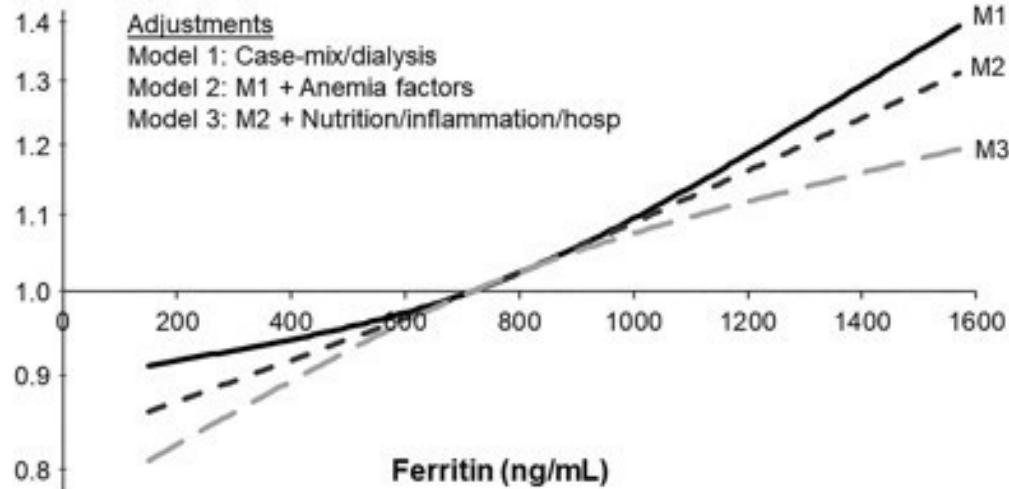
How to transition patients from ESAs to HIF-PH inhibitors?

Is pairing with iron important?

optimal treatment targets may differ worldwide

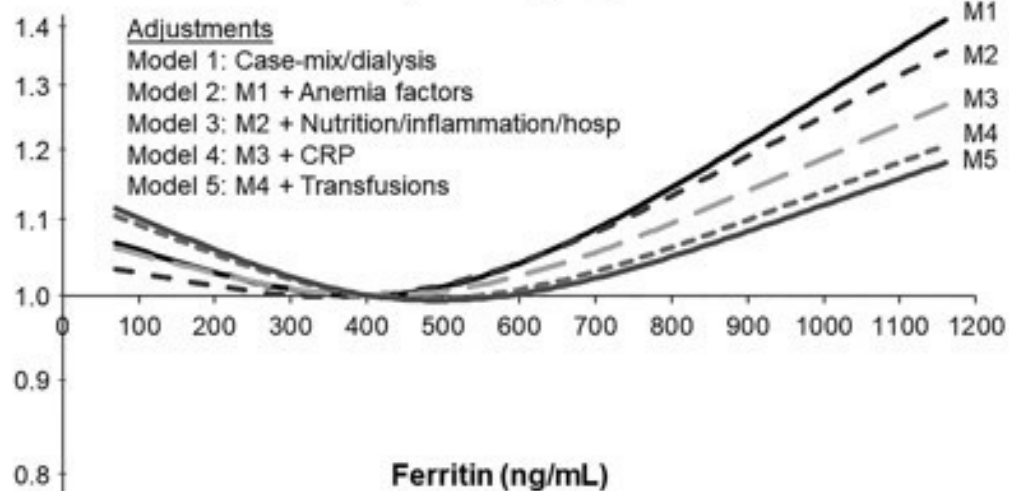
A Ferritin and mortality in the USA

Hazard Ratio vs. median ferritin (Ref= 718 ng/mL)



