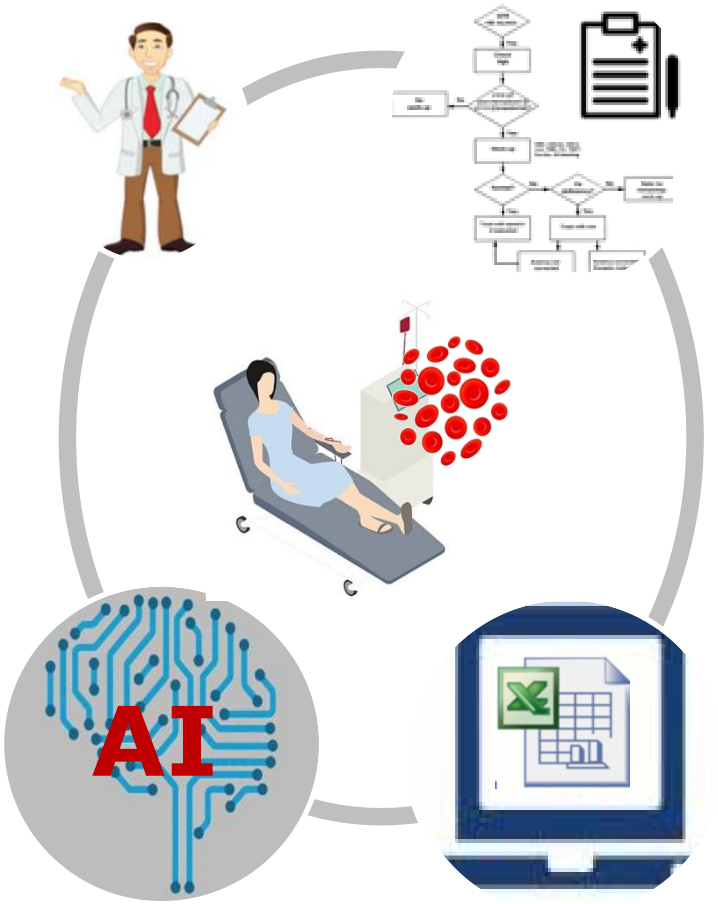
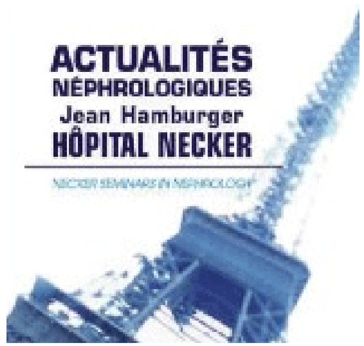




Optimizing Anemia Management: From Algorithm to Artificial Intelligence

Emeritus Professor Bernard Canaud
Montpellier University, School of Medicine, Montpellier-F
& Senior Scientist, Global Medical Office FMC-France, Fresnes-F

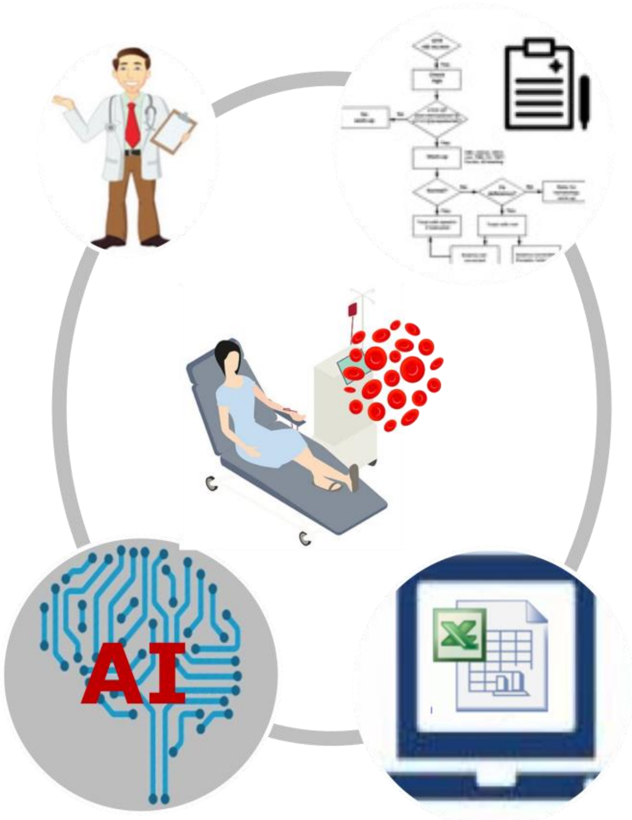
Disclosure

Prof. Bernard Canaud

I have the following potential conflicts of interest to report:

