

**Berliner DialyseSeminar**

# **Kidney disease in Japan**

**Masaomi Nangaku**

**President of the Asian Pacific Society of Nephrology  
Vice Dean of the University of Tokyo School of Medicine**

# 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-Hakko-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**

# Apology after Japanese train departs 20 seconds early



A rail company in Japan has apologised after one of its trains departed 20 seconds early.

Management on the Tsukuba Express line between Tokyo and the city of Tsukuba say they "sincerely apologise for the inconvenience" caused.

In a statement, [the company said the train had been scheduled to leave at 9:44:40 local time but left at 9:44:20.](#)

# New law of “Work style reform” by the Japanese government

**Mandatory use of five days of paid leave per year**

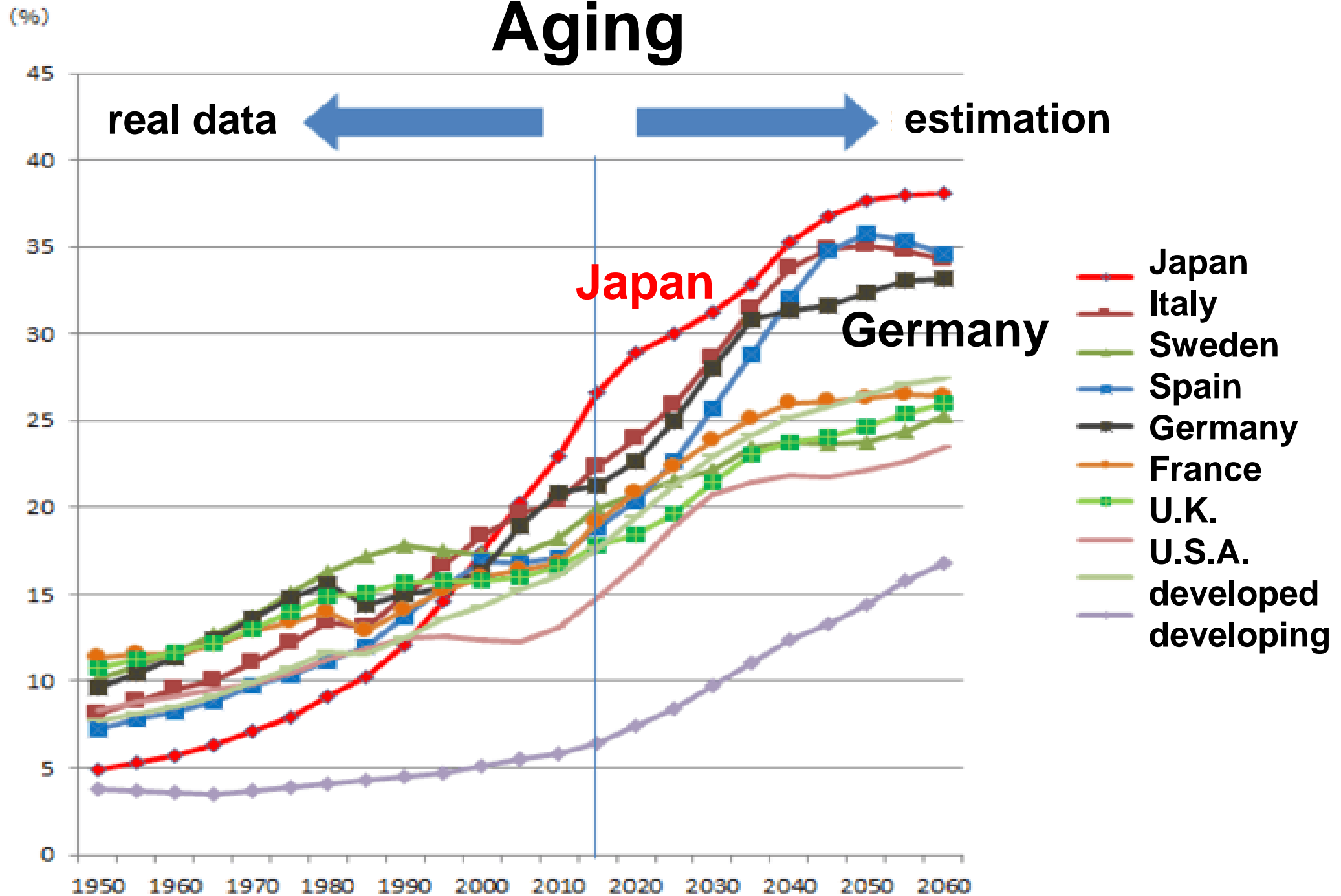


According to health ministry statistics, about 10 percent of hospital doctors, mainly in large institutions, put in 1,900 hours of overtime work a year -- a figure over the proposed maximum.

Rank	Country	Life-expectancy (WHO 2018)
1	Japan	84.2
2	Switzerland	83.3
3	Spain	83.1
4	Australia	82.9
	Singapore	
	France	
7	Canada	82.8
	Italy	
9	South Korea	82.7
10	Norway	82.5

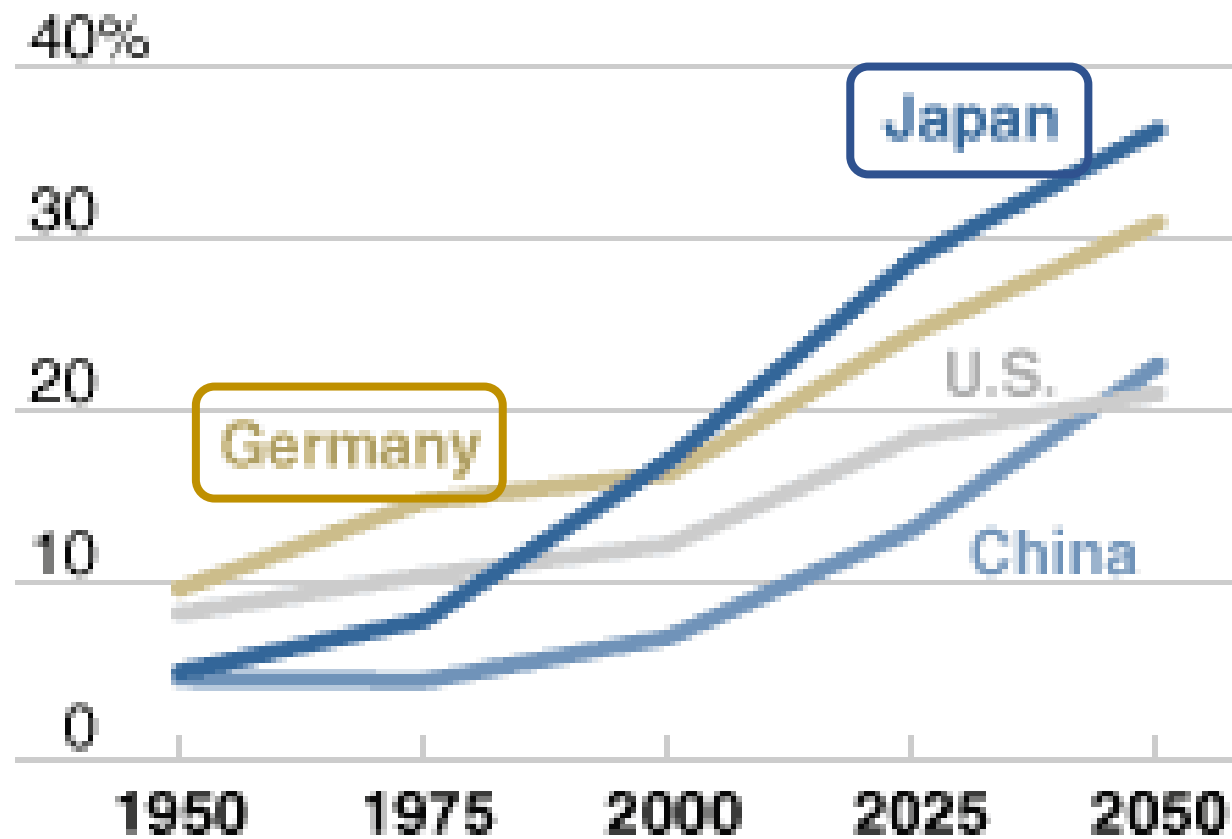
Germany 81.0

# Aging



## JAPAN GROWS OLD

Japan's percentage of population over 65 is growing faster than any other nation.



Source: Population Division, DESA, United Nations

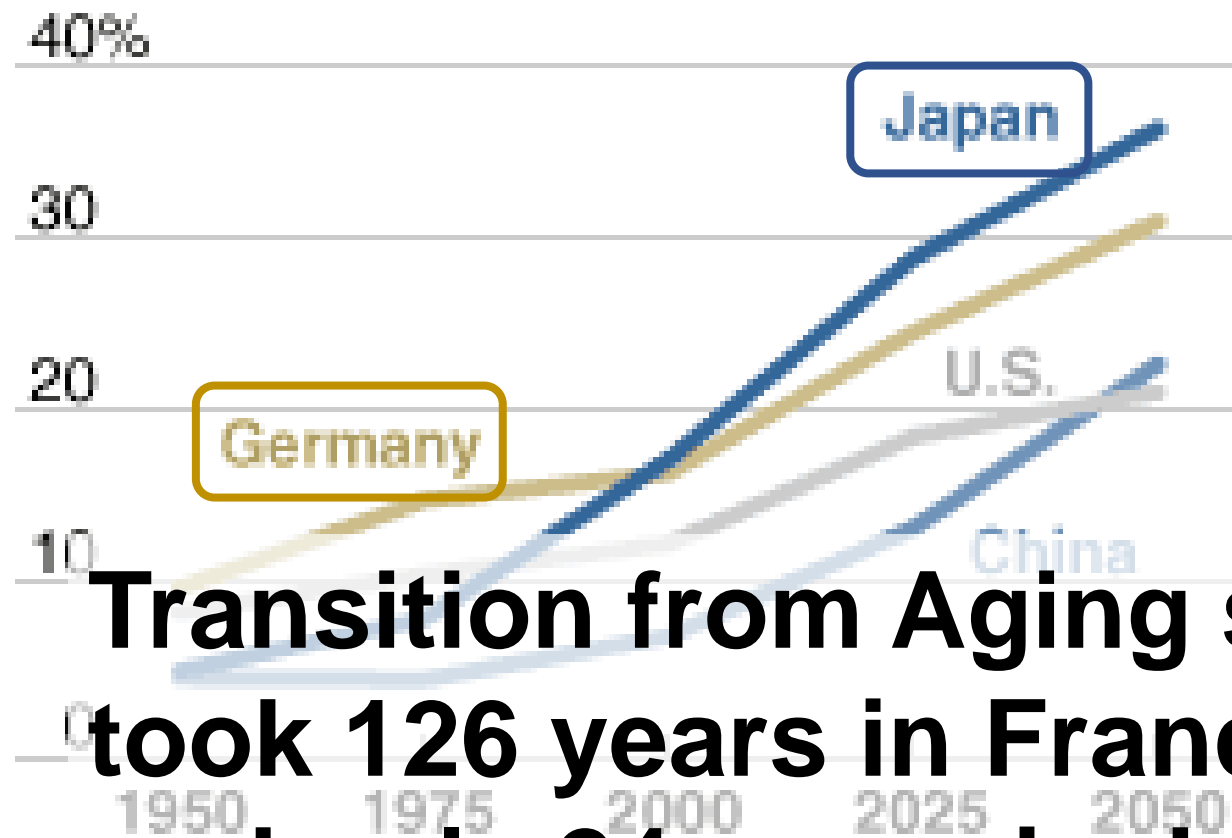
**Percentage of elderly people (aged 65+)**

**Aging society  $\geq 7\%$**

**Aged society  $\geq 14\%$**

## JAPAN GROWS OLD

Japan's percentage of population over 65 is growing faster than any other nation.



**Transition from Aging society to Aged society took 126 years in France, 85 years in Sweden, and only 24 years in Japan.**

Source: Population Division, DESA, United Nations

**Percentage of elderly people (aged 65+)**

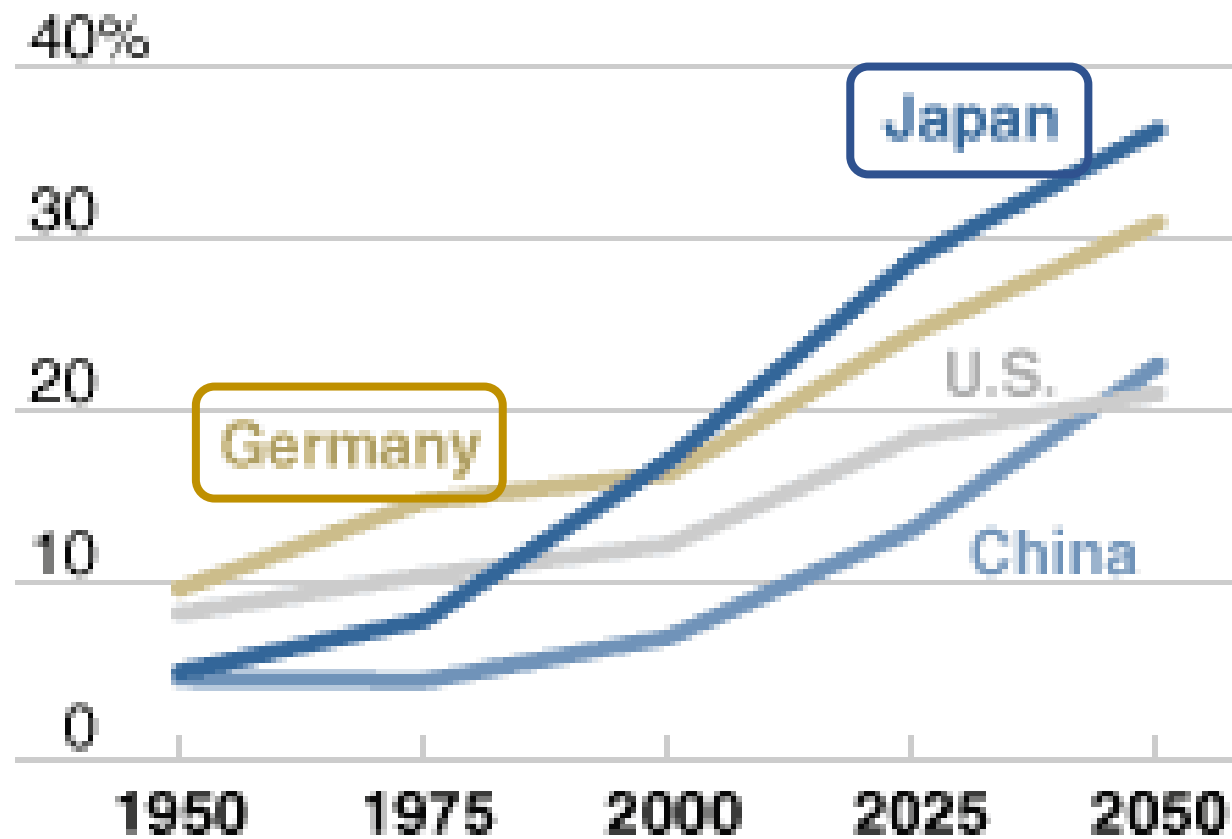
**Aging society  $\geq 7\%$**

**Aged society  $\geq 14\%$**



## JAPAN GROWS OLD

Japan's percentage of population over 65 is growing faster than any other nation.



Source: Population Division, DESA, United Nations

**Percentage of elderly people (aged 65+)**

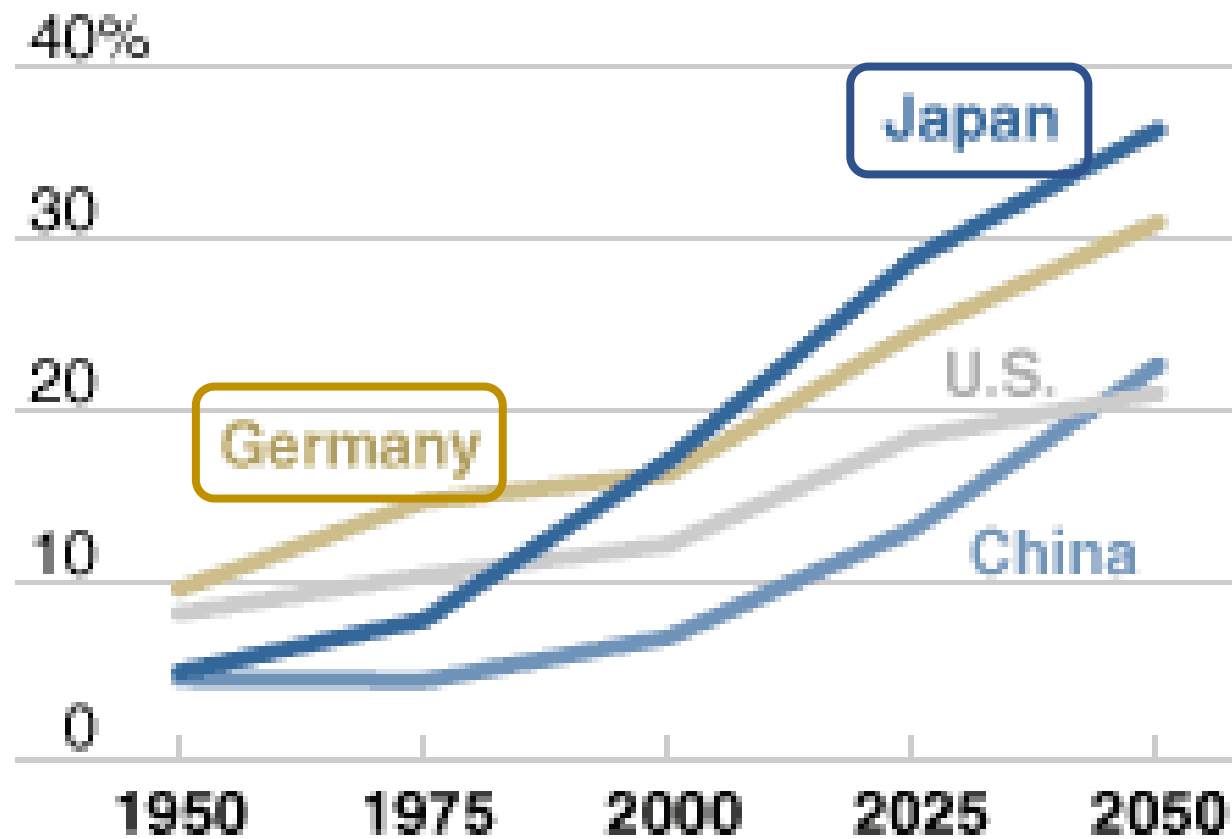
**Aging society  $\geq 7\%$**

**Aged society  $\geq 14\%$**

**Super aged society  $\geq 21\%$**

## JAPAN GROWS OLD

Japan's percentage of population over 65 is growing faster than any other nation.



