Cellular responses against anemia and hypoxia

Oxygen transport (EPO, Transferrin)
Vascular regulation (VEGF, adrenomedullin, HO-1)
Glucose uptake and glycolysis (Glut-1, Aldolase A)
Anti-oxidative enzymes (SODs, catalase)

Hirakawa, Nangaku, et al. J Diabetes Investig 2017
High altitude training: 'Altitude Doping'

It's the legal version of blood doping. Instead of taking drugs to stimulate the production of red blood cells, many endurance athletes spend time in the thin air of high altitudes.

The body responds to the thin air at high altitudes by producing proteins in the HIF family. HIF stimulates the production of red blood cells and builds capillaries to deliver more oxygen to the muscles.
altitude-induced hypoxia reduces erythropoietin requirements in HD patients

change in Hct

change in EPO dosing

isoelectric focusing analysis of urine to detect recombinant ESA
ESA in CKD
Anemia is more prevalent in DKD

A cross-sectional survey of 820 patients with diabetes

Thomas et al. Diabetes Care 2003
The phase II StudY of BArdoxolone methyl in patients with chronic Kidney disease and type 2 diabetes; TSUBAKI study

ASN Kidney Week press briefing on Friday, Nov 3
Presentation at the session of Late Breaking Clinical Trial (High-Impact Clinical Trials) Saturday, Nov 4
Target hemoglobin of anemia in CKD

Observational study

Interventional study
Baseline patient hemoglobin levels and subsequent mortality risk: J-DOPPS

Overall RR = 0.89 (p = 0.003) per 1 g/dl higher haemoglobin

Akizawa et al. NDT 2008
Anemia and prognosis of CKD patients
meta-analysis

- Collins, 2001 (66,761 incident HD patients)
- Ofsheun, 2003 (44,550 prevalent HD patients)
- Warady, 2003 (1,942 prevalent HD and PD pediatric patients)
- Locatelli, 2004 (4,591 prevalent HD patients)
- Li, 2004 (50,579 incident HD patients)
- Li, 2004 (8,267 incident PD, non-DM patients)
- Li, 2004 (5,707 incident PD, DM patients)

Volkova & Arab. AJKD 2006
Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)

HR 0.78 [95%CI, 0.53-1.14]
Group 1: target Hb 13.0-15.0
Group 2: target Hb 10.5-11.5

# TREAT study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Darbepoetin alfa N = 2012</th>
<th>Placebo N = 2026</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Composite</td>
<td>632 (31.4)</td>
<td>602 (29.7)</td>
<td>1.05 (0.94-1.17)</td>
<td>0.41</td>
</tr>
<tr>
<td>Death</td>
<td>412 (20.5)</td>
<td>395 (19.5)</td>
<td>1.05 (0.92-1.21)</td>
<td>0.48</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>205 (10.2)</td>
<td>229 (11.3)</td>
<td>0.89 (0.74-1.08)</td>
<td>0.24</td>
</tr>
<tr>
<td>MI</td>
<td>124 (6.2)</td>
<td>129 (6.4)</td>
<td>0.96 (0.75-1.22)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td><strong>101 (5.0)</strong></td>
<td><strong>53 (2.6)</strong></td>
<td><strong>1.92 (1.38-2.68)</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>41 (2.0)</td>
<td>49 (2.4)</td>
<td>0.84 (0.55-1.27)</td>
<td>0.40</td>
</tr>
<tr>
<td>Renal Composite</td>
<td>652 (32.4)</td>
<td>618 (30.5)</td>
<td>1.06 (0.95-1.19)</td>
<td>0.29</td>
</tr>
<tr>
<td>ESRD</td>
<td>338 (16.8)</td>
<td>330 (16.3)</td>
<td>1.02 (0.87-1.18)</td>
<td>0.83</td>
</tr>
</tbody>
</table>
ESA hypo responsiveness: TREAT study

Death, myocardial infarction, apoplexy, heart failure, or hospitalization due to cardiac ischemia

EPO hyporesponsiveness: RISCAVID study

ESAs resistance index (ERI): the weekly ESAs dose / kgBW / Hb (g/dL)

Panichi et al. Nephrol Dial Transplant 2011
# Erythropoietin hyporesponsiveness in Japanese HD patients: possible role of statins