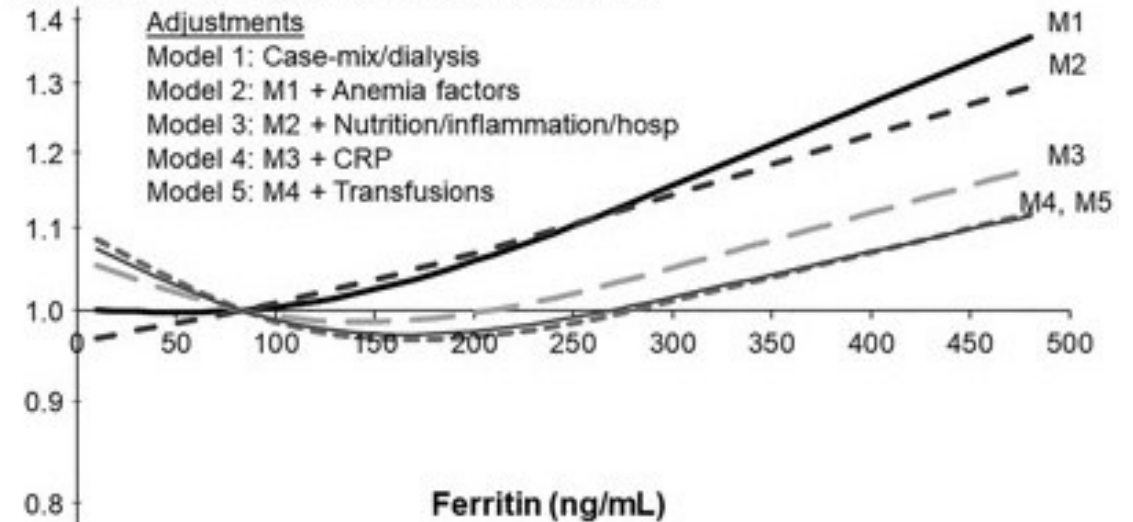
B Ferritin and mortality in Europe

Hazard Ratio vs. median ferritin (Ref= 405 ng/mL)