Source: Population Division, DESA, United Nations

**Percentage of elderly people (aged 65+)**

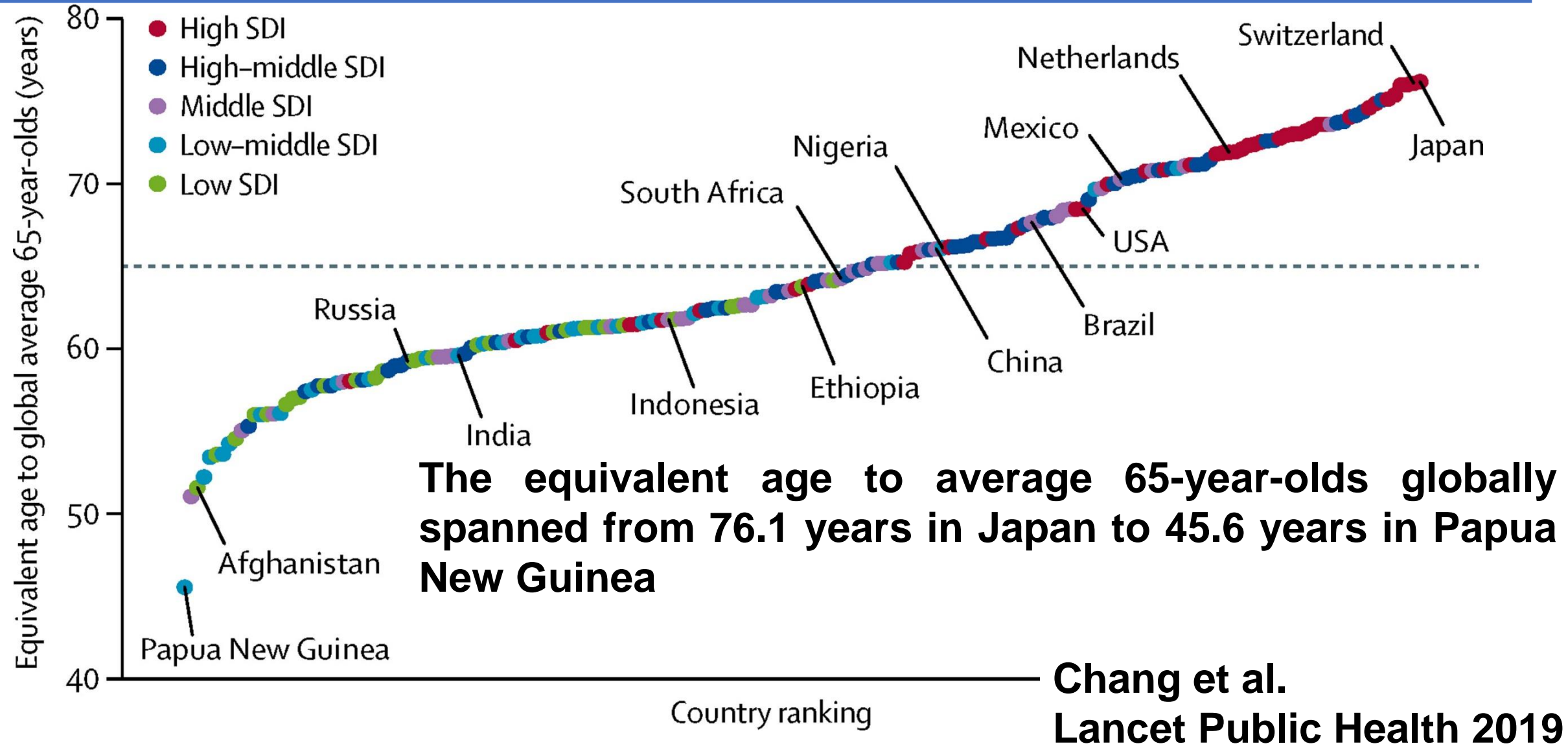
**Aging society  $\geq 7\%$**

**Aged society  $\geq 14\%$**

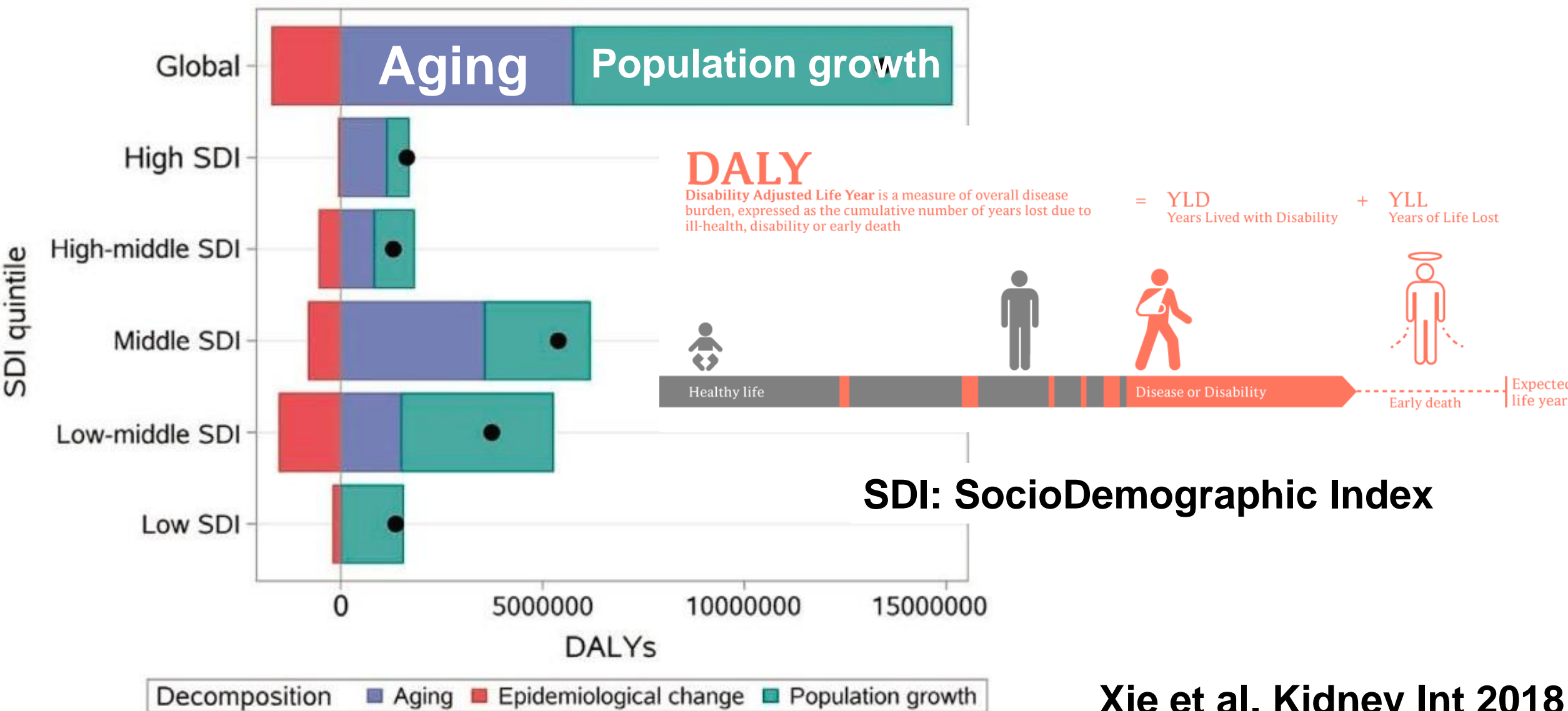
**Super aged society  $\geq 21\%$**

**Super-super aged society  $\geq 28\%$**

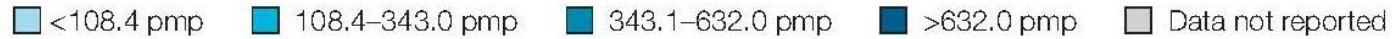
# Measuring population ageing: an analysis of the Global Burden of Disease Study 2017



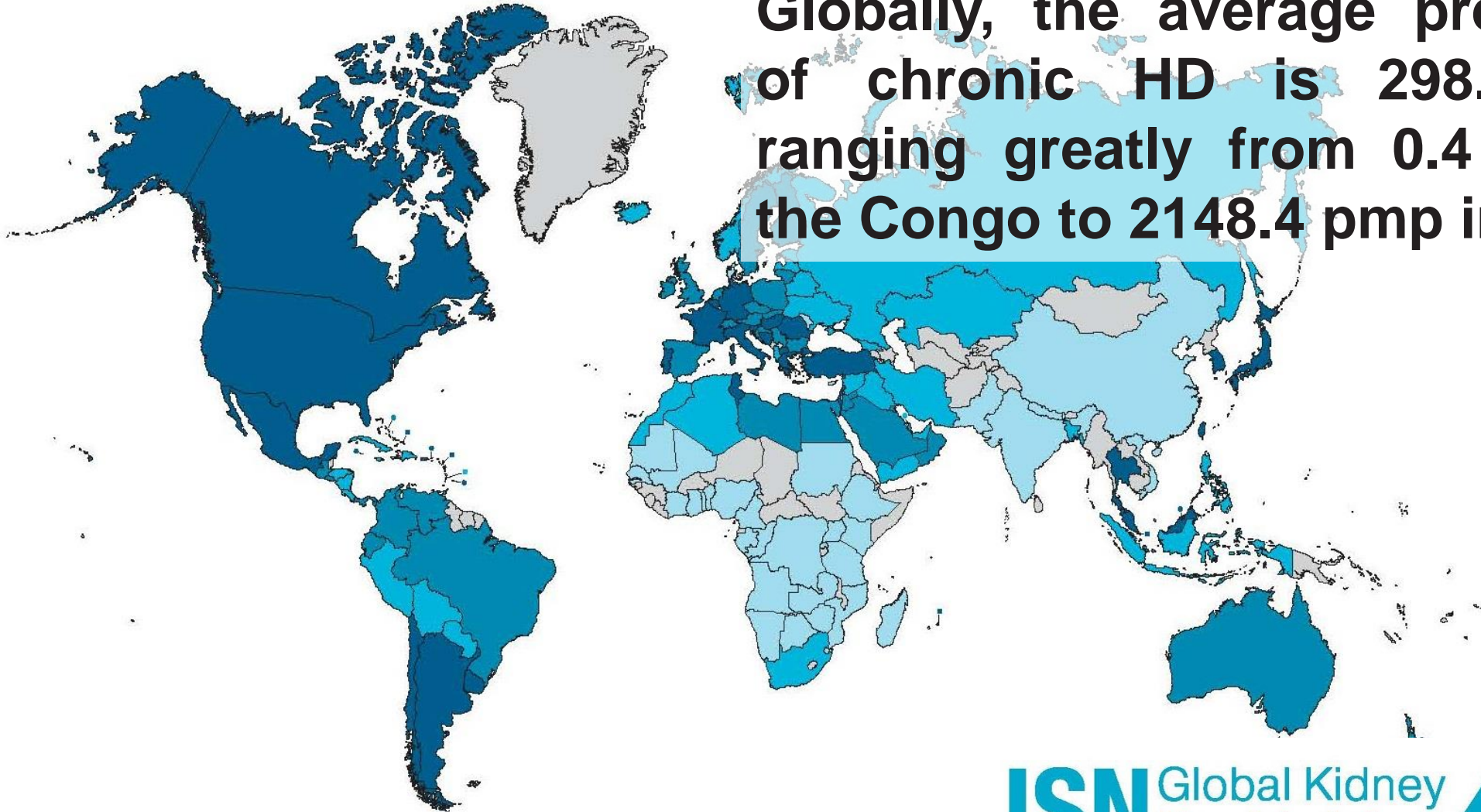
# Changes in CKD DALYs according to population-level determinants from 1990 to 2016



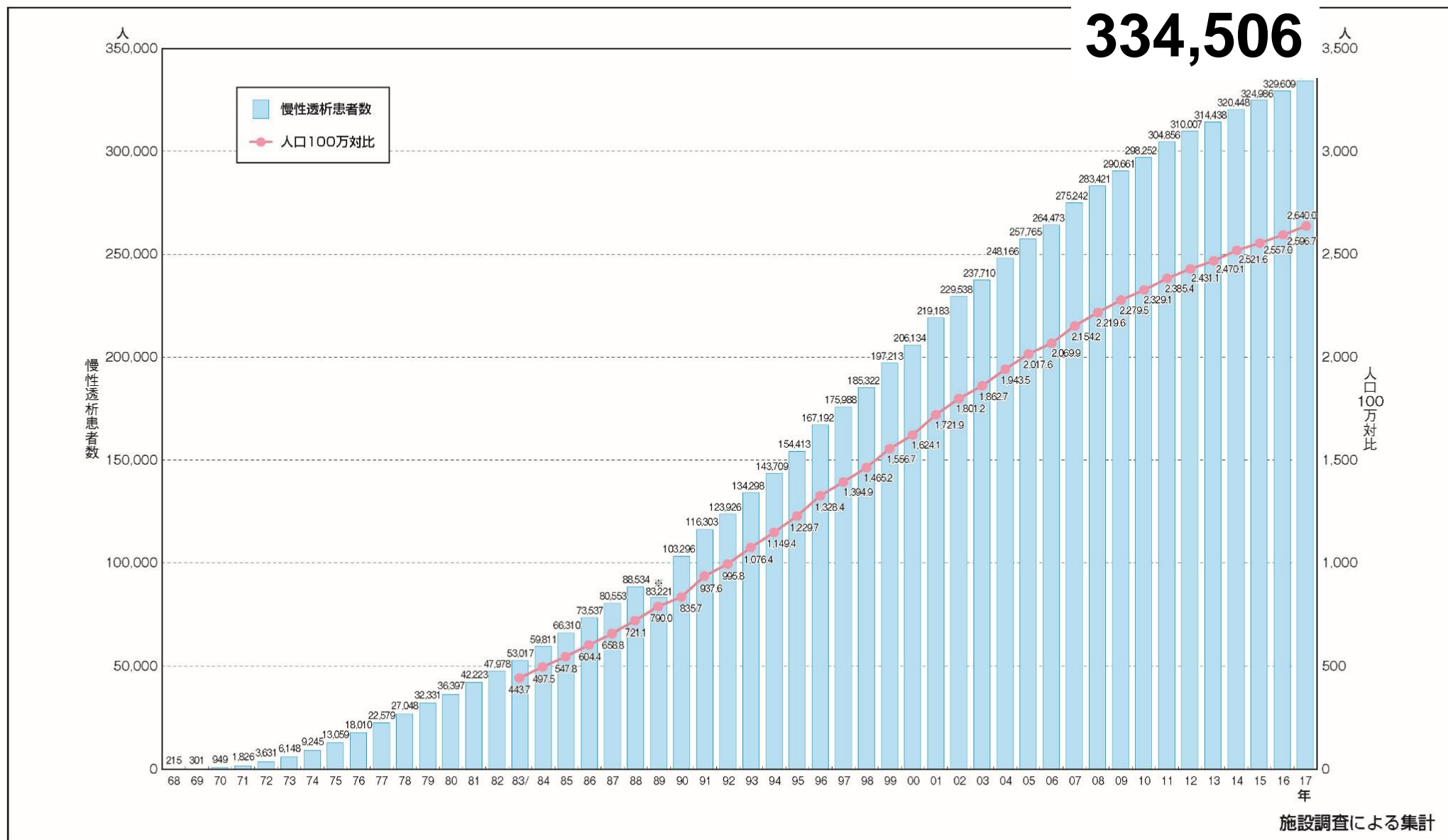
# Global prevalence of chronic dialysis

 <108.4 pmp 108.4–343.0 pmp 343.1–632.0 pmp >632.0 pmp Data not reported

Globally, the average prevalence of chronic HD is 298.4 pmp, ranging greatly from 0.4 pmp in the Congo to 2148.4 pmp in **Japan**.



# Maintenance Dialysis patients in Japan



『一般社団法人日本透析医学会「わが国の慢性透析療法の現況（2017年12月31日現在）」』



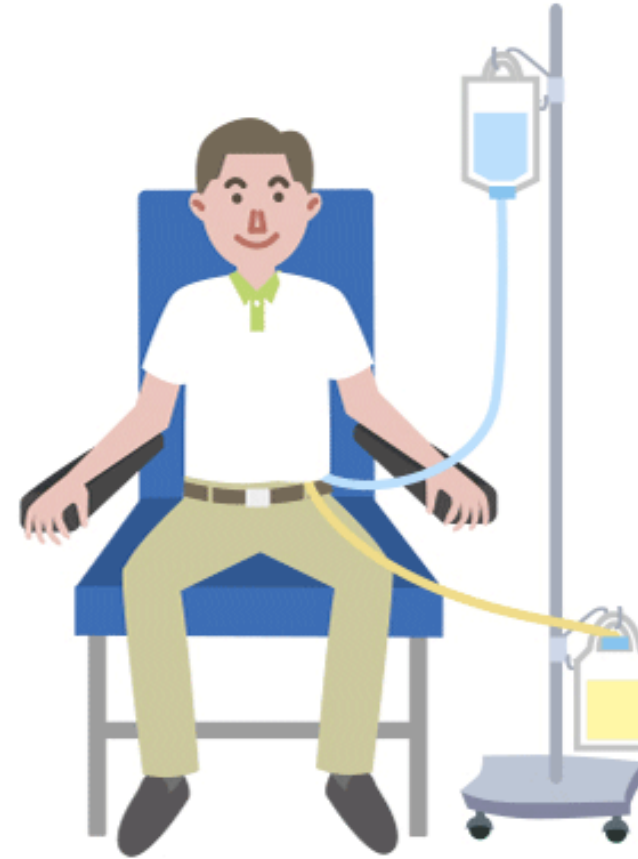
# Hybrid therapy

## Combination of HD and PD

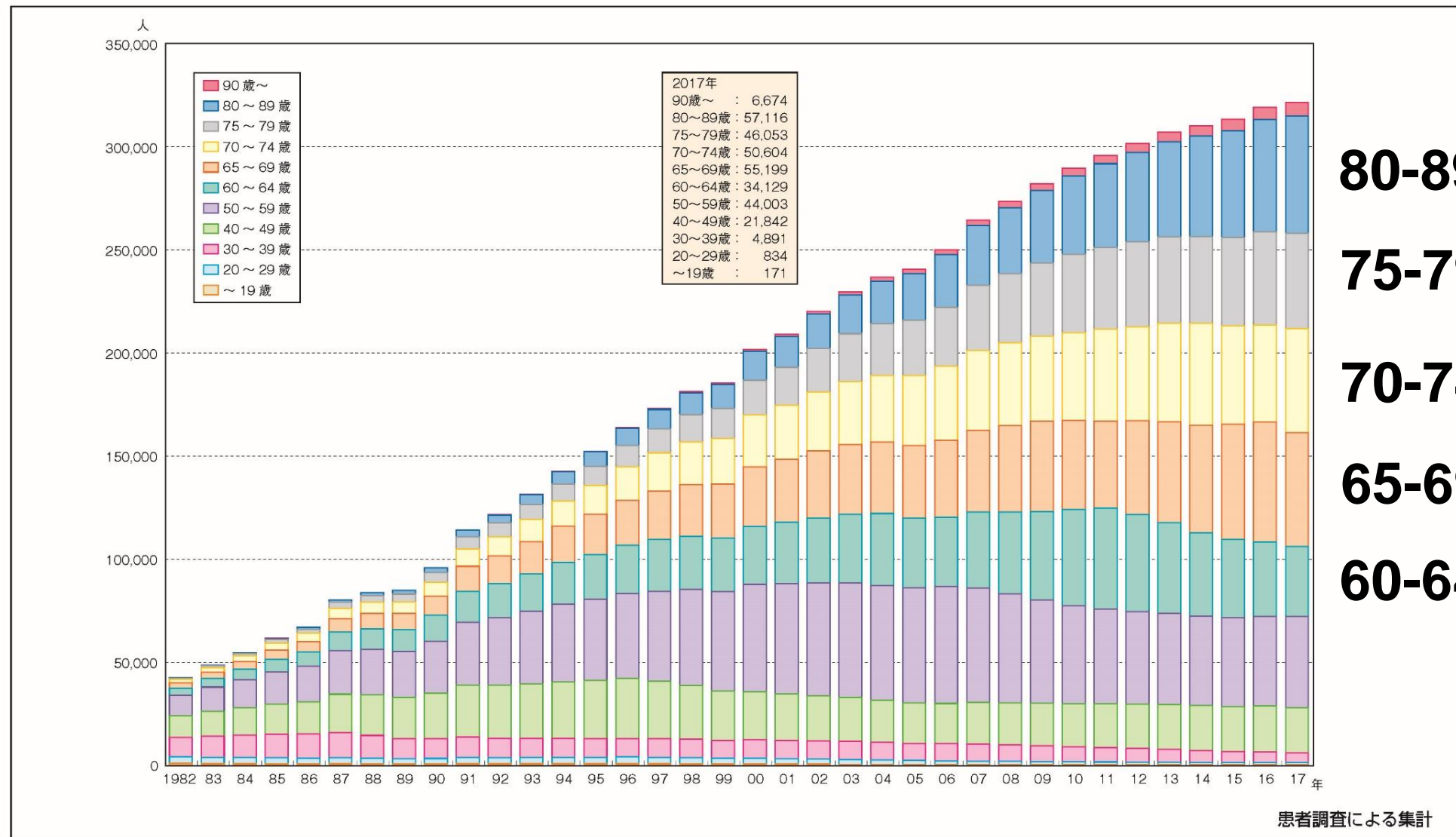
Hemodialysis



Peritoneal dialysis



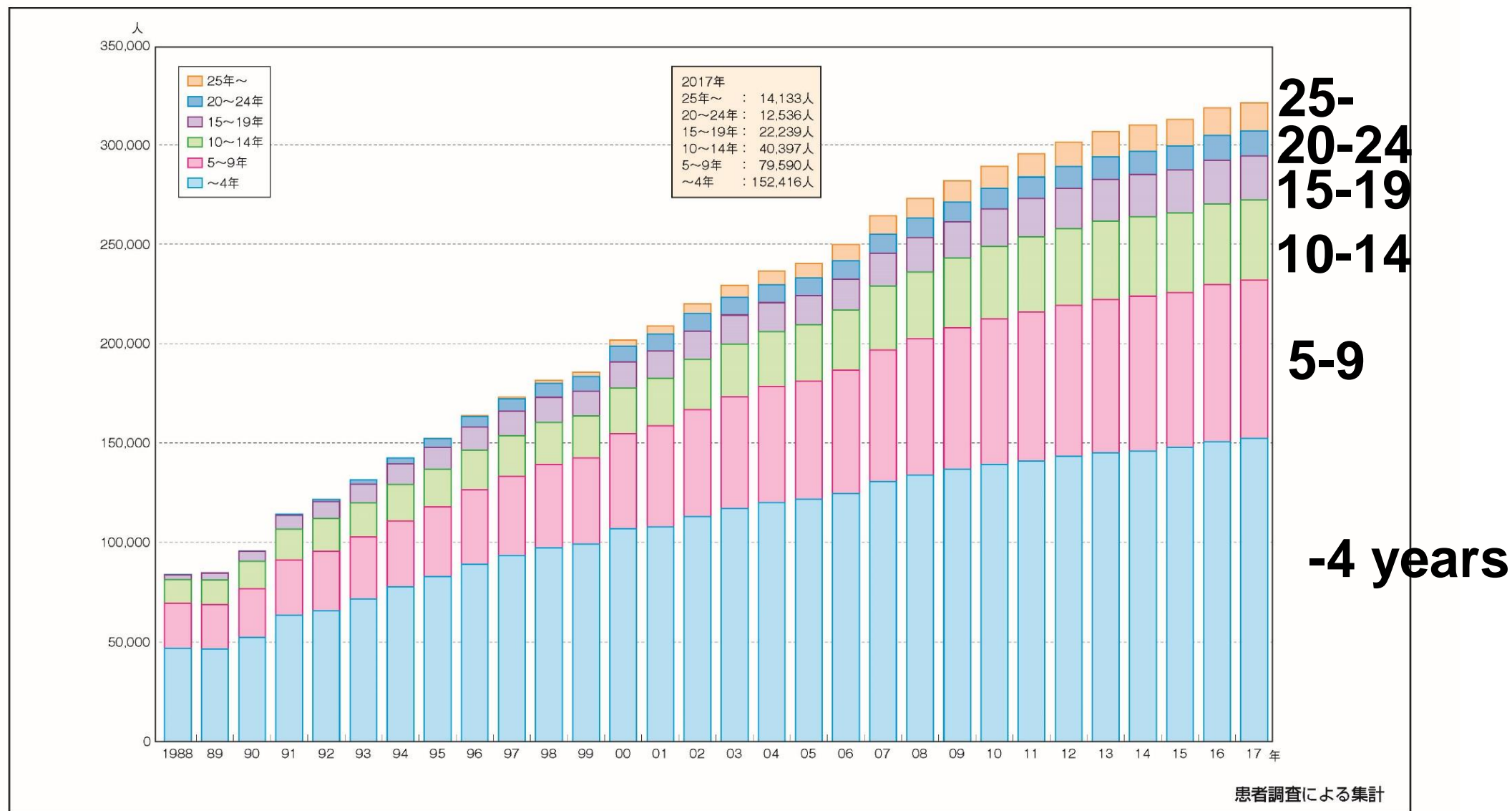
# Maintenance dialysis patients : Age distribution