### a. Association between statin prescription and subsequent ESA hyporesponsiveness by increasing levels of adjustment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Statin Rx</th>
<th>Number of patients</th>
<th>Number of events, n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>model 1^b</td>
</tr>
<tr>
<td>Hgb &lt;10 g/dL</td>
<td>+</td>
<td>585</td>
<td>66 (11.3)</td>
<td>0.88 (0.67–1.13)</td>
</tr>
<tr>
<td>ESA dose* &gt;500 units/week</td>
<td></td>
<td></td>
<td></td>
<td>model 2^c</td>
</tr>
<tr>
<td></td>
<td>−</td>
<td>3,017</td>
<td>394 (13.1)</td>
<td>0.86 (0.65–1.14)</td>
</tr>
</tbody>
</table>

ESAs, erythropoiesis-stimulating agents; Hgb, hemoglobin.

^Mircera doses were converted to darbepoetin doses using a 1.2:1 ratio, and darbepoetin doses were converted to epoetin doses using a 250:1 ratio.

^Model 1: adjusted for DOPPS phase and accounting for facility clustering.

^Model 2: adjusted for model 1 + age, gender, vintage, 11 summary comorbidities and post dialysis weight.

^Model 3: adjusted for model 2 + Kt/V, treatment time, hospitalization in past 3 months.

^Model 4: adjusted for model 3 + CRP, albumin, TSAT, ferritin.

### b. Association between statin prescription and subsequent ESA resistance index by increasing levels of adjustment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Statin Rx</th>
<th>Number of patients</th>
<th>Average ERI</th>
<th>Ratio of means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>model 1^b</td>
</tr>
<tr>
<td>logERI^f</td>
<td>+</td>
<td>585</td>
<td>10.1</td>
<td>0.92 (0.87–0.97)</td>
</tr>
<tr>
<td></td>
<td>−</td>
<td>3,017</td>
<td>10.7</td>
<td>0.99 (0.94–0.89)</td>
</tr>
</tbody>
</table>

ERIs, erythropoiesis-stimulating agents; ERI, ESA resistance index.

^Mircera doses were converted to darbepoetin doses using a 1.2:1 ratio, and darbepoetin doses were converted to epoetin doses using a 250:1 ratio.

^Model 1: adjusted for DOPPS phase and accounting for facility clustering.

^Model 2: adjusted for model 1 + age, gender, vintage, 11 summary comorbidities and post dialysis weight.

^Model 3: adjusted for model 2 + Kt/V, treatment time, hospitalization in past 3 months.

^Model 4: adjusted for model 3 + CRP, albumin, TSAT, ferritin.

^ERI = ESA/(dry weight x Hgb).
Kidney outcome in CREATE

Secondary endpoint

Kidney outcome in TREAT

composite endpoint

No. at risk
DA 2,012 1,910 1,762 1,544 1,207 820 552 309 134
placebo 2,026 1,915 1,748 1,519 1,193 842 540 312 123

Month
0 6 12 18 24 30 36 42 48

Hb値

12.5g/dL (IQR: 12.0-12.8)

10.6g/dL (IQR: 9.9-11.3)

投与量
176μg (IQR: 104-305)
225 +/− 208 μg
0μg (IQR: 0-5)
5 +/− 1 μg

darbepoietin
darbepoietin
placebo
### High Target Hemoglobin With Erythropoiesis-Stimulating Agents Has Advantages in the Renal Function of Non-Dialysis Chronic Kidney Disease Patients

Yoshiharu Tsubakihara,¹ Fumitake Gejyo,² Shinichi Nishi,⁴ Yasuhiko Iino,⁵ Yuzou Watanabe,⁸ Masashi Suzuki,³ Akira Saito,⁹ Takashi Akiba,⁶ Hideki Hirakata,¹⁰ and Tadao Akizawa⁷

#### Trial design
Multi-center, randomized, open-labelled trial

#### Subject
Non-HD CKD patients
- Hb <10.0 g/dL, serum creatinine 2.0 – 6.0 mg/dL

<table>
<thead>
<tr>
<th>Group</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Hb</td>
<td>(target Hb 11.0–13.0 g/dL) treated with darbepoietin (n = 161)</td>
</tr>
<tr>
<td>Low Hb</td>
<td>(target Hb 9.0–11.0 g/dL) treated with epoetin-alpha (n = 180)</td>
</tr>
<tr>
<td>Fe supplementation</td>
<td>to keep TSAT &gt;20% and ferritin &gt;100 ng/mL</td>
</tr>
</tbody>
</table>
Risks of kidney events