C Ferritin and mortality in Japan

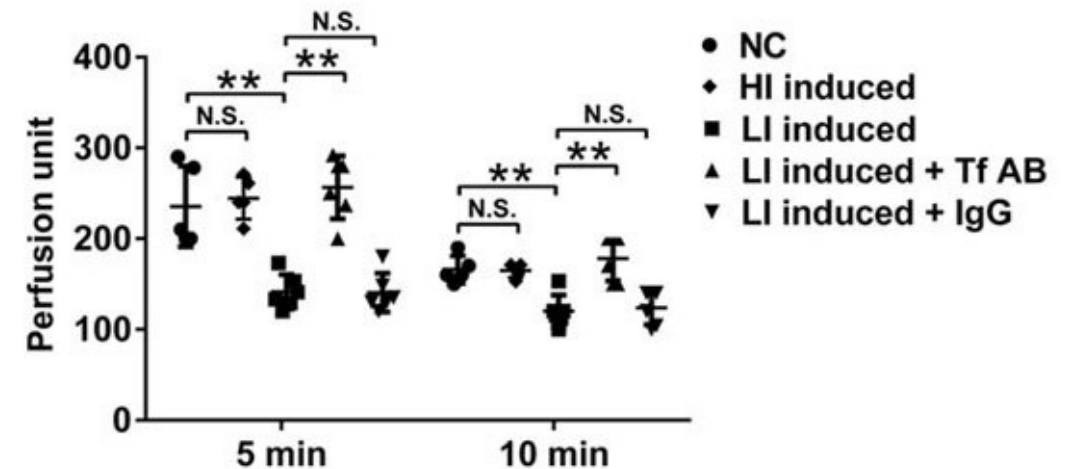
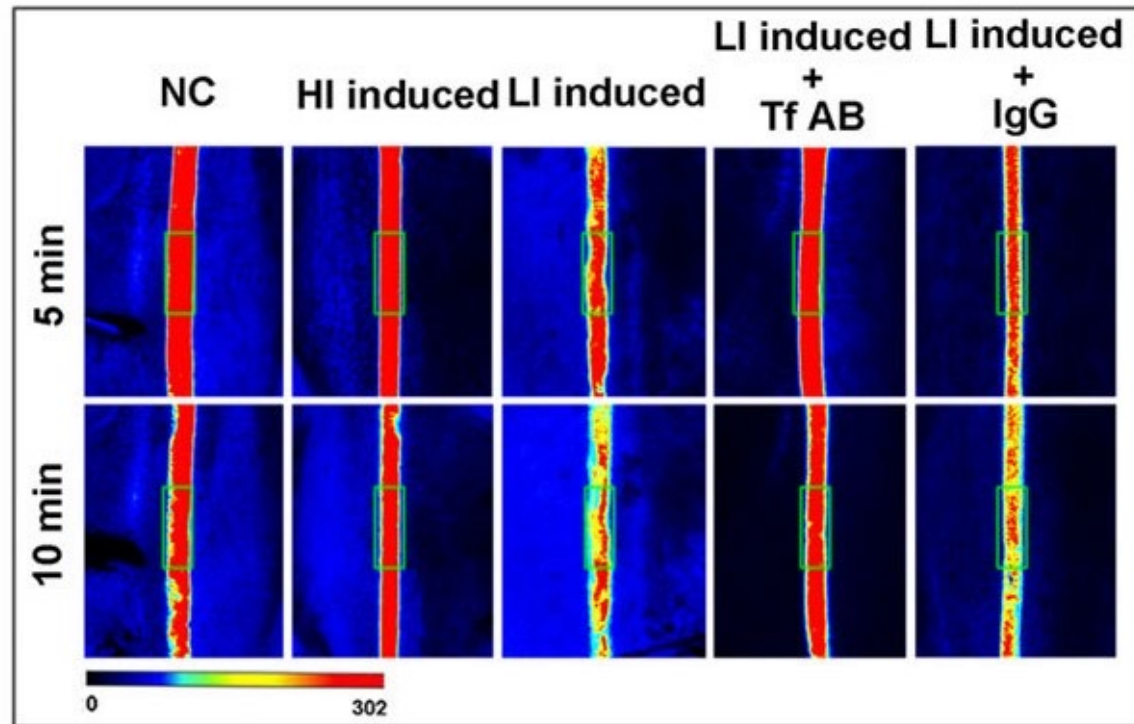
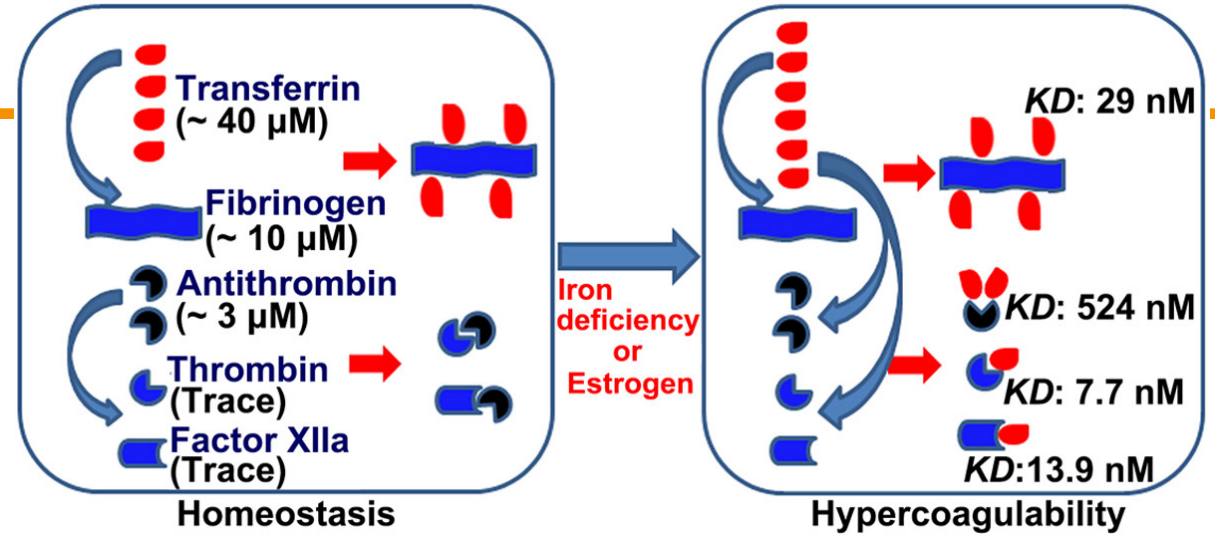
Hazard Ratio vs. median ferritin (Ref= 83 ng/mL)



Karaboyas et al.