『一般社団法人日本透析医学会「わが国の慢性透析療法の現況（2017年12月31日現在）」』

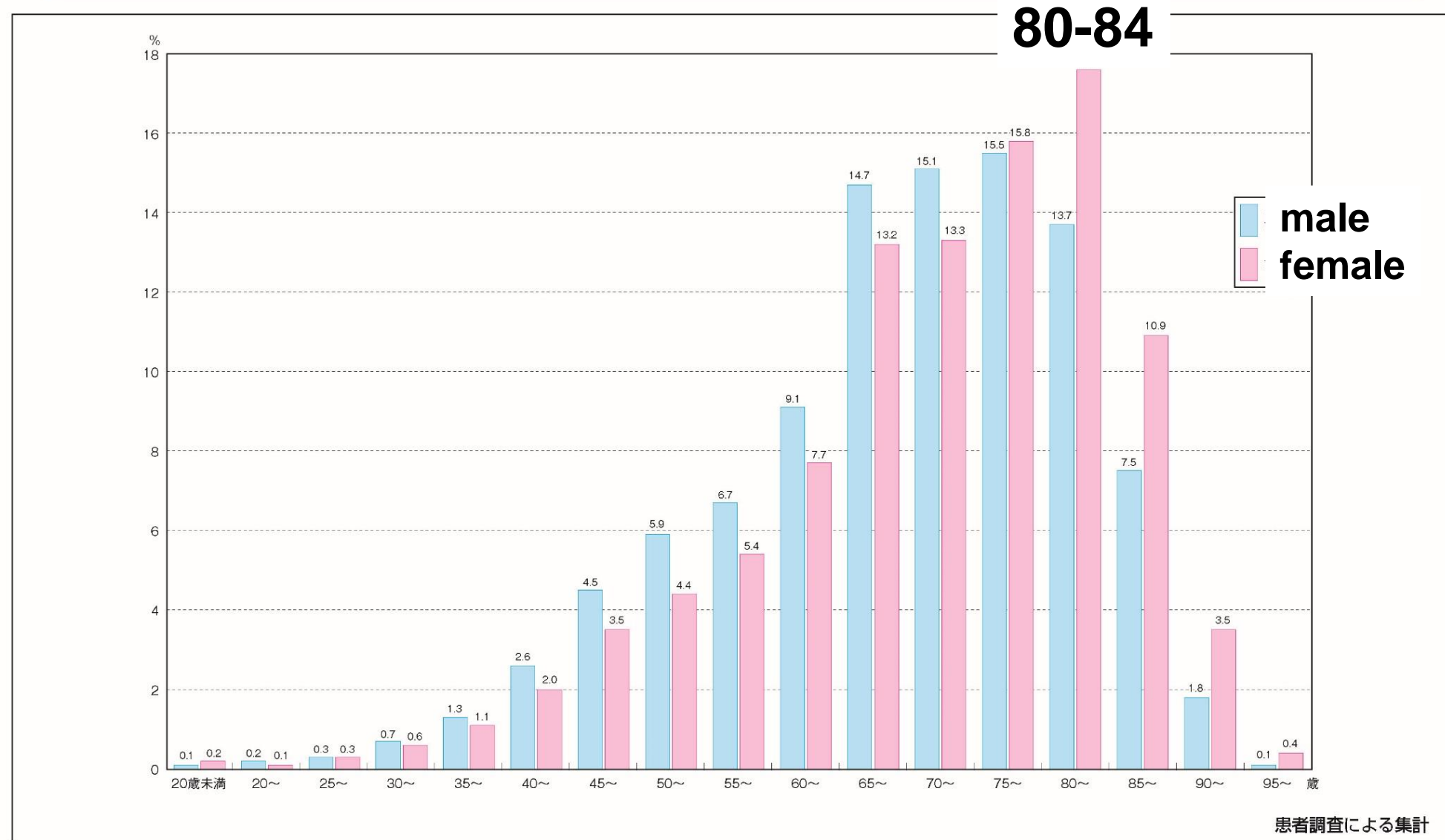


# Dialysis patients in Japan: Dialysis vintage



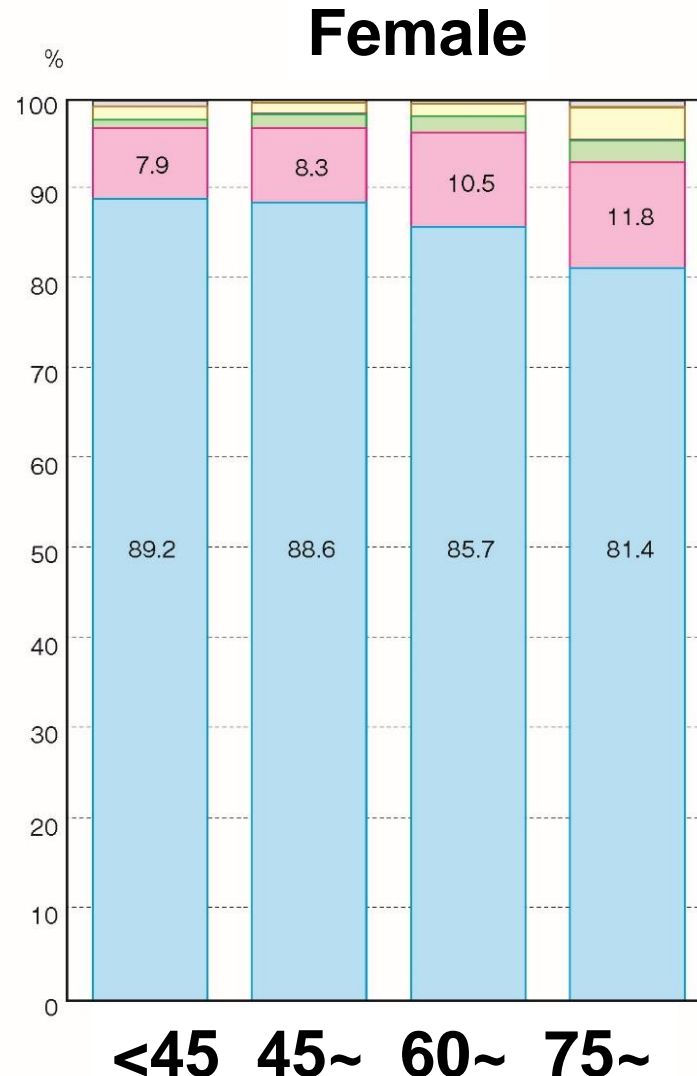
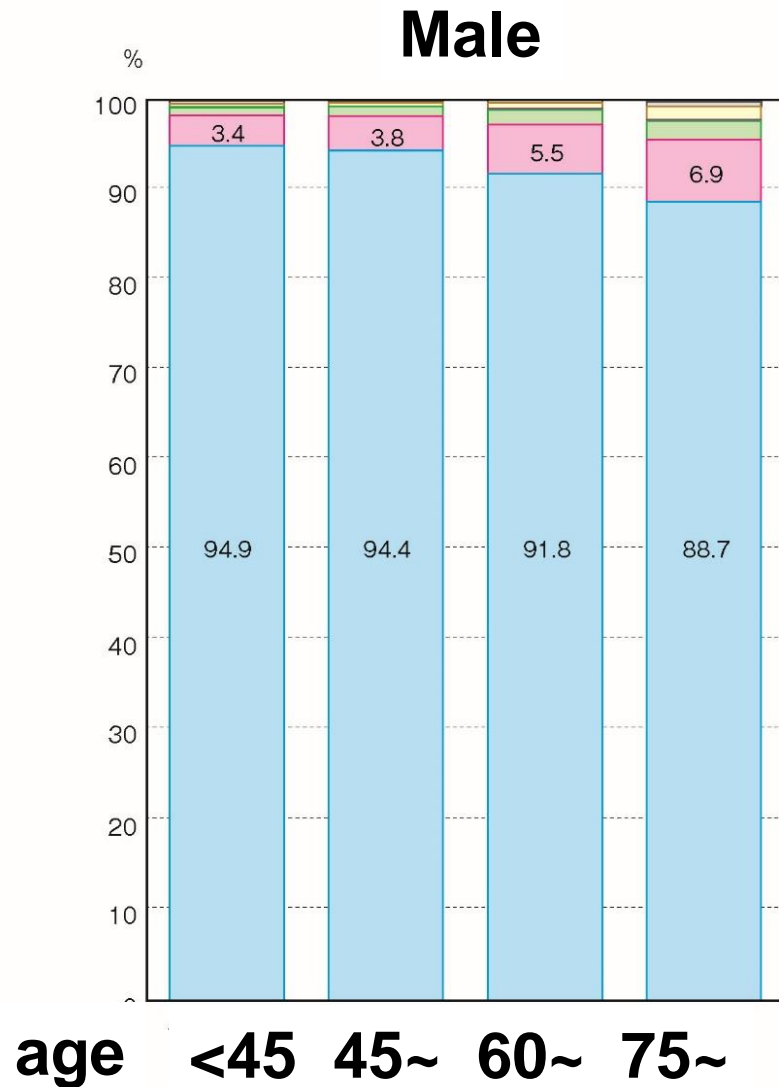
『一般社団法人日本透析医学会「わが国の慢性透析療法の現況（2017年12月31日現在）」』

# Indicent dialysis patients : Age and sex distribution



『一般社団法人日本透析医学会「わが国の慢性透析療法の現況（2017年12月31日現在）」』

# Vascular access in Japan

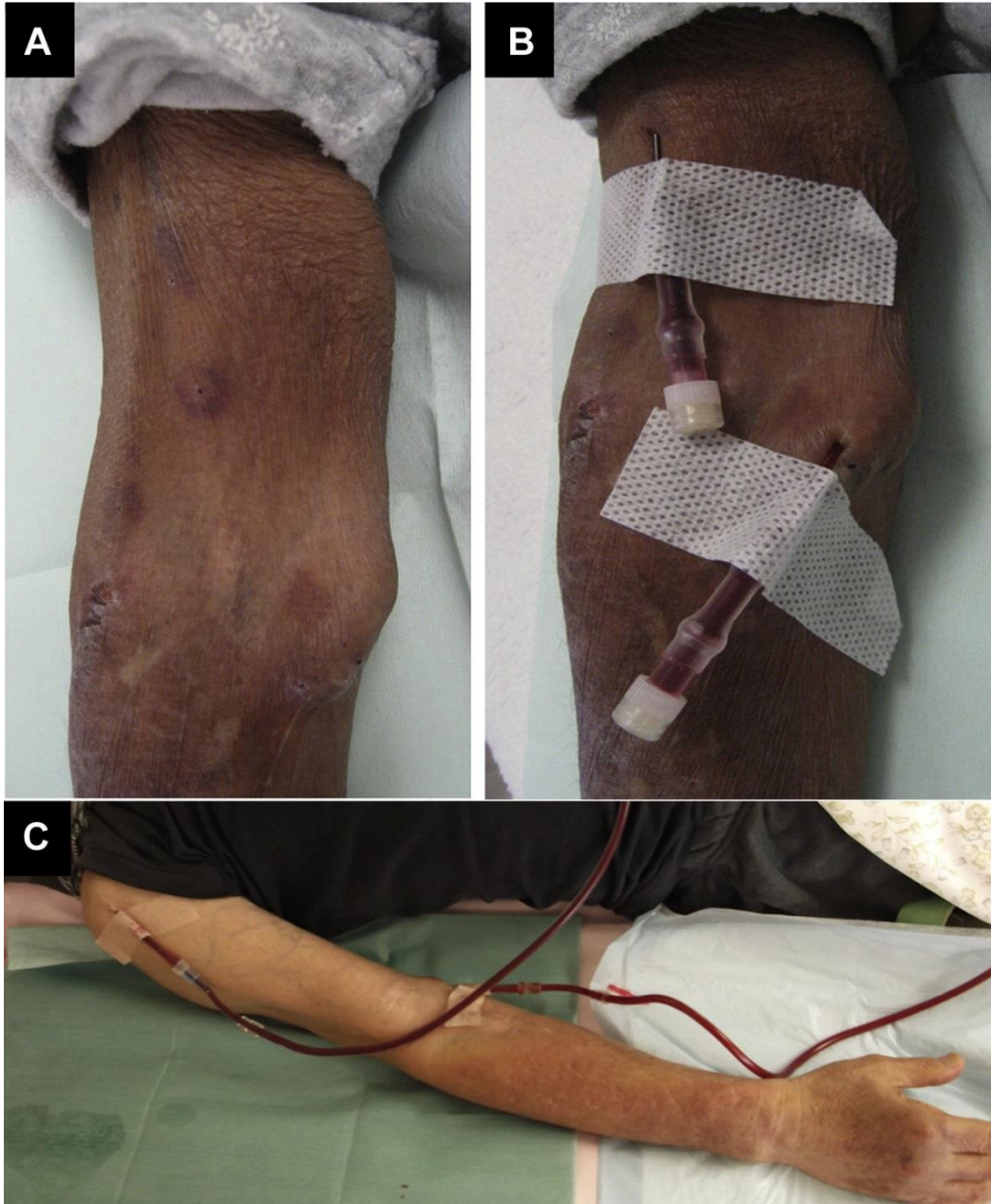


**Permanent catheter**  
**Arterial superficialization**  
**AV graft**

**AV fistula**

患者調査による集計

# Representative views of superficialized brachial artery



**A, The returning vein is the cephalic vein in the right upper arm. Modest aneurysmal changes of the superficialized BA can be seen.**

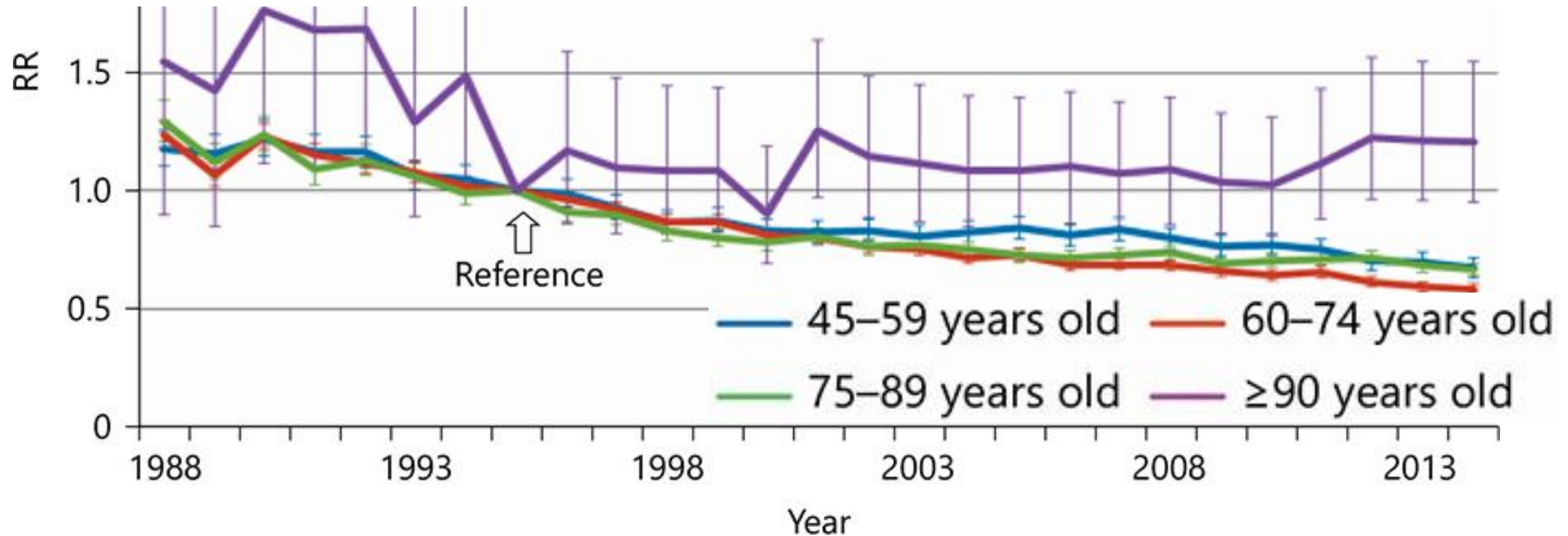
**B, Both the vein and artery were cannulated with a 16-G needle.**