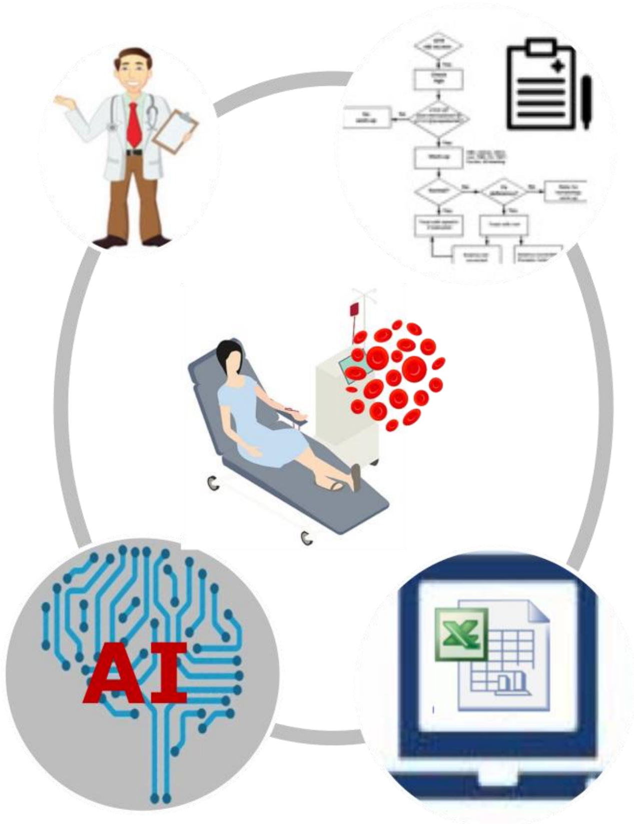
- ☐ **Scientific consultant for industry (FMC)**
- ☐ Shareholder in a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s)
- ☐ I do not have any potential conflict of interest

Agenda: From Algorithm to Artificial Intelligence



- Renal anemia: lesson learned in few decades
- Anemia correction: ESA, as a disruptive treatment in CKD treatment
- Anemia management: from clinical to artificial intelligence support
- Take home message: what’s next