Cox proportional hazards model adjusted by age, sex, and randomization factors

Baseline serum Cr
1.1

Diabetes
1.02

Age
0.95

Gender (female vs male)
0.95

Hb (high vs low)
0.71

Baseline Hb
0.69

29% risk reduction

Tsubakihara et al. Ther Apher Dial 2012
No differences in adverse effects (cardiovascular) between the high Hb group and the low Hb group

Mainly hypertension

Tsubakihara et al.
Ther Apher Dial 2012
post-hoc analysis

CKD stage G4

CKD stage G5

Tsubakihara et al. Ther Apher Dial 2015
post-hoc analysis

non-diabetic

Tsubakihara et al. Ther Apher Dial 2015
Elderly people are more tolerant to low Hb levels

<table>
<thead>
<tr>
<th>Hb Level</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb &lt; 9g/dL</td>
<td>3.79</td>
<td>[2.79 – 5.16]</td>
<td>p=0.01</td>
</tr>
<tr>
<td>9g/dL ≤ Hb &lt; 10g/dL</td>
<td>1.47</td>
<td>[1.08 – 2.02]</td>
<td>p=0.04</td>
</tr>
<tr>
<td>10g/dL ≤ Hb &lt; 11g/dL</td>
<td>1.00</td>
<td>[ref]</td>
<td>p for trend = 0.003</td>
</tr>
<tr>
<td>11g/dL ≤ Hb &lt; 12g/dL</td>
<td>0.93</td>
<td>[0.66 – 1.31]</td>
<td>p=0.75</td>
</tr>
<tr>
<td>Hb ≥ 12g/dL</td>
<td>1.32</td>
<td>[0.89 – 1.94]</td>
<td>p=0.9</td>
</tr>
</tbody>
</table>

*Type 3 p-value p=0.03*
treatment of anemia in CKD: ESA

JSDT
Guideline of anemia in CKD 2015
Target Hb level and criterion for initiation of treatment of renal anemia

In adult HD patients, the target Hb levels to be maintained are in the range of 10–12 g/dL in the blood samples collected at the beginning of the week of HD. (1C)
Target Hb level and criterion for initiation of treatment of renal anemia

In adult CKD patients in the predialysis phase, the target Hb levels to be maintained are in the range of 11–13 g/dL. (2C) However, if the patient has a history of serious CVD or complications, or if it is medically necessary, dose reduction or the discontinuation of medication should be considered when the Hb level exceeds 12 g/dL. (not graded)
Target Hb level and criterion for initiation of treatment of renal anemia

In the actual treatment of HD, PD, and CKD patients in the predialysis phase, it is recommended to determine the target Hb levels according to the pathological conditions of individual patients by referring to the values provided above. (1C)
Novel ally for treatment of anemia in CKD: HIF activator (PHD inhibitor)
roxadustat in HD patients: hemoglobin

United States, Russia, Hong Kong

<table>
<thead>
<tr>
<th>arm</th>
<th>n</th>
<th>mean (±SE) ΔHb\text{max} (g/dL)</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD, no iron</td>
<td>23</td>
<td>2.8 (±0.2)</td>
<td>95.7%</td>
</tr>
<tr>
<td>HD, oral iron</td>
<td>12</td>
<td>3.5 (±0.5)</td>
<td>91.7%</td>
</tr>
<tr>
<td>HD, IV iron</td>
<td>10</td>
<td>3.5 (±0.4)</td>
<td>100.0%</td>
</tr>
<tr>
<td>PD, oral iron</td>
<td>10</td>
<td>3.3 (±0.2)</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Besarab et al. JASN 2016
HIF activation as novel treatment of anemia in CKD

Phase 2a study of roxadustat in subjects with anemia and CKD (G3 or G4): hepcidin levels

Besarab et al. Nephrol Dial Transplant 2015
roxadustat maintenance dose requirements were independent of baseline CRP levels

Provenzano et al. AJKD 2016
HIF-1 activates insulin-induced gene 2 (Insig-2) transcription