**C, No superficial veins were available and only the cephalic vein at the shoulder was used as a returning vein.**



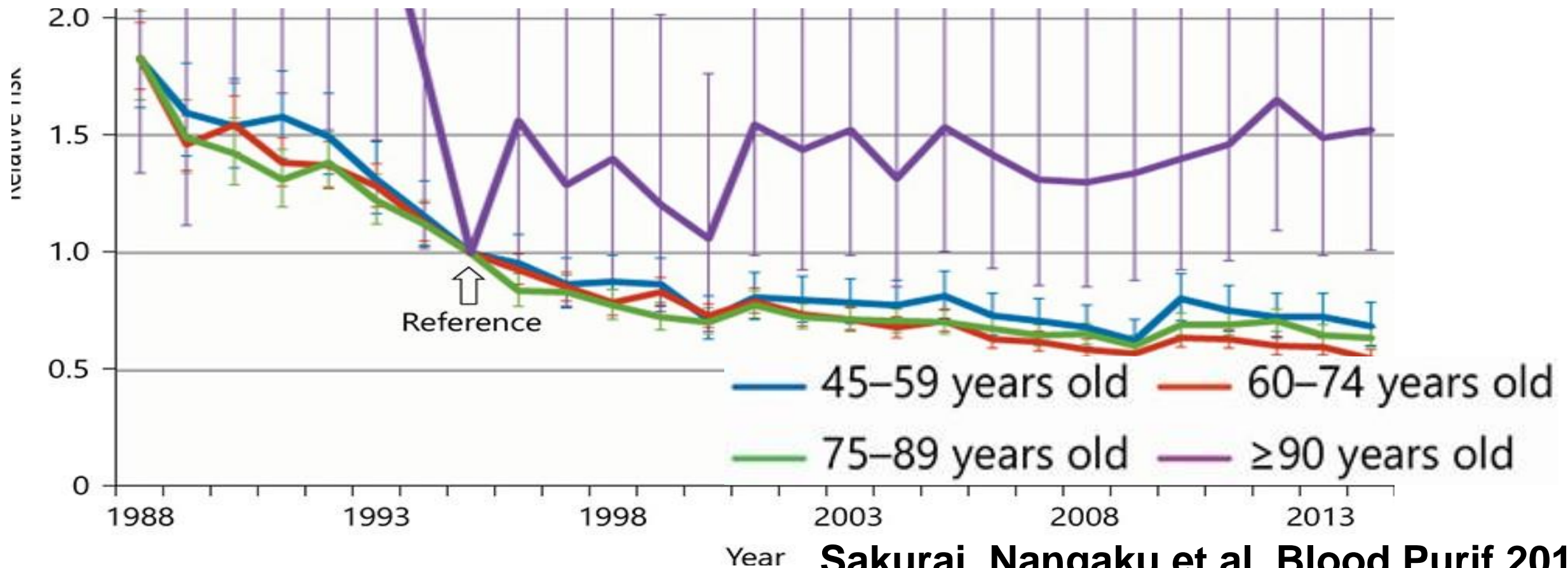
# Trends in all-cause mortality of Japanese dialysis patients by age group

Relative risk of all-cause mortality remains unchanged only for the age group of patients 90 years or older



# Trends in mortality due to heart failure of Japanese dialysis patients by age group

Relative risks of mortality due to heart failure have been decreasing in age groups younger than 90 years old



Sakurai, Nangaku et al. Blood Purif 2019

# **Strategies for the super-aged dialysis population**

---

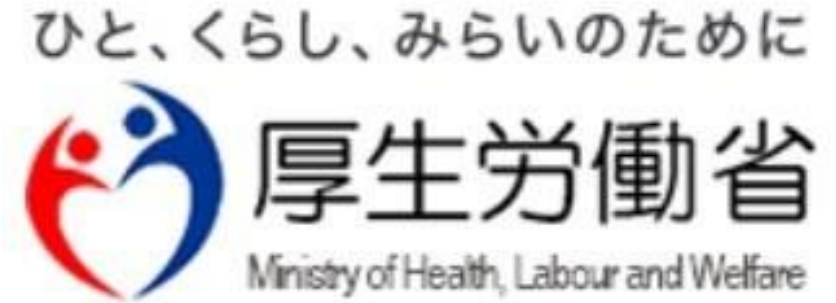
**Survival in the super-aged group ( $\geq 90$  years) is still mostly unimproved.**

**In terms of cause-specific survival, especially death due to heart failure differs distinctly between this group and the remaining elderly patients, indicating that improving their survival is difficult.**

**Alternative dialysis goals could therefore be considered. The major dialysis objective in this population could be to maintain quality of life and limit functional impairment.**

# Kidney Disease Control Commission Meeting Report

## Overall goals



**To prevent CKD exacerbation while maintaining and improving the QOL of patients with CKD, including those receiving dialysis and transplantation, through early detection and diagnosis of CKD based on few subjective symptoms and implementation and maintenance of appropriate high-quality treatment at an early stage**



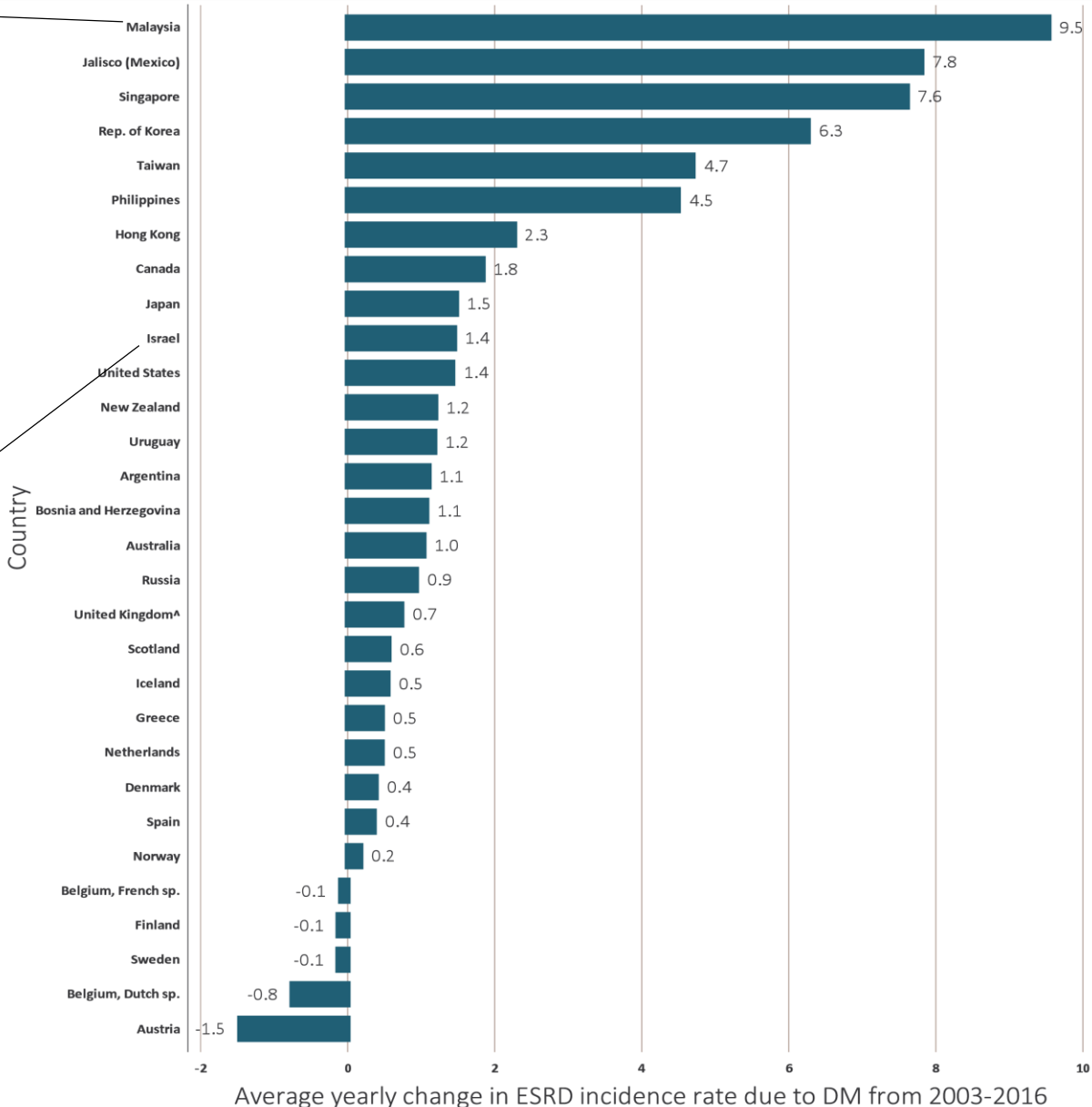
# Kidney Disease Control Commission Meeting Report

## Key Performance Indicators (KPI)

- 1. Local public organizations will work on measures against kidney disease based on this report** with the participation of several other associated parties, such as other administrative bodies, companies, schools, and families.
- 2. Primary care physicians, medical staff, and medical institutions specialized in renal disease cooperate** and improve the CKD medical treatment system.
- 3. To reduce the number of patients newly introduced to dialysis per year to 35,000 by 2028.** The number of new dialysis patients in 2016 was ~39,000.

# Yearly change in the incidence rate of treated ESRD due to diabetes (per million population/year) 2003-2016

Malaysia  
Mexico  
Singapore  
Rep. of Korea  
Taiwan  
Philippines  
Hong Kong  
Canada  
Japan  
Israel

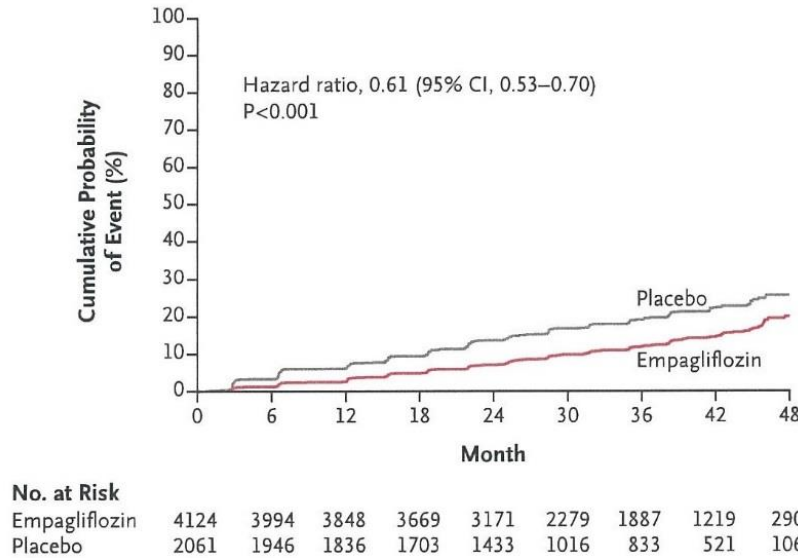


Data source: Special analyses, USRDS ESRD Database. Data presented only for countries from which relevant information were available. Estimates derived from linear regression. Abbreviation: ESRD, end-stage renal disease. NOTE: Data collection methods vary across countries, suggesting caution in making direct comparisons.

# Protection by SGLT2 inhibitors

## EMPA-REG OUTCOME

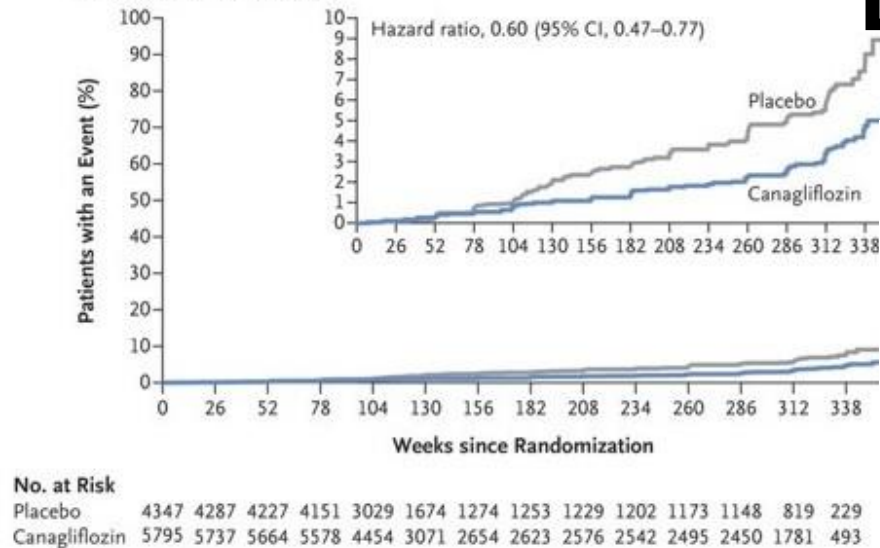
A Incident or Worsening Nephropathy



Wanner et al. N Engl J Med 2016

## CANVAS

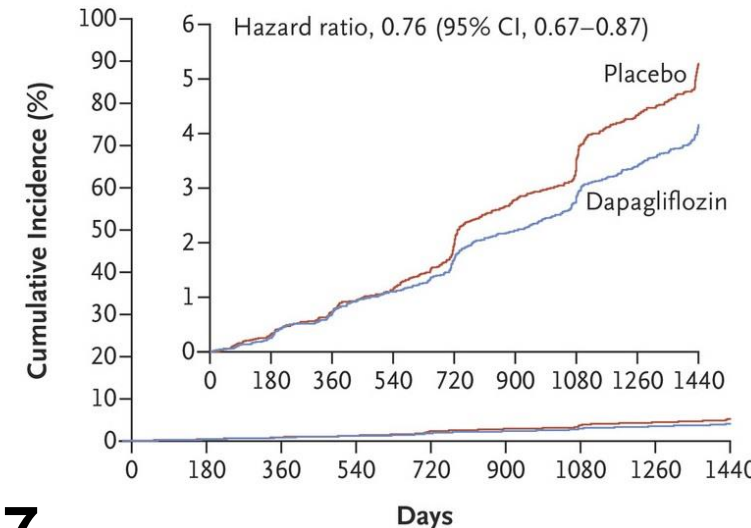
Composite of 40% Reduction in eGFR, Requirement for Renal-Replacement Therapy, or Death from Renal Causes



Neal et al. N Engl J Med 2017

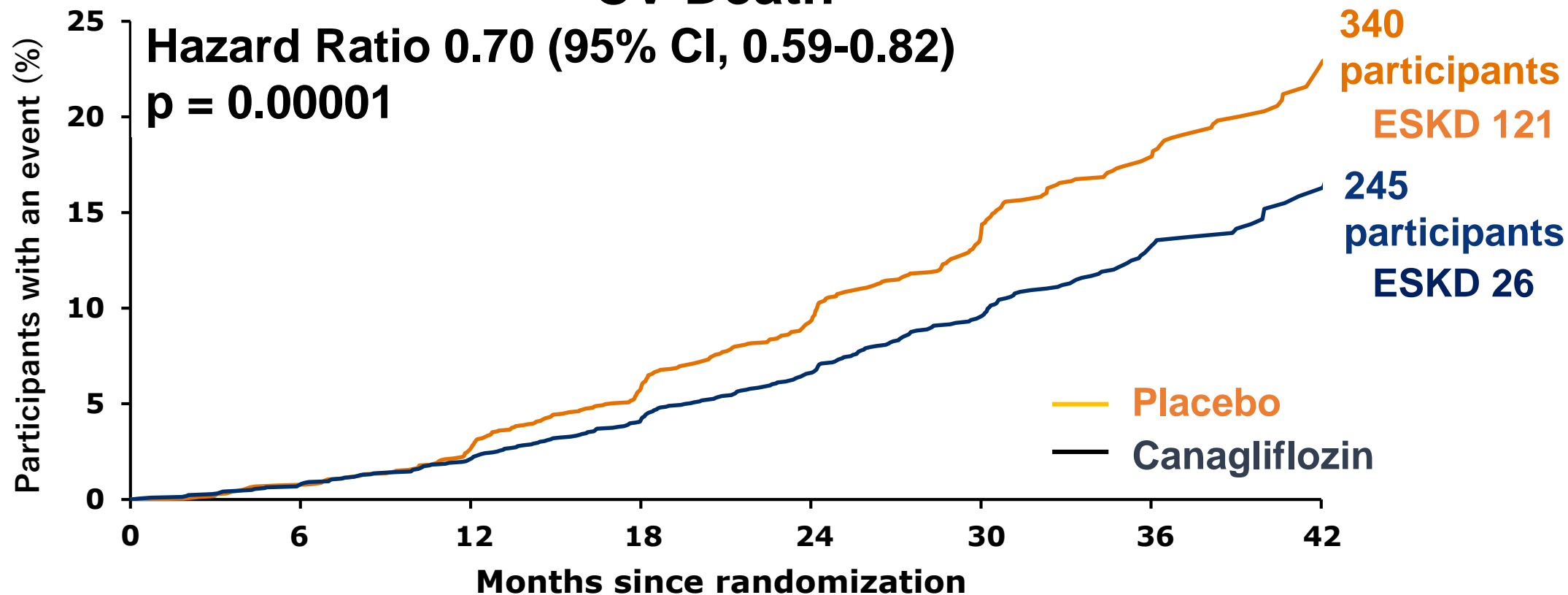
## DECLARE-TIMI 58

C Renal Composite









Wiviott et al. N Engl J Med 2018

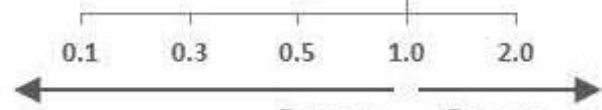
# Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

# SGLT2 inhibitor and kidney outcomes in Asian patients: EMPA-REG OUTCOME

	Empagliflozin		Placebo		Hazard ratio (95% CI)	Hazard ratio (95% CI)	p-value for race-by- treatment interaction
	n with event/N (%)	rate/1000 patient-yr	n with event/N (%)	rate/1000 patient-yr			
<b>Incident or worsening nephropathy</b>							
Overall	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53, 0.70)		0.1945
Asian	134/865 (15.5)	54.8	97/444 (21.8)	82.6	0.64 (0.49, 0.83)		
<b>Progression to macroalbuminuria</b>							
Overall	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54, 0.72)		0.1915
Asian	117/853 (13.7)	48.3	84/435 (19.3)	72.4	0.64 (0.49, 0.85)		
<b>Doubling of serum Cr, initiation of RRT or death due to kidney disease</b>							
Overall	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40, 0.75)		0.7424
Asian	18/1003 (1.8)	6.1	18/507 (3.6)	12.3	0.48 (0.25, 0.92)		



0.1 0.3 0.5 1.0 2.0

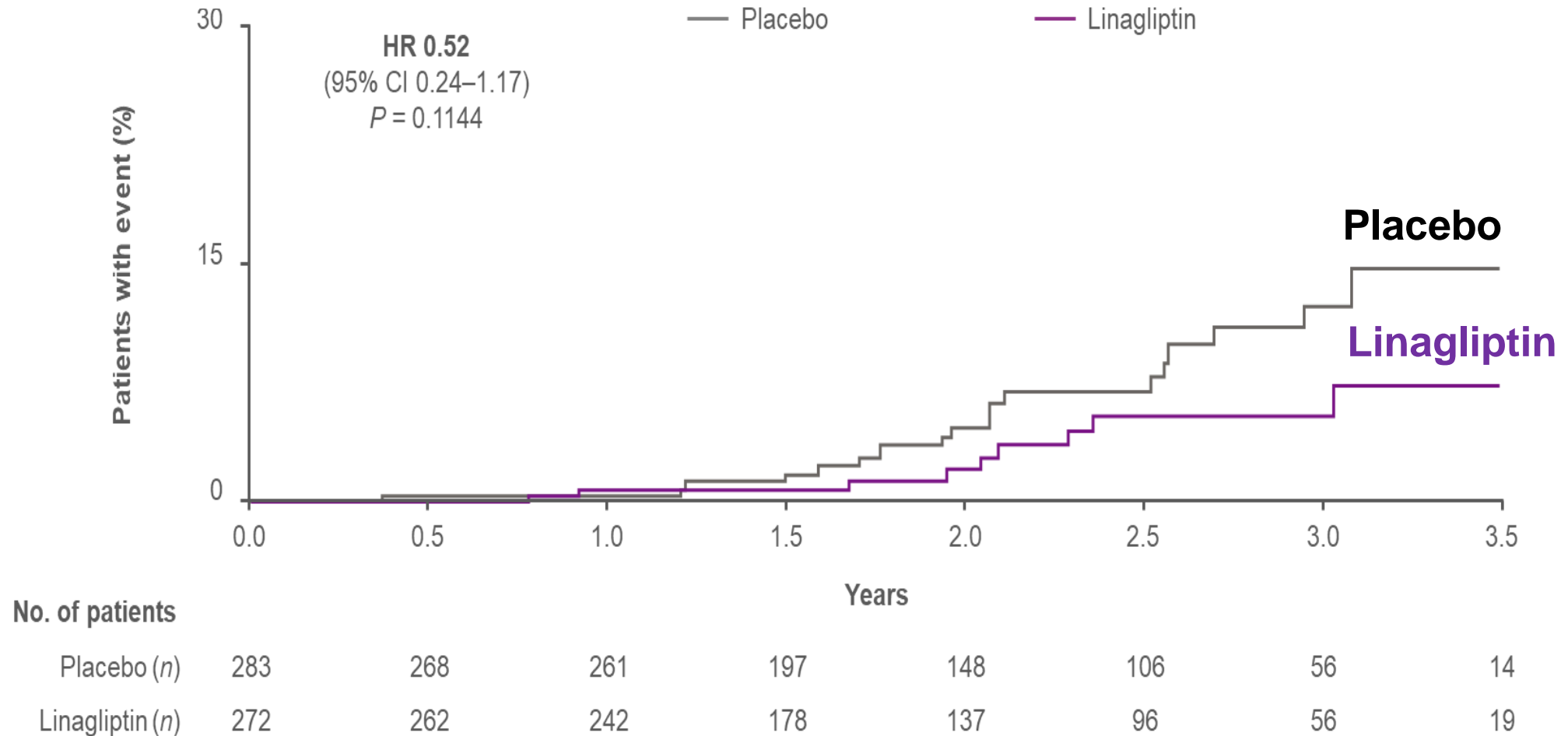
Favors empagliflozin      Favors placebo