Nephrol Dial Transplant 2018

Iron-deficiency up-regulates transferrin to induce hypercoagulability



recommendation of proper use of HIF-PH inhibitor

Chair

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MSN

Soo Kun Lim

NST

Kriengsak Vareesangthip

TSN

Chi-Chih HUNG





<Recommendation>

Iron status should be evaluated before HIF-PHI are used.

We suggest correcting iron deficiency before initiation of HIF-PHI (ferritin>100ng/ml and TSAT>20%) for all CKD patients.

Case Study:

When to stop a HIF-PH inhibitor (safety concerns)?

Thirty-five years ago, diagnosed with diabetes and got kidney transplant (his mother as a donor) fifteen years ago.

Kidney function deteriorated again due to diabetes and chronic rejection, and HD was started four years ago.

One year ago, AVF was occluded and new AVF was constructed on the other arm.

Due to pyonephropathy, the patient was referred to our hospital.

Anemia had been managed by roxadustat (100 mg every other day) at the previous hospital.

Patient information

| | |
|-----------------|--------------------|
| Sex | Male |
| Age | 73 |
| BP | 124/64 mmHg |
| Hb | 14.3 g/dL |
| Ferritin | 471 ng/mL |
| TSAT | 25% |
| Cr | 10.79 mg/dL |

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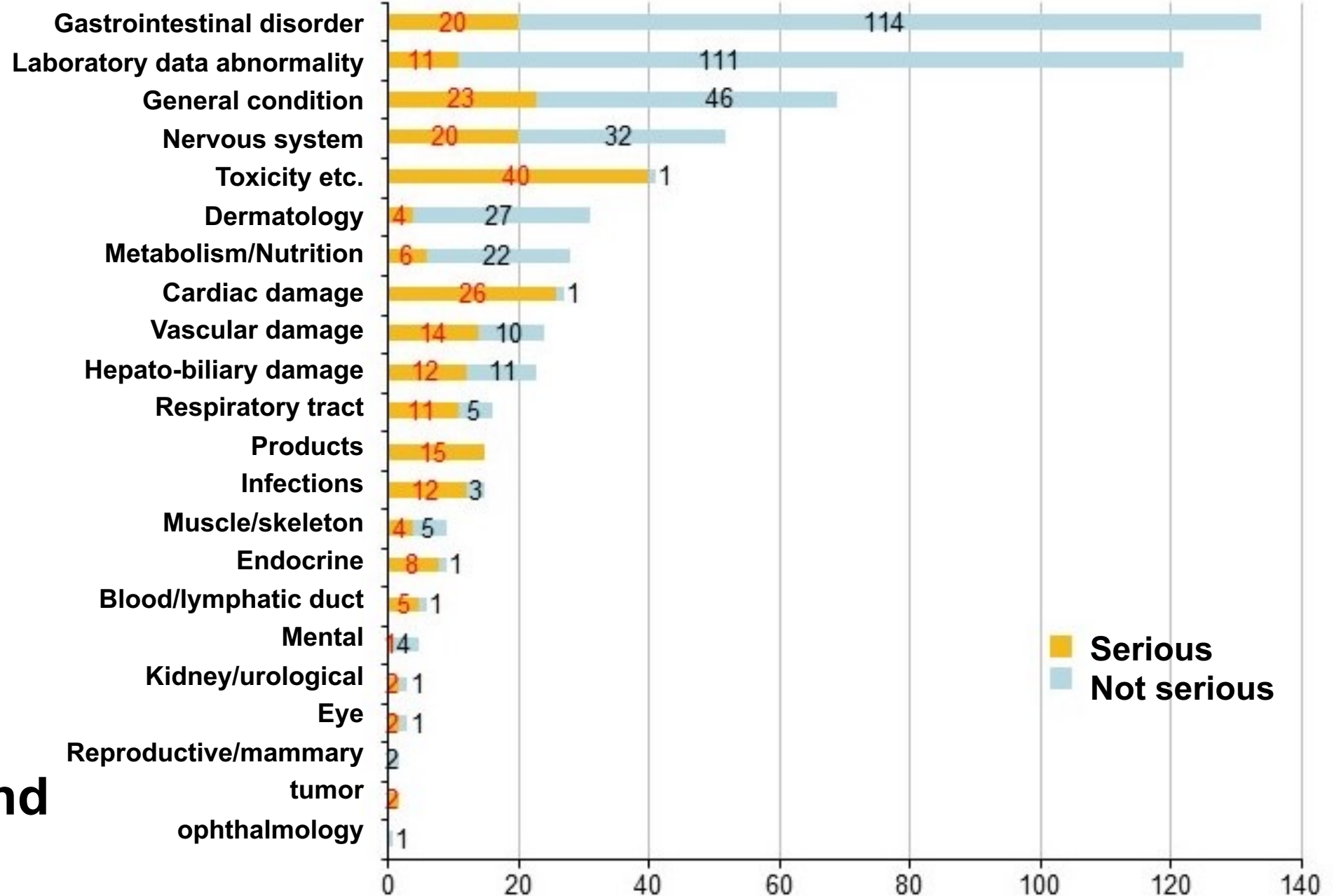
We found another thrombosis of vascular access and overshoot of Hb, and we stopped roxadustat.