Hwang et al. J Biol Chem 2017
HIF-1 activates Insig-2 transcription for degradation of HMG-CoA reductase in the liver

Hwang et al. J Biol Chem 2017

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Wild Type</th>
<th>Insig-2⁻</th>
<th>DMOG</th>
<th>Membranes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>HMGCR</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
</tr>
<tr>
<td>Insig-2</td>
<td>-20</td>
<td>-20</td>
<td>-20</td>
<td>-20</td>
</tr>
<tr>
<td>Calnexin</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
</tr>
<tr>
<td>HIF-1α</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
</tr>
<tr>
<td>LSD-1</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
</tr>
</tbody>
</table>

1. Hypoxia (DMOG)
2. Stabilization of HIF-1α
3. Enhanced expression of Insig-2 mRNA and protein
4. Accelerated ERAD of HMGCR

HMG CoA Reductase

Ubiquitination

26S Proteasome

Hwang et al. J Biol Chem 2017
phase 2 studies of roxadustat for treatment of anemia in China

Nan Chen, Jiaqi Qian, Jianghua Chen, Xueqing Yu, Changlin Mei, Chuanming Hao et al. NDT 2017
decreases from baseline for the lipid parameters in the roxadustat groups

<table>
<thead>
<tr>
<th></th>
<th>NDD study</th>
<th>DD study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>roxadustat low</td>
</tr>
<tr>
<td><strong>Total chol (mg/dL)</strong></td>
<td>8.0 (±30.0)</td>
<td>-31.7 (±25.3)</td>
</tr>
<tr>
<td><strong>LDL-chol (mg/dL)</strong></td>
<td>4 (±25.5)</td>
<td>-22.4 (±19.4)</td>
</tr>
</tbody>
</table>

Nan Chen, Jiaqi Qian, Jianghua Chen, Xueqing Yu, Changlin Mei, Chuanming Hao et al. NDT 2017
effects of daprodustat on anemia in Japanese HD patients

Akizawa, Nangaku et al. Am J Nephrol 2017
decreases from baseline for the lipid parameters at week 4 in the daprodustat groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Daprodustat</th>
<th>Daprodustat</th>
<th>Daprodustat</th>
<th>Daprodustat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 mg</td>
<td>6 mg</td>
<td>8 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td><strong>Total Chol (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline 95% CI</td>
<td>3.8</td>
<td>4.0</td>
<td>3.9</td>
<td>3.7</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>(3.5, 4.2)</td>
<td>(3.7, 4.5)</td>
<td>(3.6, 4.4)</td>
<td>(3.3, 4.2)</td>
<td>(3.6, 4.2)</td>
</tr>
<tr>
<td>Week 4 CFB 95% CI</td>
<td>5.3</td>
<td>-7.4</td>
<td>-10.8</td>
<td>-9.0</td>
<td>-14.6</td>
</tr>
<tr>
<td></td>
<td>(-0.6, 11.6)</td>
<td>(-12.2, -2.3)</td>
<td>(-15.3, -6.0)</td>
<td>(-14.9, -2.7)</td>
<td>(-19.8, -9.0)</td>
</tr>
<tr>
<td><strong>LDL-C (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline 95% CI</td>
<td>2.0</td>
<td>2.2</td>
<td>2.1</td>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>(1.7, 2.3)</td>
<td>(1.9, 2.5)</td>
<td>(1.8, 2.4)</td>
<td>(1.6, 2.3)</td>
<td>(1.8, 2.4)</td>
</tr>
<tr>
<td>Week 4 CFB 95% CI</td>
<td>4.8</td>
<td>-11.1</td>
<td>-10.8</td>
<td>-12.5</td>
<td>-17.3</td>
</tr>
<tr>
<td></td>
<td>(-10.4, 22.5)</td>
<td>(-17.2, -4.7)</td>
<td>(-17.2, -4.0)</td>
<td>(-18.8, -5.7)</td>
<td>(-24.3, -9.6)</td>
</tr>
</tbody>
</table>

Akizawa, Nangaku et al. Am J Nephrol 2017
EPO enhanced performance in a maximal exercise test leading to exhaustion, but did not improve submaximal exercise test or road race performance.
first case of doping with PHD inhibitor, FG-4592

Appropriate target Hb of ESA, iron supplementation, and PHD inhibitor as a novel treatment modality