# **Renoprotection by incretin-based drugs**

# Subgroup analysis of Asians in CARMELINA trial

international, randomized, double-blind, placebo-controlled study with linagliptin

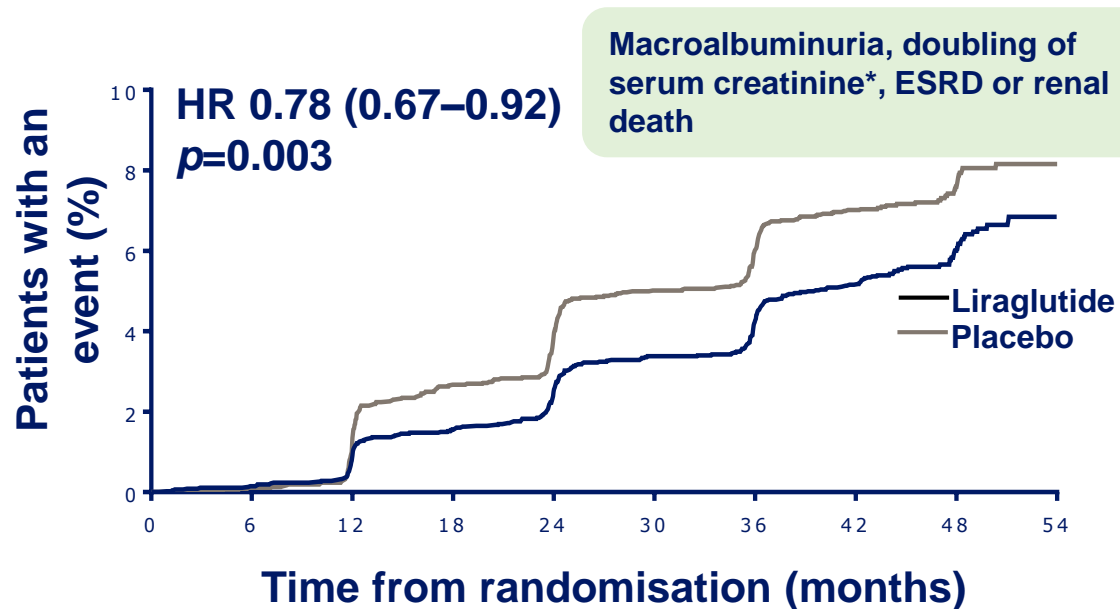
Death due to renal failure, progression to end-stage kidney disease, or eGFR<10



Inagaki, Nangaku et al. Diabetol Int *in press*

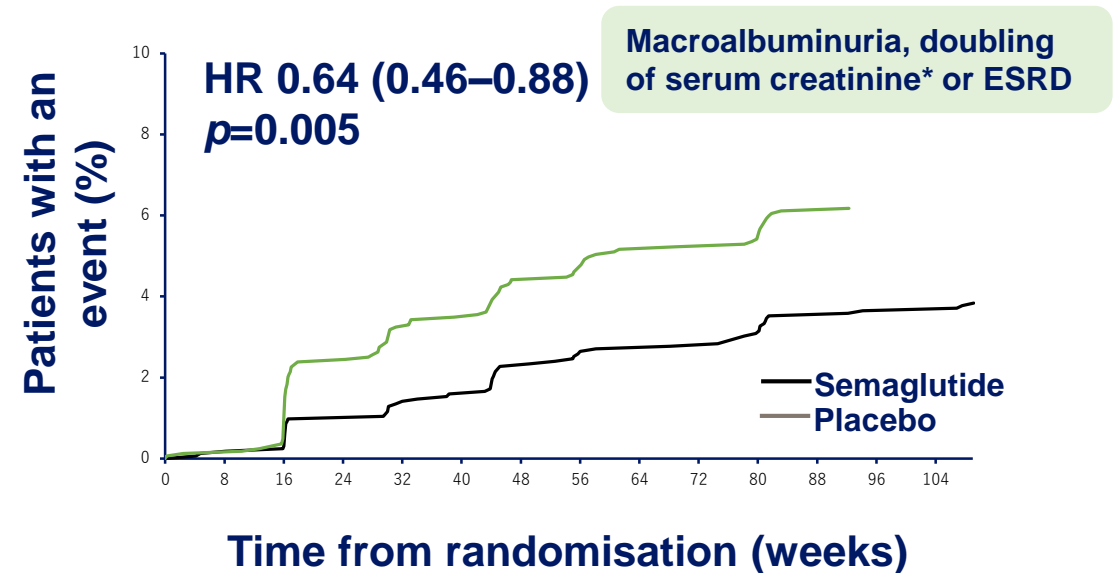
# Kidney protection by GLP-1R agonist

## LEADER



Mann et al. N Engl J Med 2017

## SUSTAIN 6

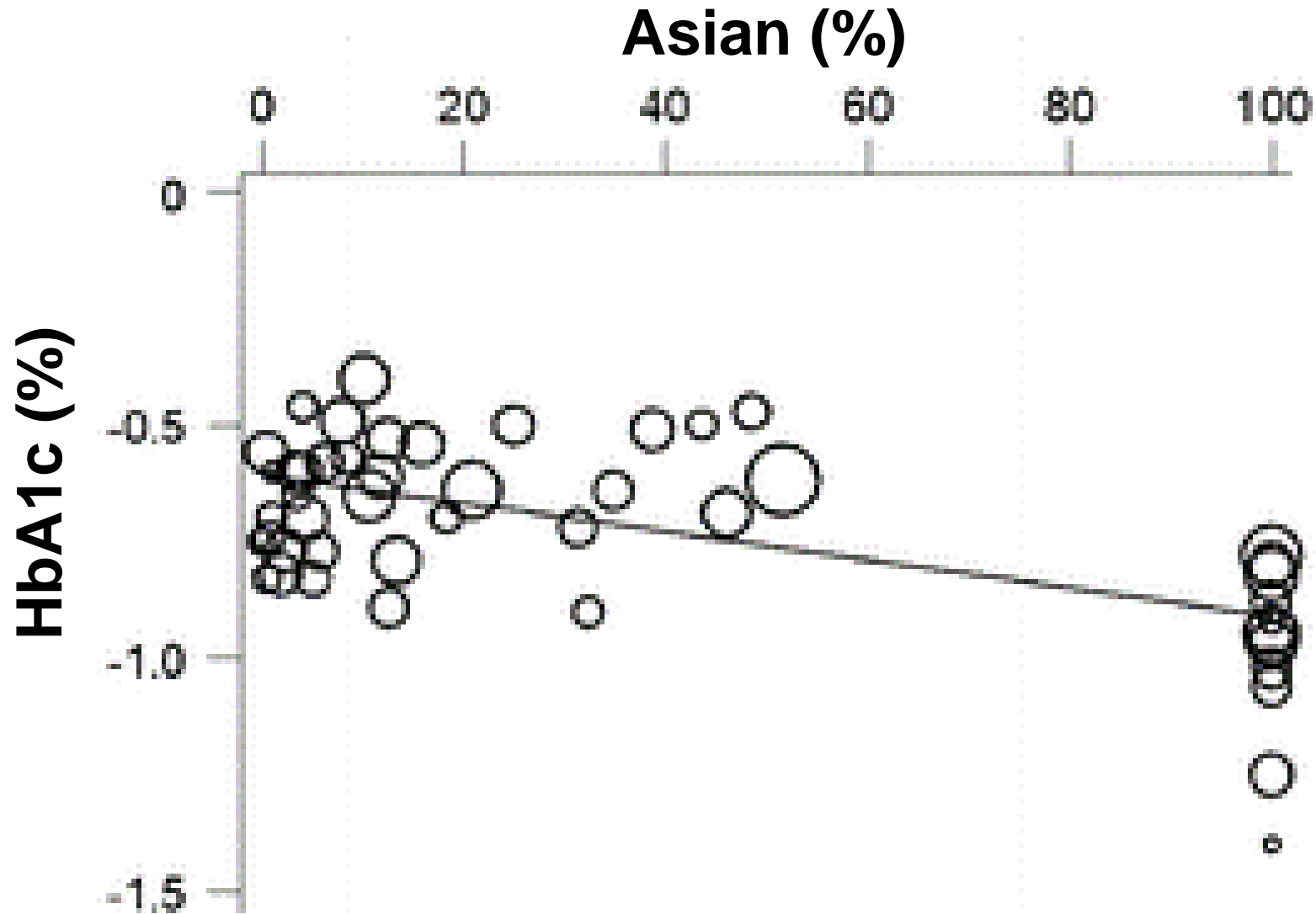


Marso et al. N Engl J Med 2016



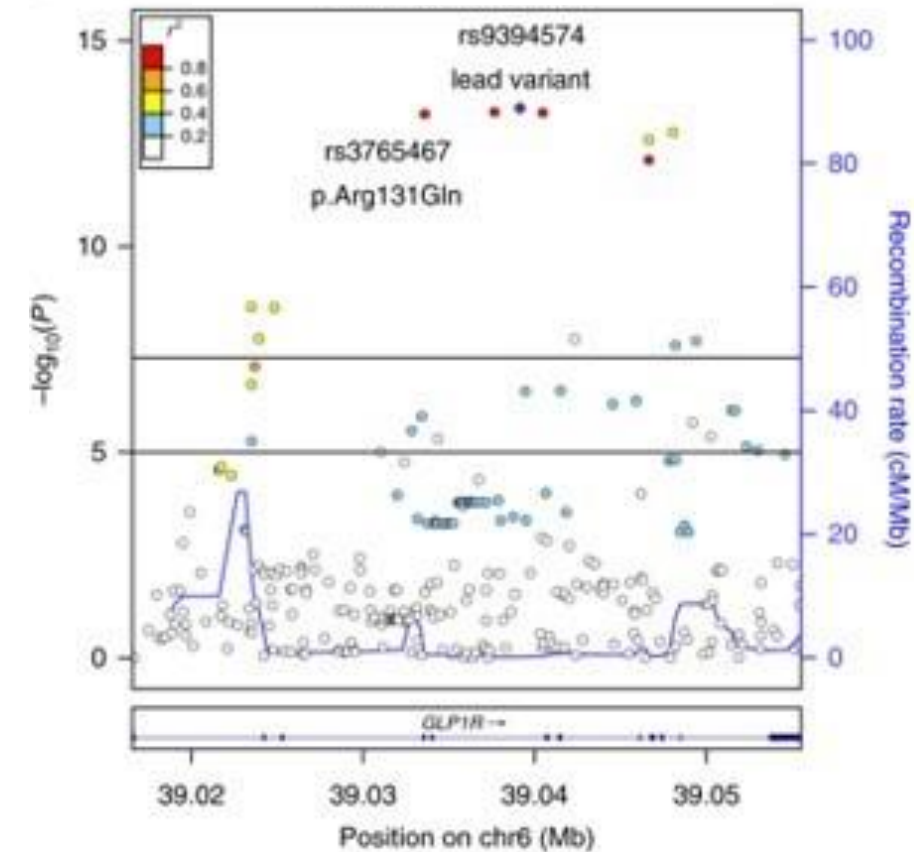
# better glucose-lowering efficacy by DPP-4 inhibitors in Asian: a systematic review and meta-analysis

---

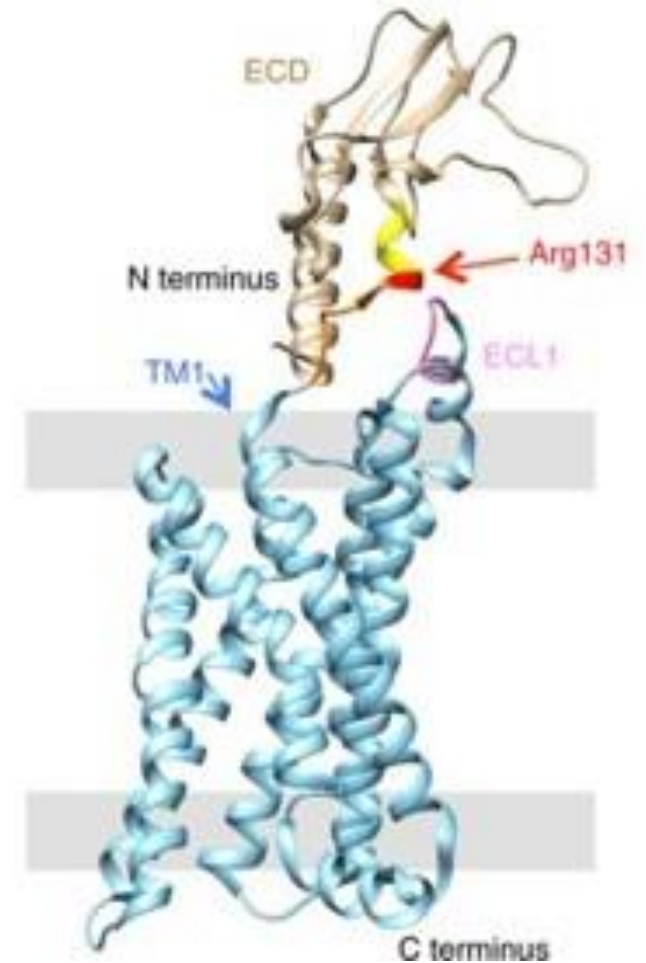
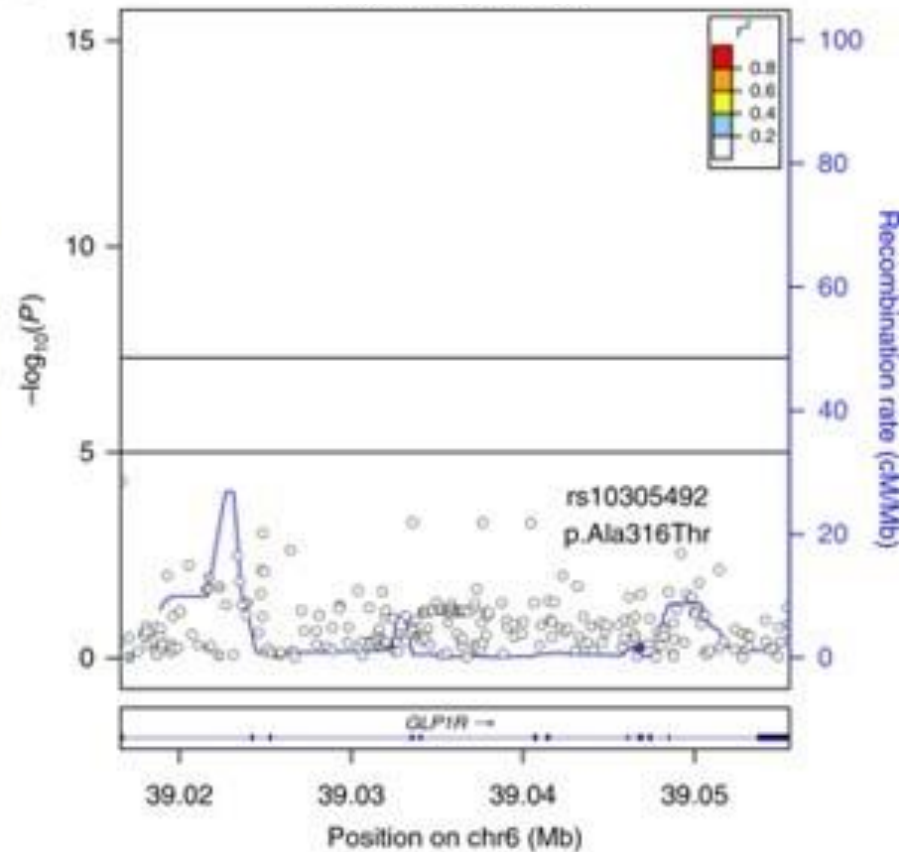


# susceptibility loci for type 2 diabetes in the Japanese population includes variants in *GLP1R*

**a Japanese T2D GWAS**



**b European T2D GWAS**



**CKD complication**  
**CKD-MBD**

**Target of iPTH**

# Effect of serum iPTH level on survival

iPTH level (pg/mL)	Number of patients	Hazard ratio	95% CI	P-value
<30	4806	0.900	0.817–0.991	0.0320
30–59	4062	0.885	0.799–0.979	0.0180
60–119	5287	0.891	0.811–0.980	0.0173
120–179	3539	0.902	0.812–1.002	NS
180–359	5259	1.000		Reference
360–719	3078	1.083	0.969–1.211	NS
720	1373	1.116	0.963–1.293	NS