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Post-marketing survey of roxadustat

409 patients, 637 cases



Nov 29 2019 ~
May 19 2020
708 hospitals and
566 clinics

| Adverse events | Total | Serious |
|------------------------------------|--------------|----------------|
| Diarrhea | 17 | |
| Hyperkalemia | 1 | 1 |
| Bladder cancer | 1 | 1 |
| Gastric cancer | 1 | 1 |
| Retinal hemorrhage | 1 | 1 |
| Brain infarction | 9 | 9 |
| Acute myocardial infarction | 5 | 5 |
| Myocardial infarction | 6 | 6 |
| Deep vein thrombosis | 4 | 4 |
| Peripheral vein thrombosis | 2 | 2 |
| Shunt occlusion | 27 | 27 |
| Shunt thrombosis | 5 | 5 |
| Dialyzer clots | 14 | 14 |

Thrombosis/embolism related events: 84 cases, 76 patients

Post-marketing survey of daprodustat

Aug 26 2020 ~ Jan 25 2021

6830 hospitals and clinics

| Retinal hemorrhage | 1 |
|----------------------------------|---|
| Age-related macular degeneration | 1 |
| Colon cancer | 1 |
| Metastasis to lymph nodes | 1 |
| malignancy | 1 |
| Rectum cancer | 1 |
| Occlusion of AV fistula | 2 |
| Thrombosis of AV fistula | 1 |
| Brain infarction | 2 |
| Deep vein thrombosis | 1 |

Post-marketing survey of vadadustat

Aug 26 2020 ~ Feb 25 2021

| Retinal hemorrhage | 0 |
|---------------------------------------|---|
| Age-related macular degeneration | 0 |
| Neoplasm (benign, malignant, unknown) | 1 |
| Occlusion of AV fistula | 0 |
| Thrombosis of AV fistula | 0 |
| Brain infarction | 2 |
| Pulmonary thrombosis | 1 |

Case Study:

Use of HIF-PH inhibitors in ESA resistant patients?

Forty years ago, diagnosed with diabetes and managed on insulin for the last 25 years

Ten years ago, referred to our hospital due to kidney dysfunction (eGFR 20) and proteinuria