Nakai et al. Ther Apher Dial 2008

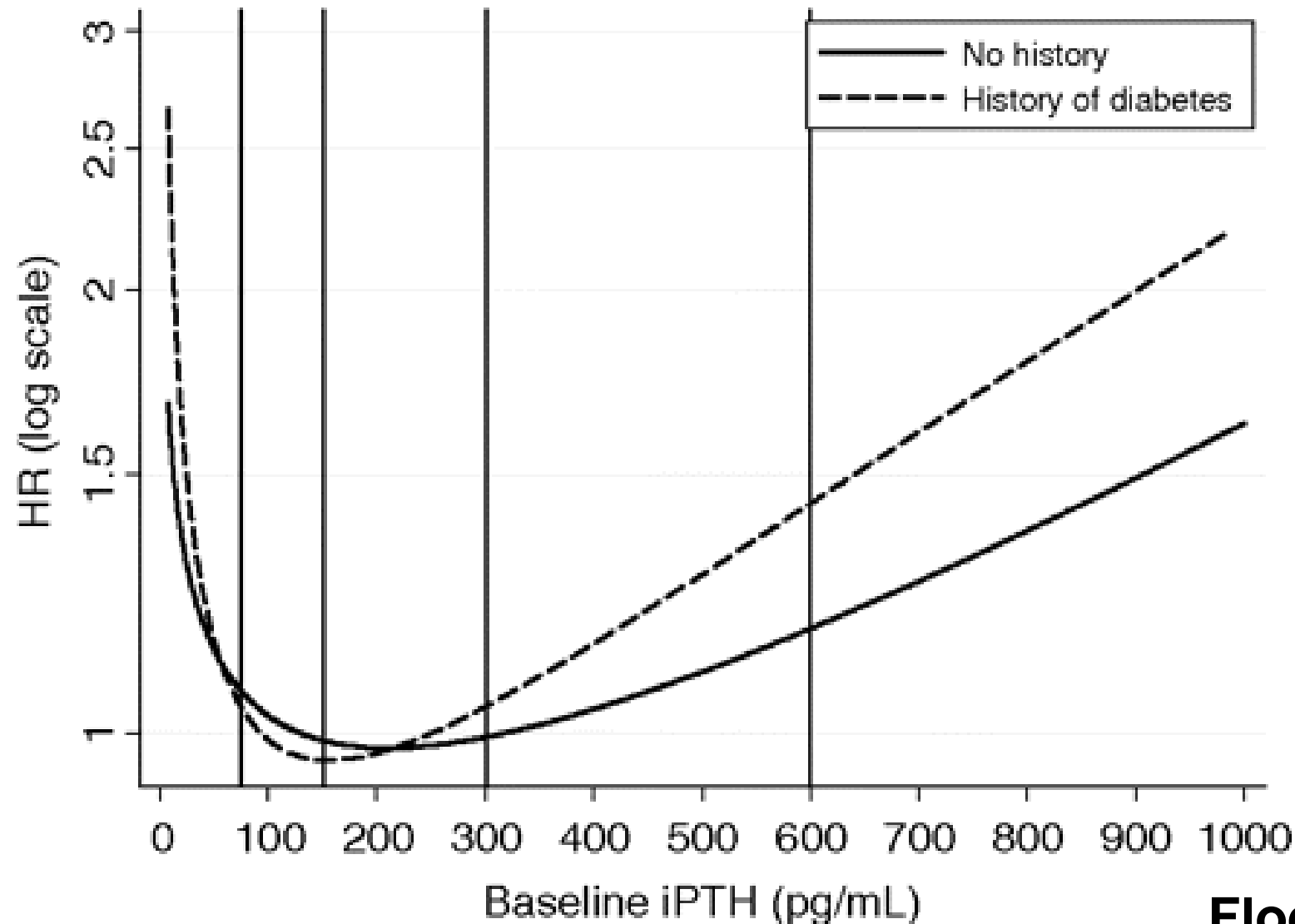


**Target iPTH range in JSDT GL 2006: 60~180**

# patients in low iPTH had increased risk of mortality

## European HD population

---



Floege et al. NDT 2011

# **Upshift of Target iPTH range**

---

## **JSDT Guideline for CKD-MBD 2012**

### **Chapter 3: Treatment of abnormal PTH levels in CKD-MBD**

**Target iPTH range: 60~240 pg/mL**

**Control of phosphate and calcium is more important than control of PTH**



# 2017 Guideline Update for CKD-MBD

## Chapter 4.2: Treatment of abnormal PTH levels in CKD-MBD

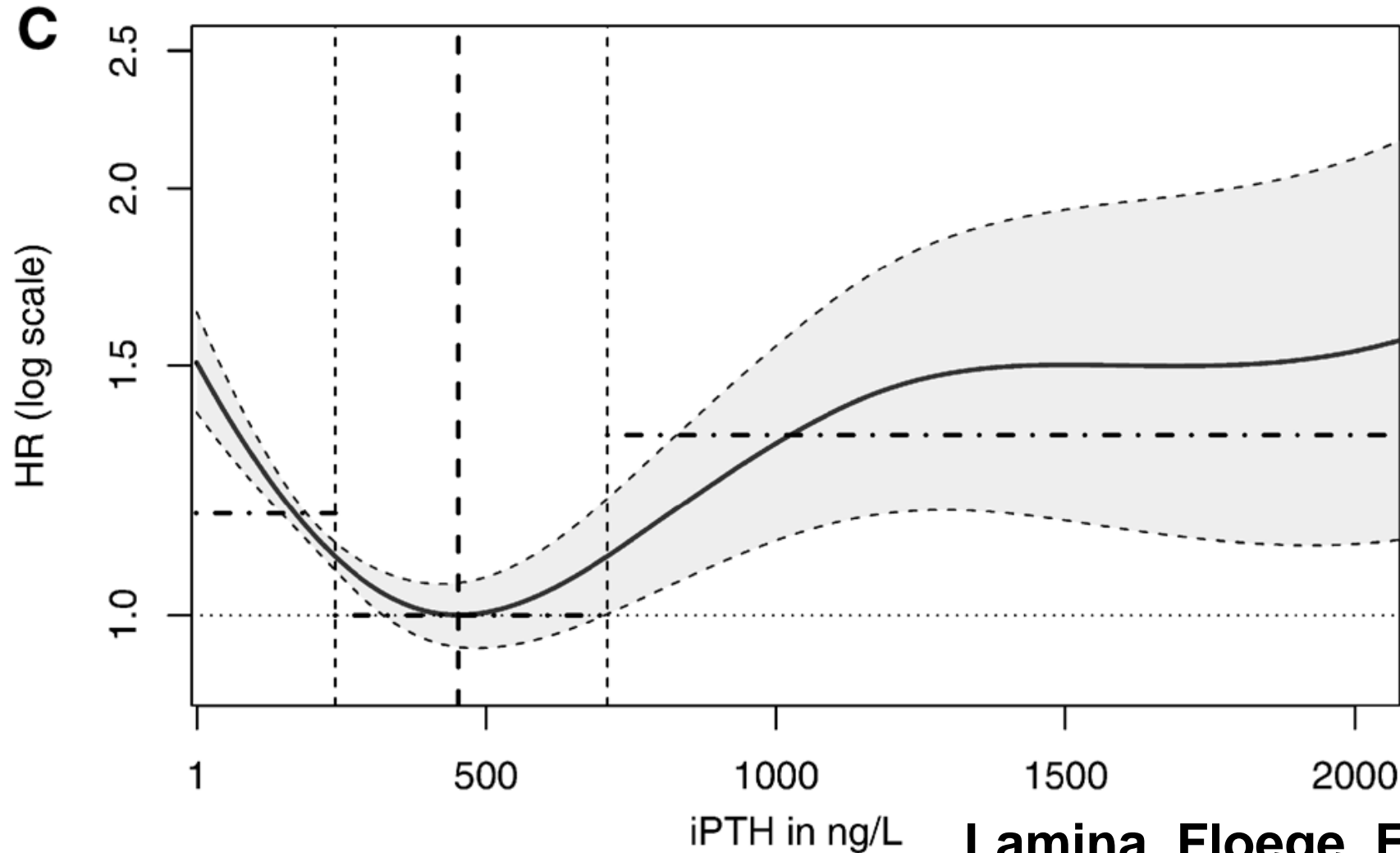
**4.2.1: In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known.**

**4.2.3: In patients with CKD G5D, we suggest maintaining iPTH levels in the range of approximately 2 to 9 times the upper normal limit for the assay (2C).**

**We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).**

# Association of changes in bone mineral parameters with mortality in HD patients: ARO cohort

For intact PTH, the lowest risk ranges were between 239 and 710 ng/L



Lamina, Floege, Eckardt et al. NDT 2019



# **Upshift of Target iPTH range**

---

## **JSDT Guideline for CKD-MBD 2012**

**Based on clinical evidence, upper limit of iPTH can be higher.**

**However, clinical evidence shows relatively short-term prognosis, and it is unknown whether this finding can be applicable to improvement of long-term prognosis.**

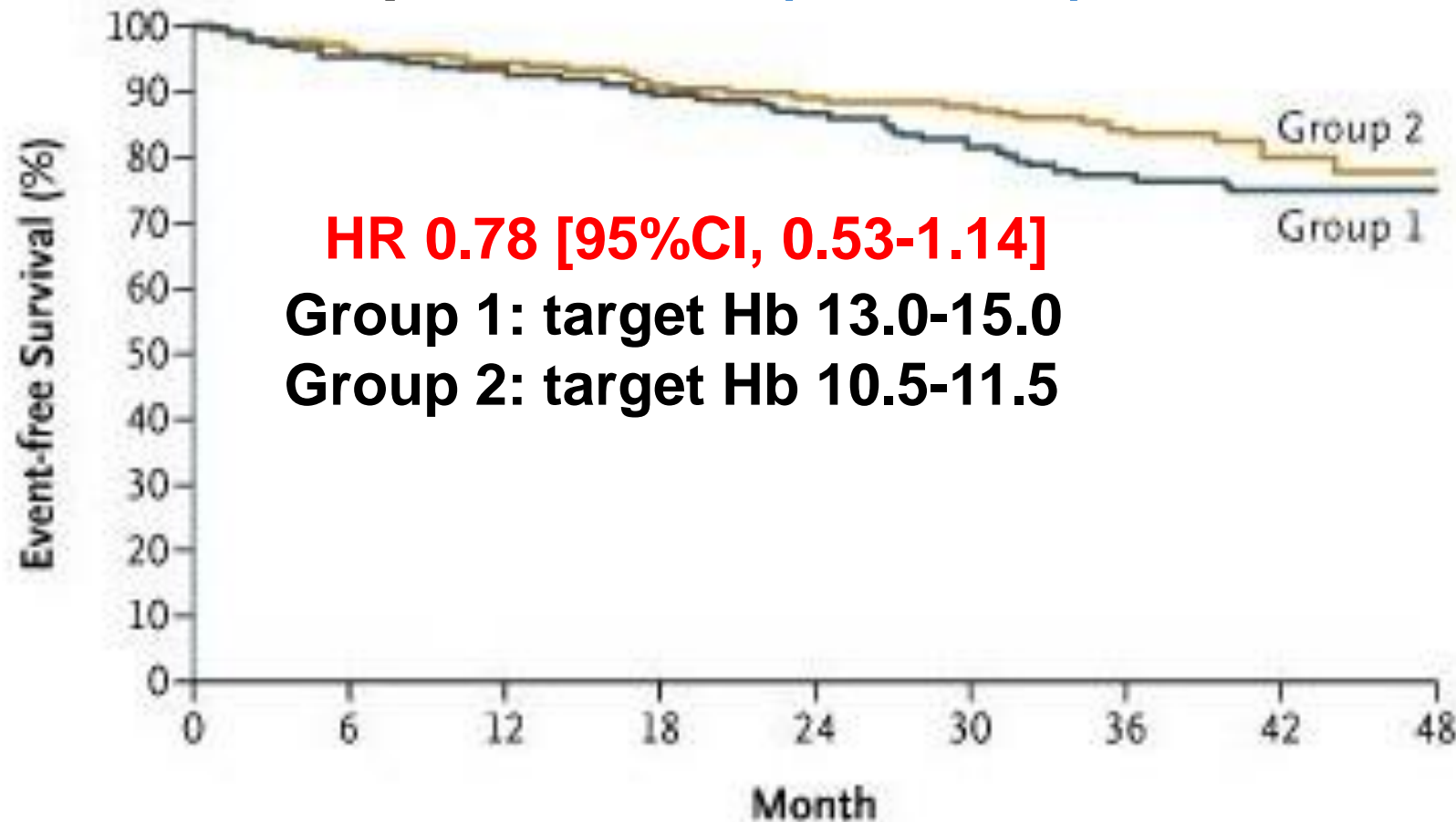
**We do not want to give an unexpected message that more severe hyperparathyroidism is acceptable by giving higher upper limit of iPTH.**

# **CKD complication Anemia**

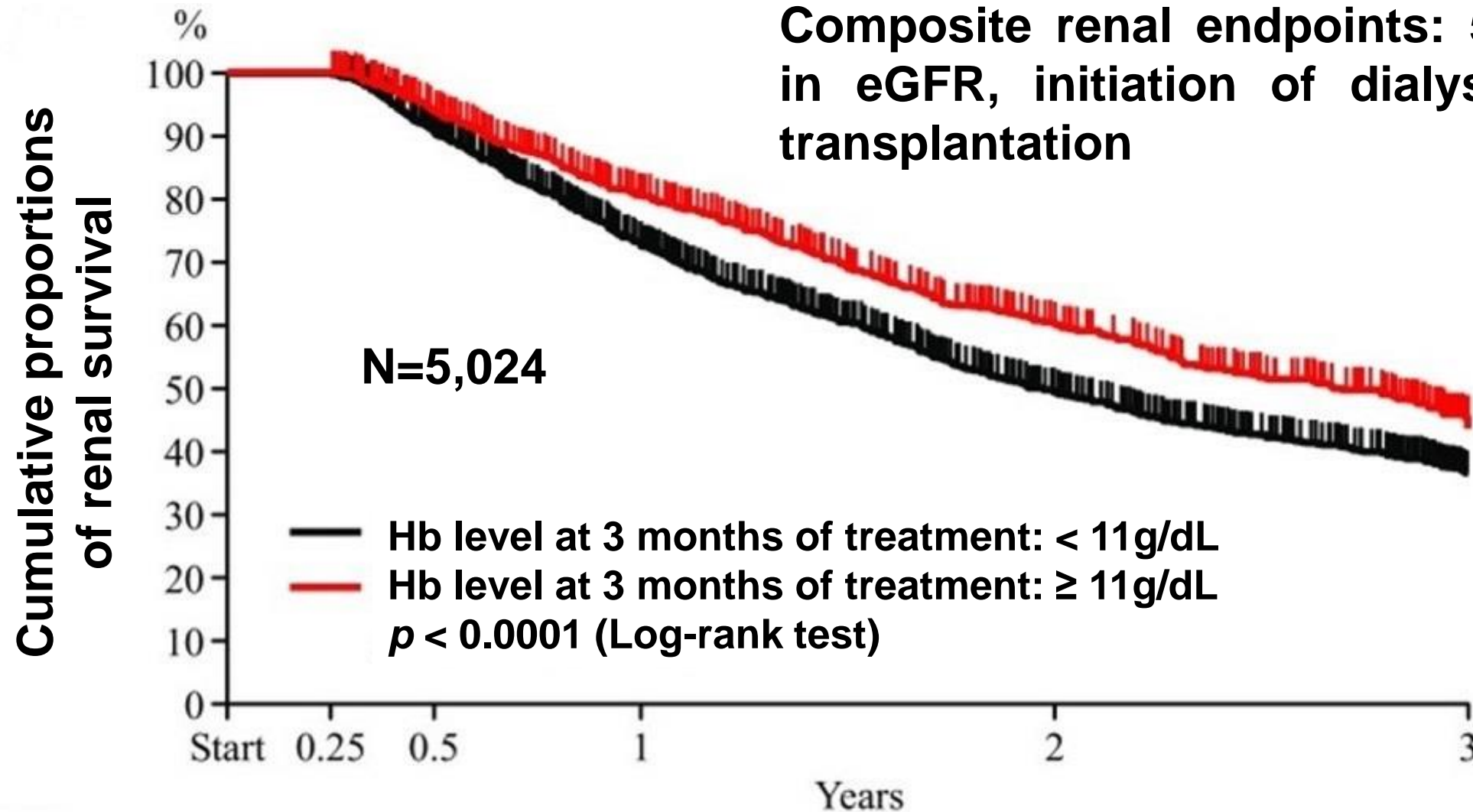
**Target of hemoglobin  
and  
new treatment**

# CREATE: primary endpoint

Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)

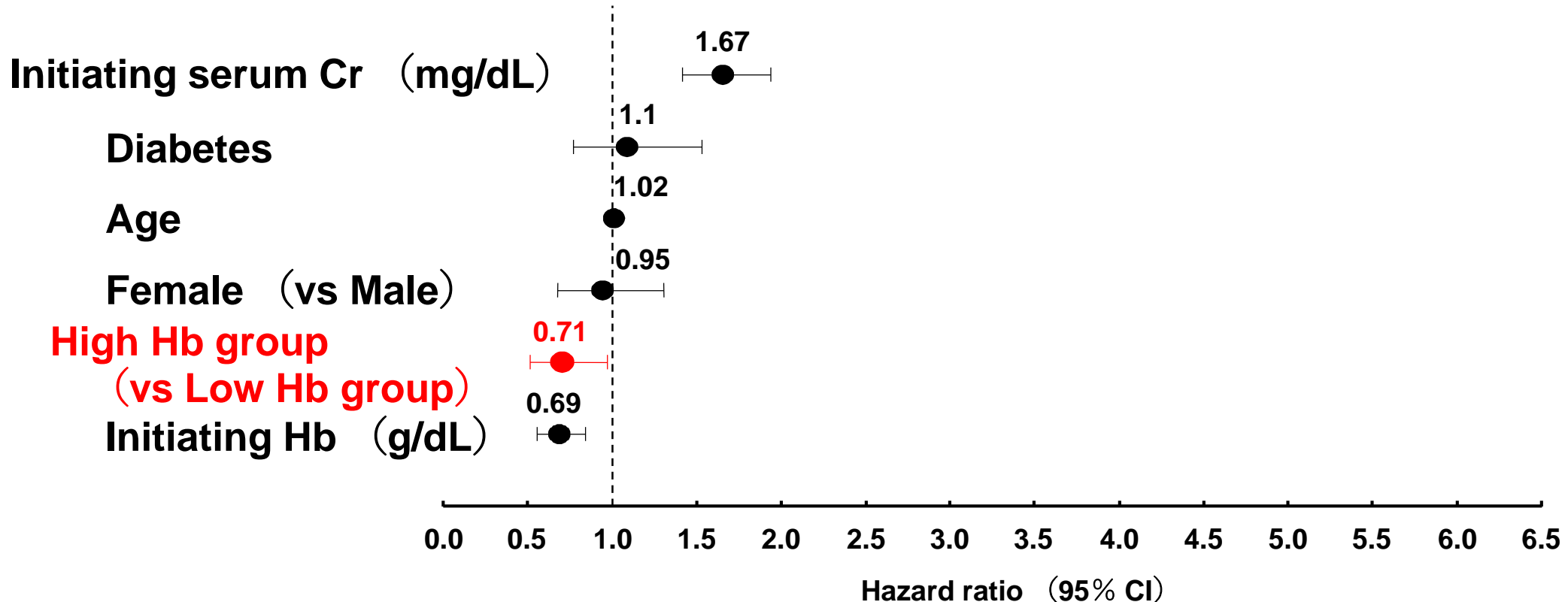


# High Hb in patients treated with darbepoetin alfa is associated with better prognosis: a post-marketing surveillance in Japan



# A21 study of Japanese CKD patients

## Hazard ratio of kidney survival



# Difference of cardiovascular events between Japan and Western countries

---

	Cardiovascular events (/1000 person · year)	apoplexy (/1000 person · year)
<b>CHOIR</b>	<b>51.7</b>	<b>5.4</b>
<b>CREATE</b>	<b>58.0</b>	<b>7.2</b>
<b>TREAT</b>	<b>76.4</b>	<b>9.5</b>
<b>A21</b>	<b>15.6</b>	<b>2.1</b>
<b>Gonryo (G3-5)</b>	<b>21.8</b>	<b>8.6</b>

# JSDT anemia guideline in CKD 2015

---

**Target Hb should be 11~13 g/dL for non-HD CKD patients and PD patients, and 10~12 g/dL for HD patients, respectively.**

**Target Hb should be individualized based on the personal conditions of the patient.**



# 18<sup>th</sup> Asian Colloquium in Nephrology



*Best Practices in Kidney Care in Asia*

*19 – 21 July 2019*

**Incorporating:** SOTANC - State-Of-The-Art Nephrology Course (Nursing)  
Singapore Society of Nephrology Annual Scientific Meeting  
Asia Renal Association - Asian Nephrology Conference

## **Anemia in CKD/ESKD: Is it still EPO?"**

**Masaomi Nangaku**

# Nobel Prize in Medicine 2019



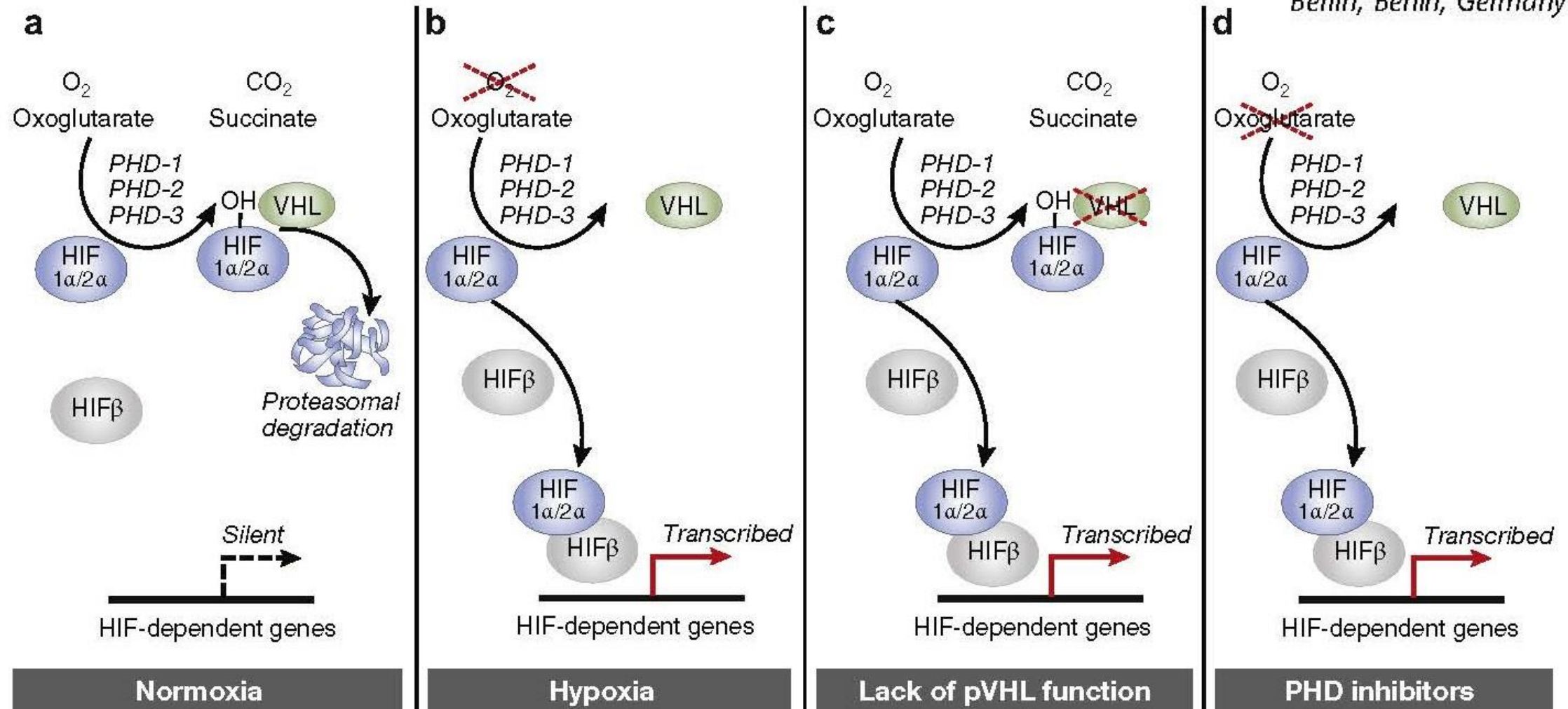
**The Nobel Prize in Physiology or Medicine was jointly awarded to three scientists — William G. Kaelin Jr., Peter J. Ratcliffe and Gregg L. Semenza — for their work on how cells sense and adapt to oxygen availability. 7 Oct, 2019**

# The noblesse of kidney physiology

*Kidney International* (2019) **96**, 1250–1253; <https://doi.org/10.1016/j.kint.2019.10.007>

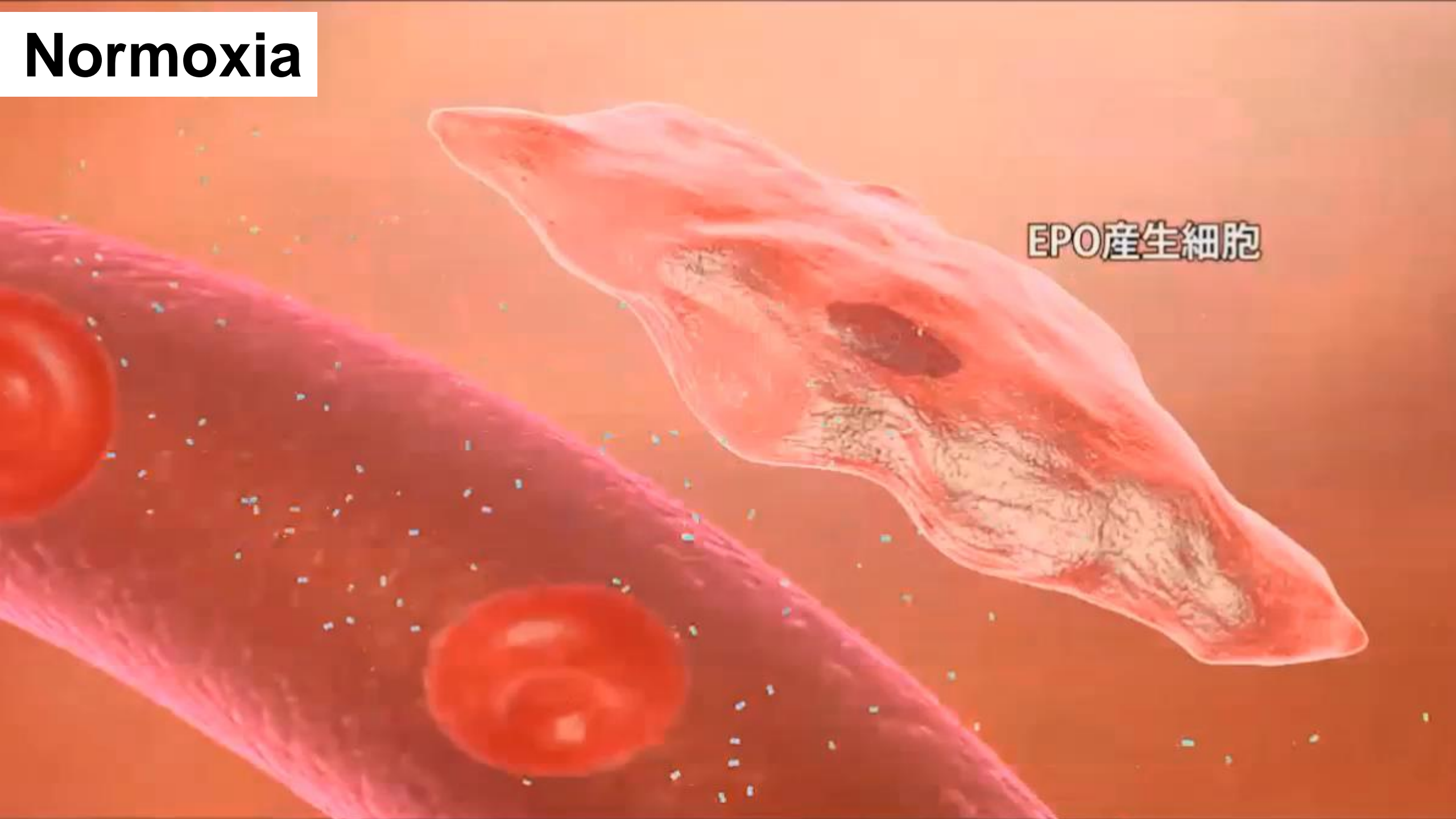
Kai-Uwe Eckardt<sup>1</sup>

<sup>1</sup>Department of Nephrology and Medical Intensive Care, Charité—Universitätsmedizin Berlin, Berlin, Germany

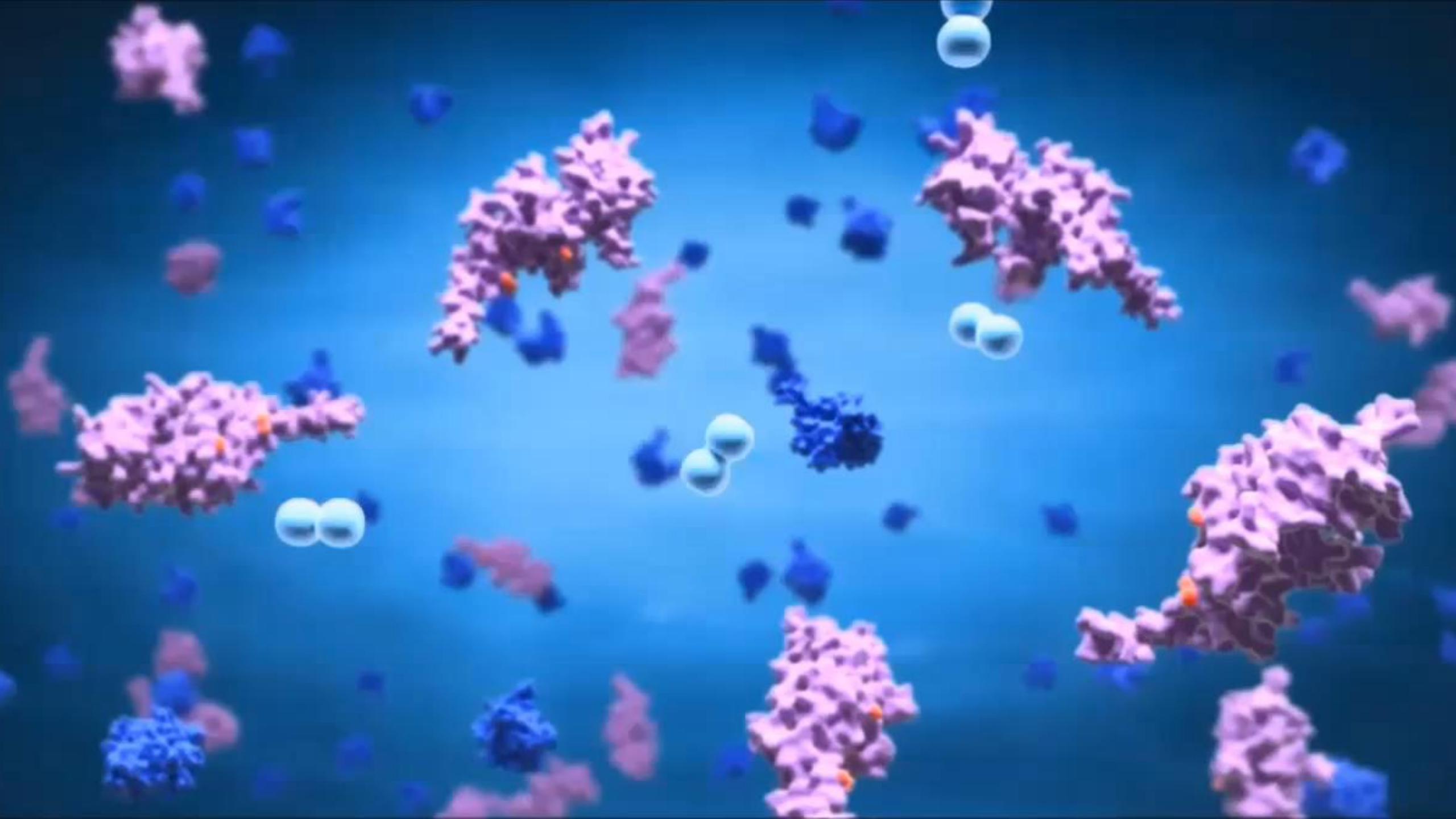




# Normoxia



EPO產生細胞



**Normoxia**



**Hypoxia**





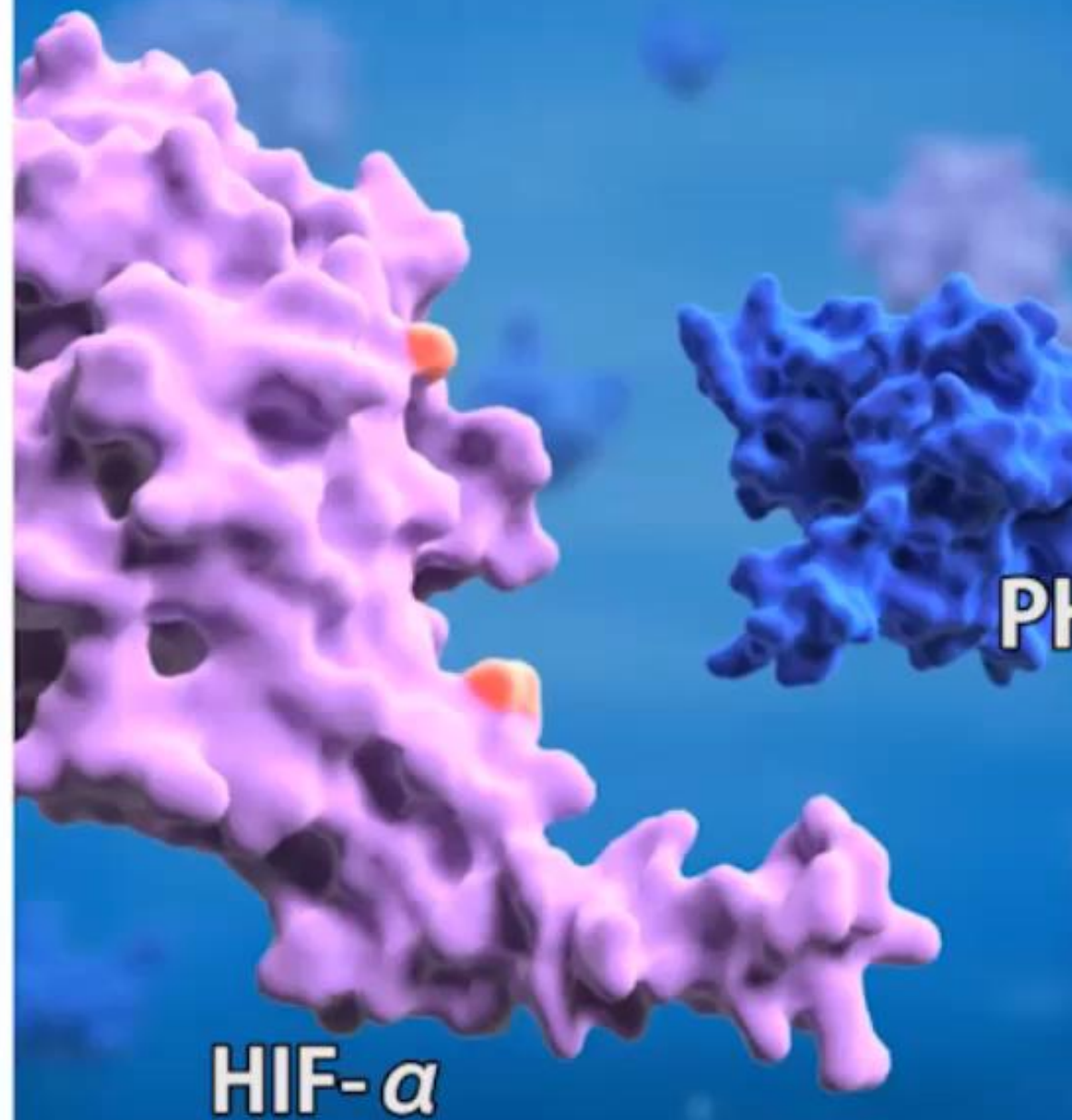




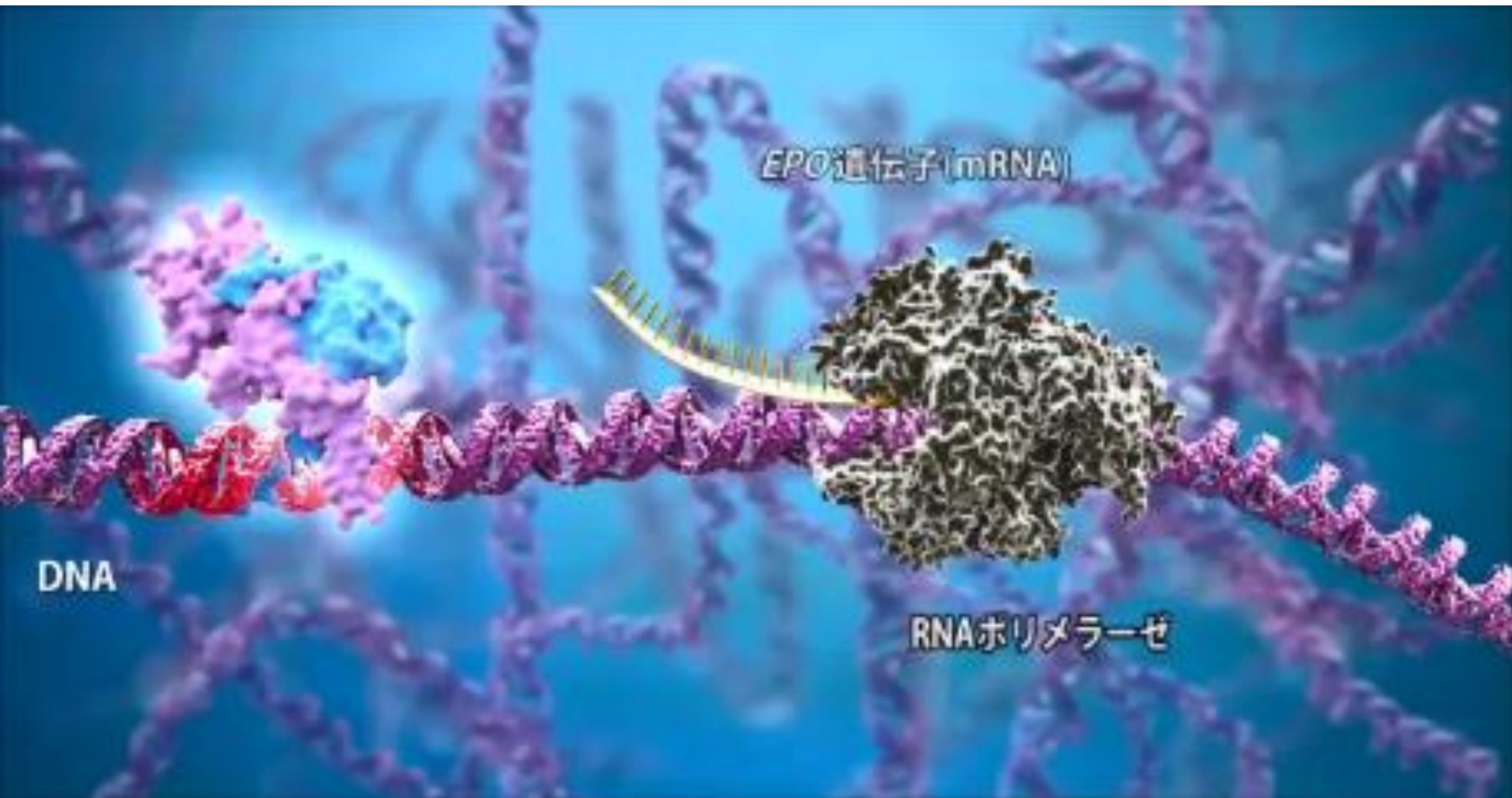
通常酸素濃度下



低酸素濃度下







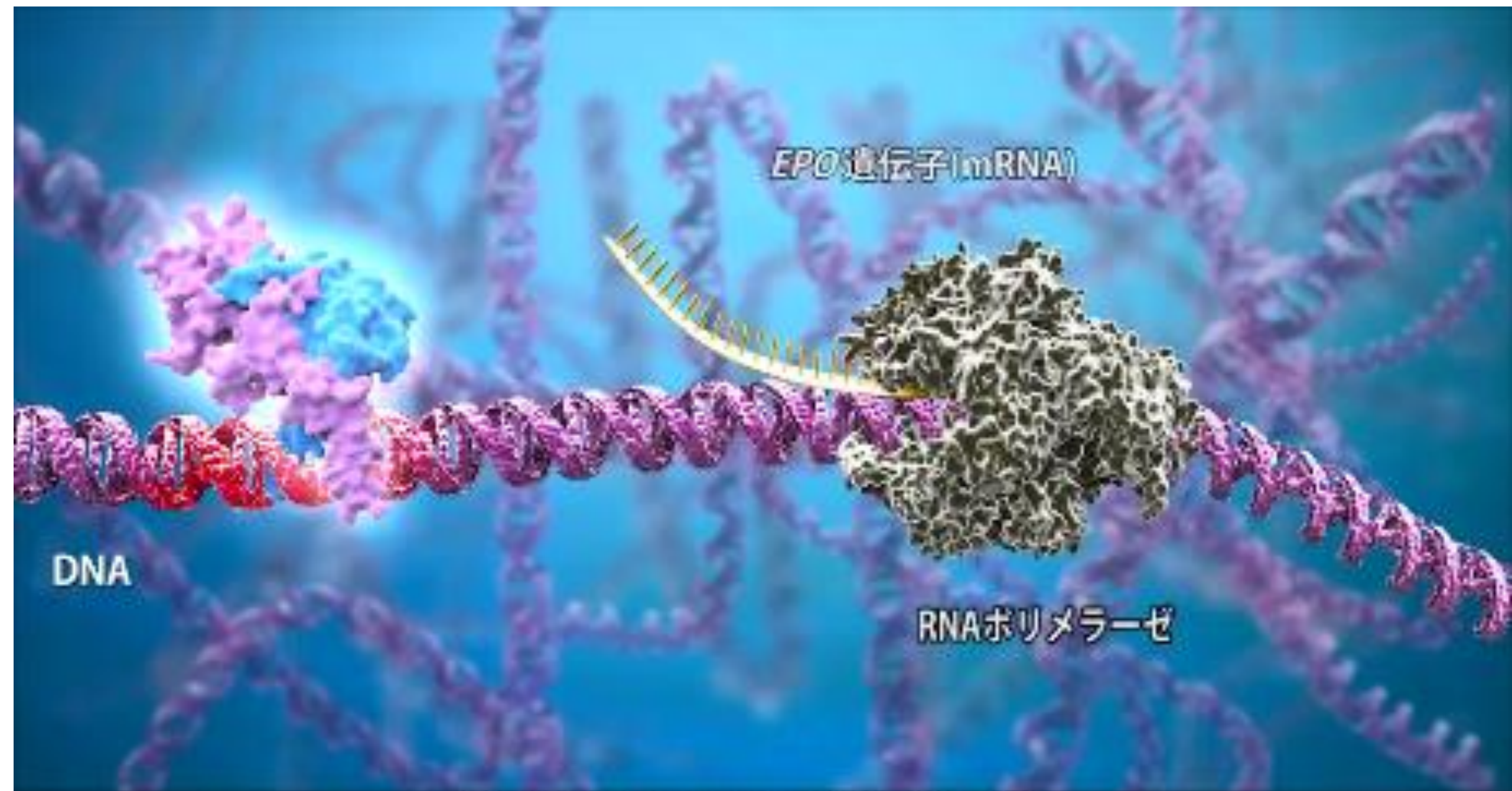
EPO遺伝子(mRNA)