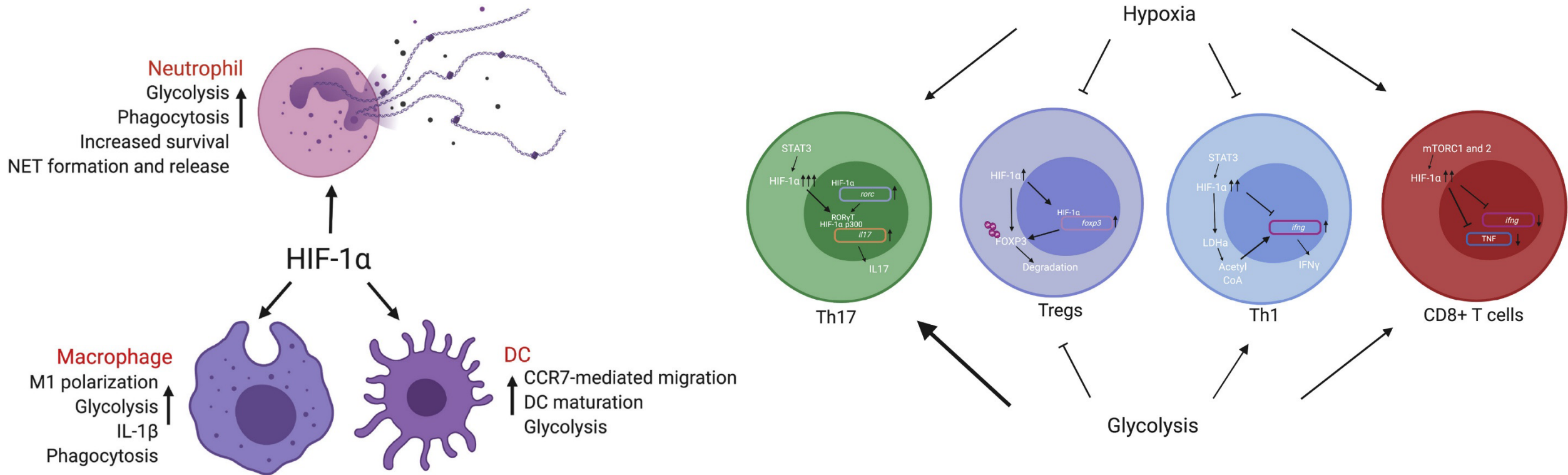
| Patient information | |
|----------------------------|--------------------------------------|
| Sex | Female |
| Age | 82 |
| BP | 168/78 mmHg |
| Hb | 8.2 g/dL |
| Ferritin | 404 ng/mL |
| TSAT | 22% |
| eGFR | 6.4 mL/min/1.73 m² |

Four years ago, darbepoietin was started and Hb level was maintained at about 8 g/dL with 180 µg/month of darbepoietin

Darbepoietin was changed to enarodustat (2mg every day)

| | Before conversion | Week 2 | Week 4 | Week 6 | Week 10 | Week 12 | Week 16 |
|-----------------|--------------------------|---------------|---------------|---------------|----------------|----------------|----------------|
| Hb | 8.2 | 8.4 | 9.1 | 9.1 | 9.8 | 10.1 | 10.3 |
| Ferritin | 404 | | | | | 518 | |
| TSAT | 22 | | | | | 33 | |

HIF in Immunity and Inflammation



Cost

| | |
|--------------------------------------|---|
| darbepoetin alpha 20µg/wk | epoetin beta pegol 100µg/4wk |
| 3436 yen/wk | 17947/4 = 4487 yen/wk |

| | | | | |
|---|--------------------------------|---------------------------------|--------------------------------|---------------------------------|
| roxadustat (100 mg) 3 Tab/wk | daprodustat 8mg/day | vadadustat 450mg/day | enarodustat 4mg/day | molidustat 100mg/day |
| 4197 yen/wk | 4583 yen/wk | 4128 yen/wk | 3403 yen/wk | 3993 yen/wk |

Reimbursement for HD patients (technical fee)

| | Prescription of HIF-PH inhibitor | HD type 1 | HD type 2 | HD type 3 |
|-------------------|----------------------------------|-----------|-----------|-----------|
| Less than 4 hours | In-house prescription | 19240 yen | 18840 yen | 18840 yen |
| | Out-of-hospital prescription | 17980 yen | 17580 yen | 17580 yen |
| 4~5 hours | In-house prescription | 20840 yen | 20440 yen | 19990 yen |
| | Out-of-hospital prescription | 19580 yen | 19180 yen | 18730 yen |
| More than 5 hours | In-house prescription | 22190 yen | 21740 yen | 21290 yen |
| | Out-of-hospital prescription | 20930 yen | 20480 yen | 20030 yen |

Dialyzer (1500 yen) and dialysate (1000 yen) are reimbursed separately.