DNA

RNAポリメラーゼ

EPO遺伝子の転写が促進されます。





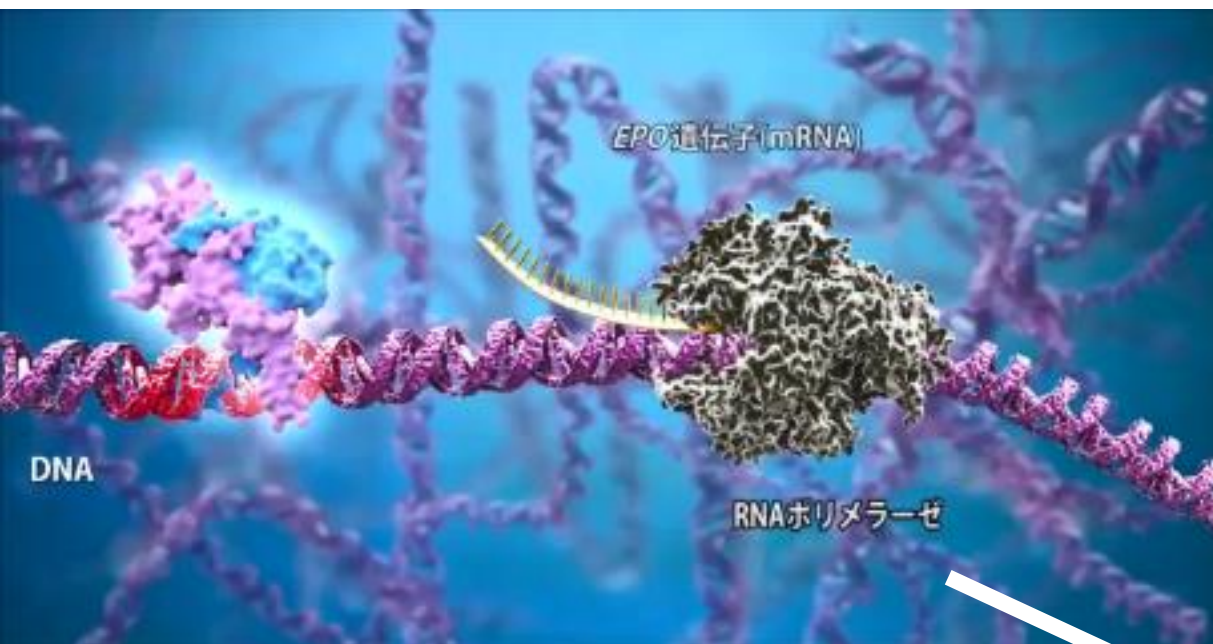
EPO遺伝子(mRNA)

DNA

RNAポリメラーゼ

EPO遺伝子の転写が促進されます。





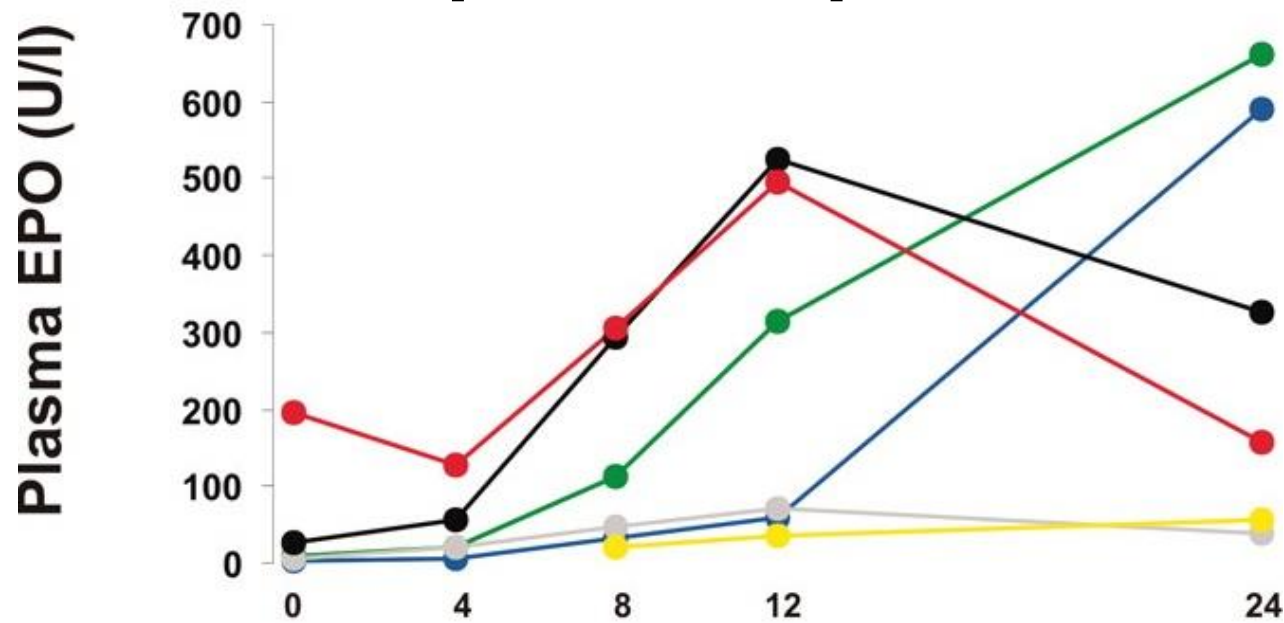
EPO遺伝子の転写が促進されます。



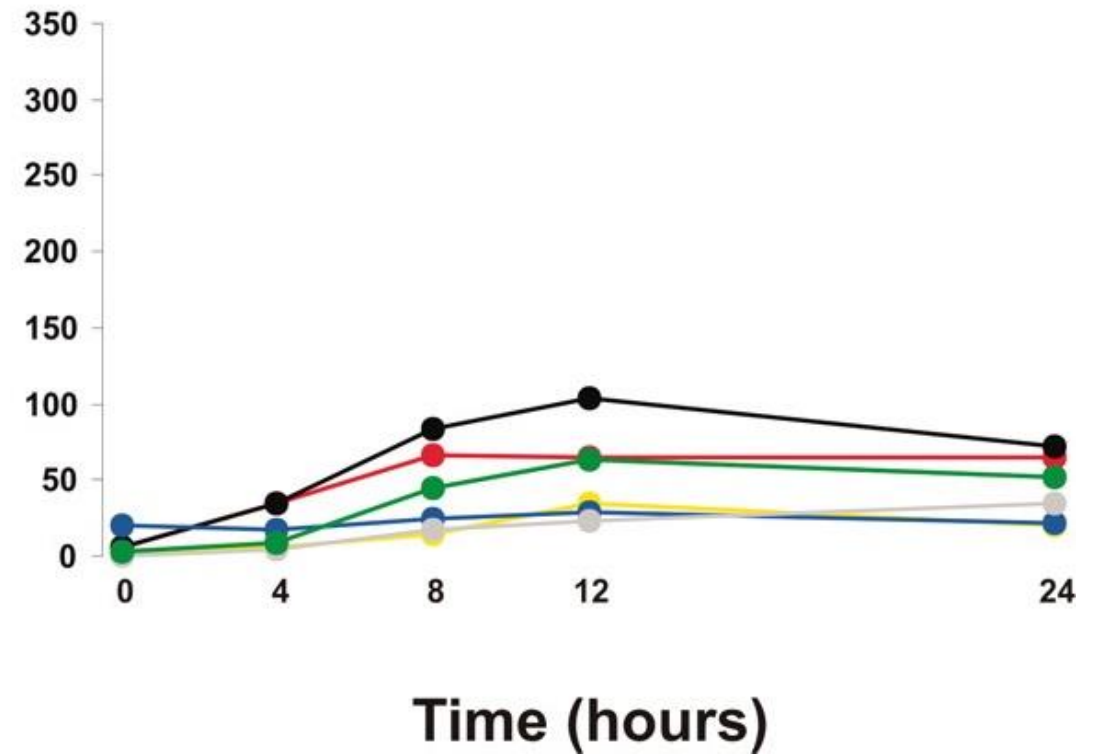
EPO遺伝子の転写が促進されます。

# HIF activator increases plasma-EPO levels in HD patients with and without remaining kidney

## nephric HD patients



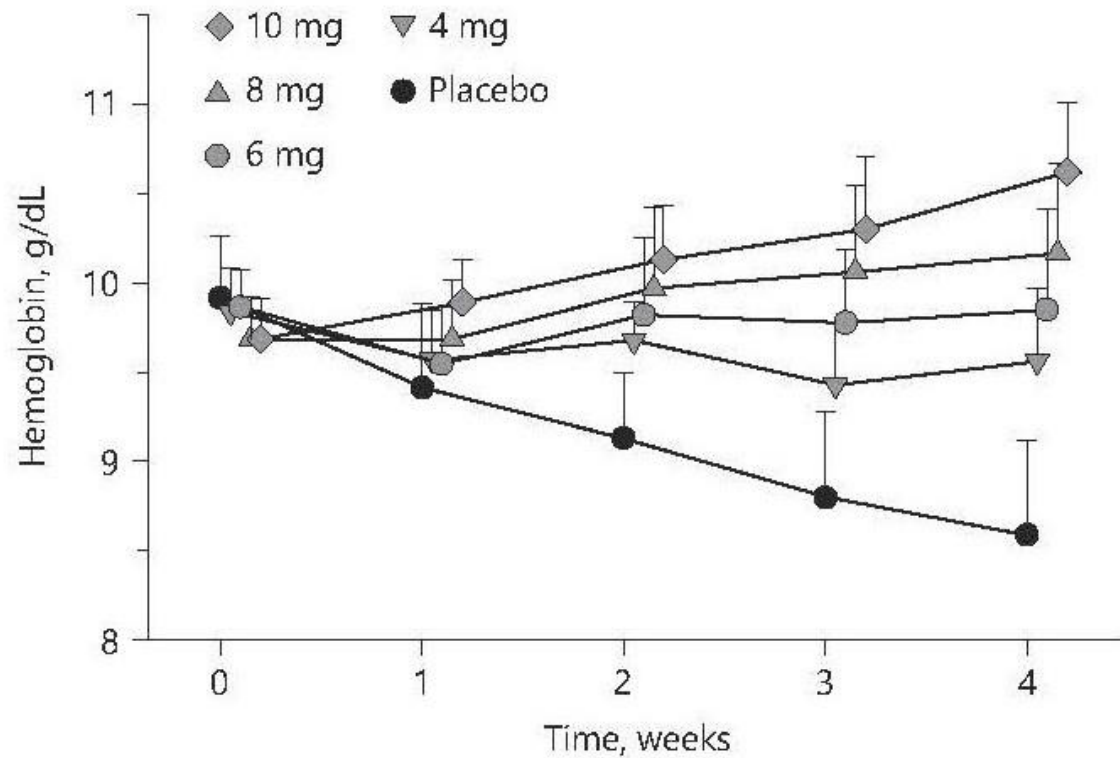
## anephric HD patients



# Daprodusutat improves anemia in CKD

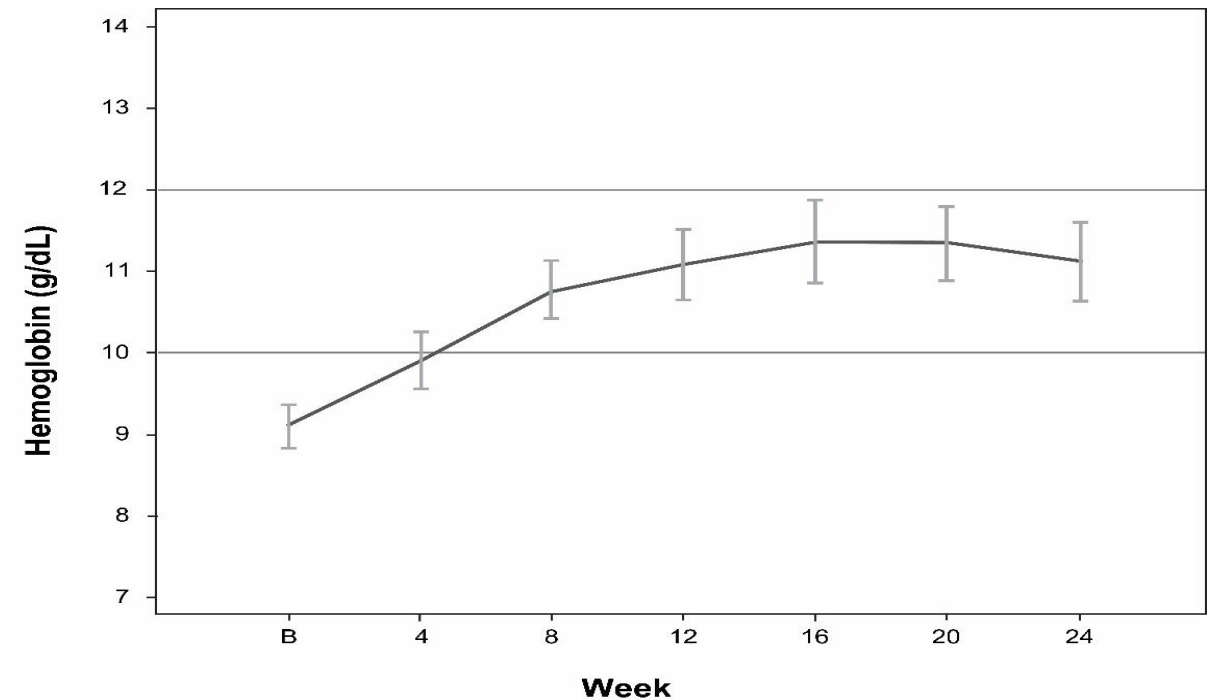
daprodustat in Japanese HD patients

phase 2



Akizawa, Nangaku et al.  
Am J Nephrol 2017

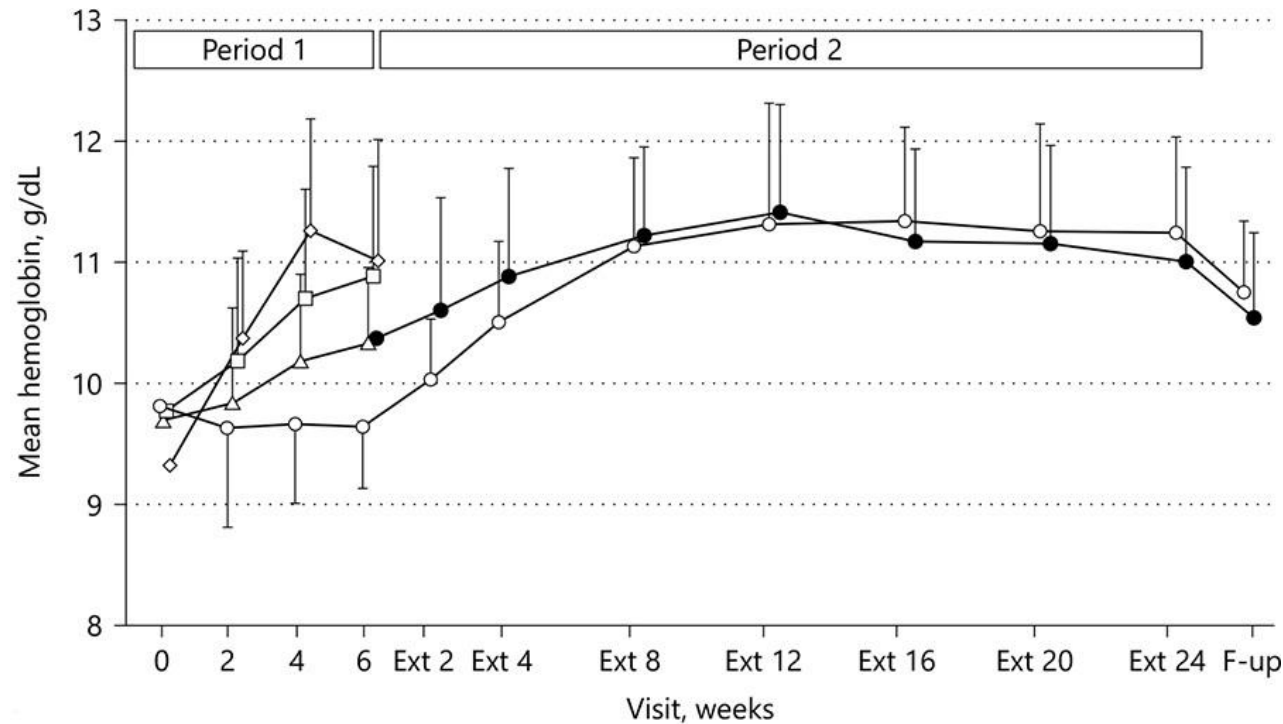
phase 3



Tsubakihara, Nangaku et al.  
Ther Apher Dial 2019

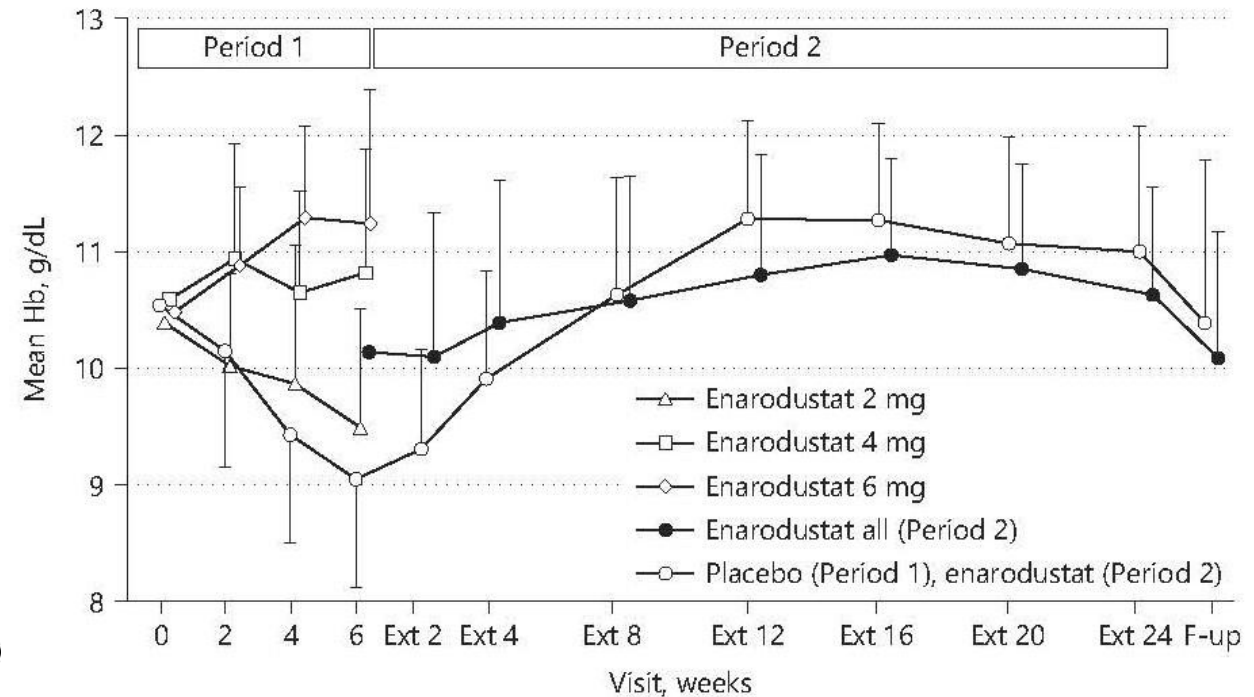
# Enarodustat improves anemia in CKD

## enarodustat in Japanese non-HD patients



Akizawa, Nangaku et al.  
Am J Nephrol 2019

## enarodustat in Japanese HD patients



Akizawa, Nangaku et al.  
Nephron 2019



ORIGINAL ARTICLE

# Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

N. Chen, C. Hao, B.-C. Liu, H. Lin, Caili Wang, C. Xing, X. Liang, G. Jiang,  
Zhengrong Liu, X. Li, L. Zuo, L. Luo, J. Wang, M. Zhao, Zhihong Liu, G.-Y. Cai,  
L. Hao, R. Leong, Chunrong Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu

# Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis

N. Chen, C. Hao, X. Peng, H. Lin, A. Yin, L. Hao, Y. Tao, X. Liang, Z. Liu, C. Xing,  
J. Chen, L. Luo, L. Zuo, Y. Liao, B.-C. Liu, R. Leong, C. Wang, C. Liu, T. Neff,  
L. Szczech, and K.-H.P. Yu

**Became available on Nov 20 as bundled**

**20mg tablet 387.4 JPY = 3.2 EUR**

**50mg tablet 819.2 JPY = 6.8 EUR**

**100mg tablet 1443.5 JPY = 12.0 EUR**

N. Chen, C. Hao, B.-C. Liu, H. Lin, Caili Wang, C. Xing, X. Liang, G. Jiang, Zhengrong Liu, X. Li, L. Zuo, L. Luo, J. Wang, M. Zhao, Zhihong Liu, G.-Y. Cai, L. Hao, R. Leong, Chunrong Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu

## **Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis**

N. Chen, C. Hao, X. Peng, H. Lin, A. Yin, L. Hao, Y. Tao, X. Liang, Z. Liu, C. Xing, J. Chen, L. Luo, L. Zuo, Y. Liao, B.-C. Liu, R. Leong, C. Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu





**Kai-Uwe Eckardt**

**Juergen Floege**