Agenda: From Algorithm to Artificial Intelligence



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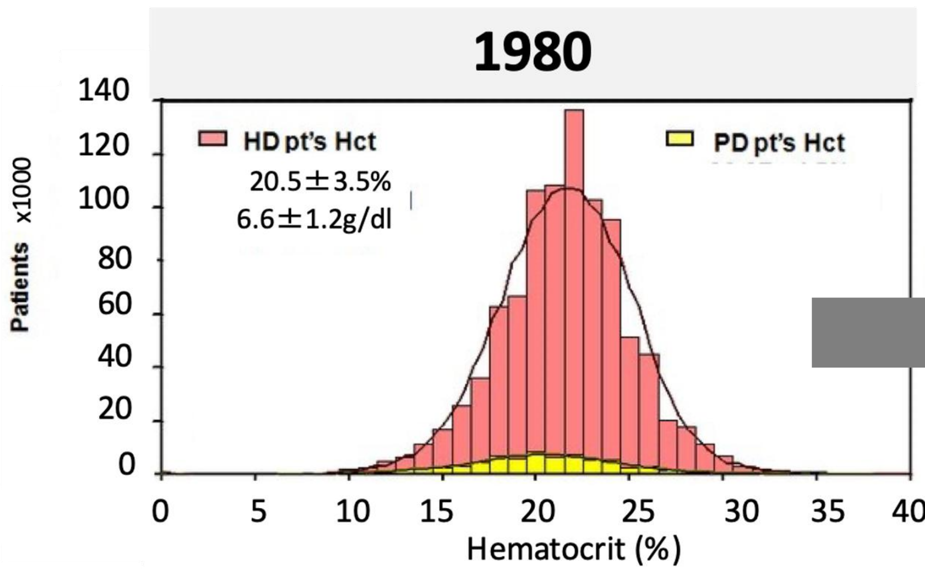
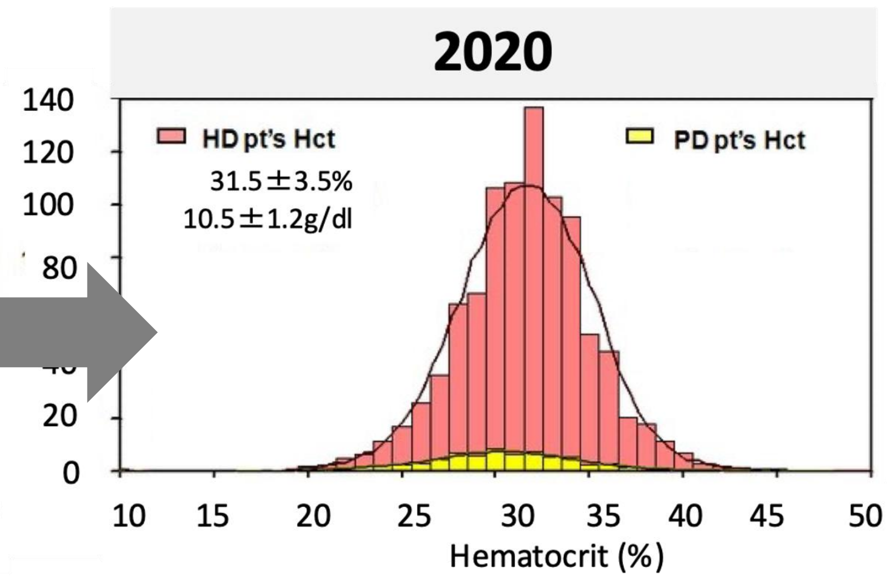
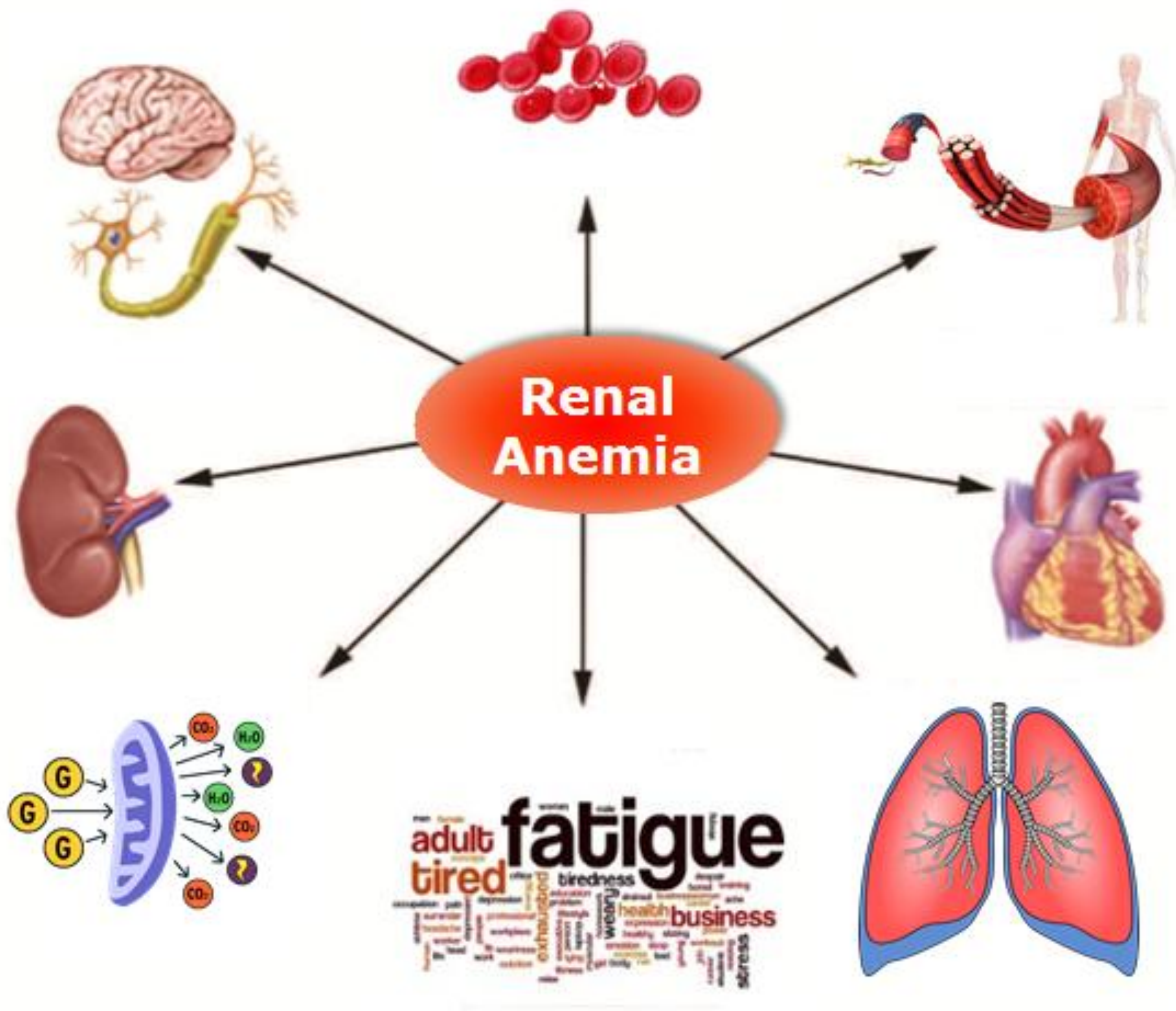
Forty Years of Dialysis in Pictures

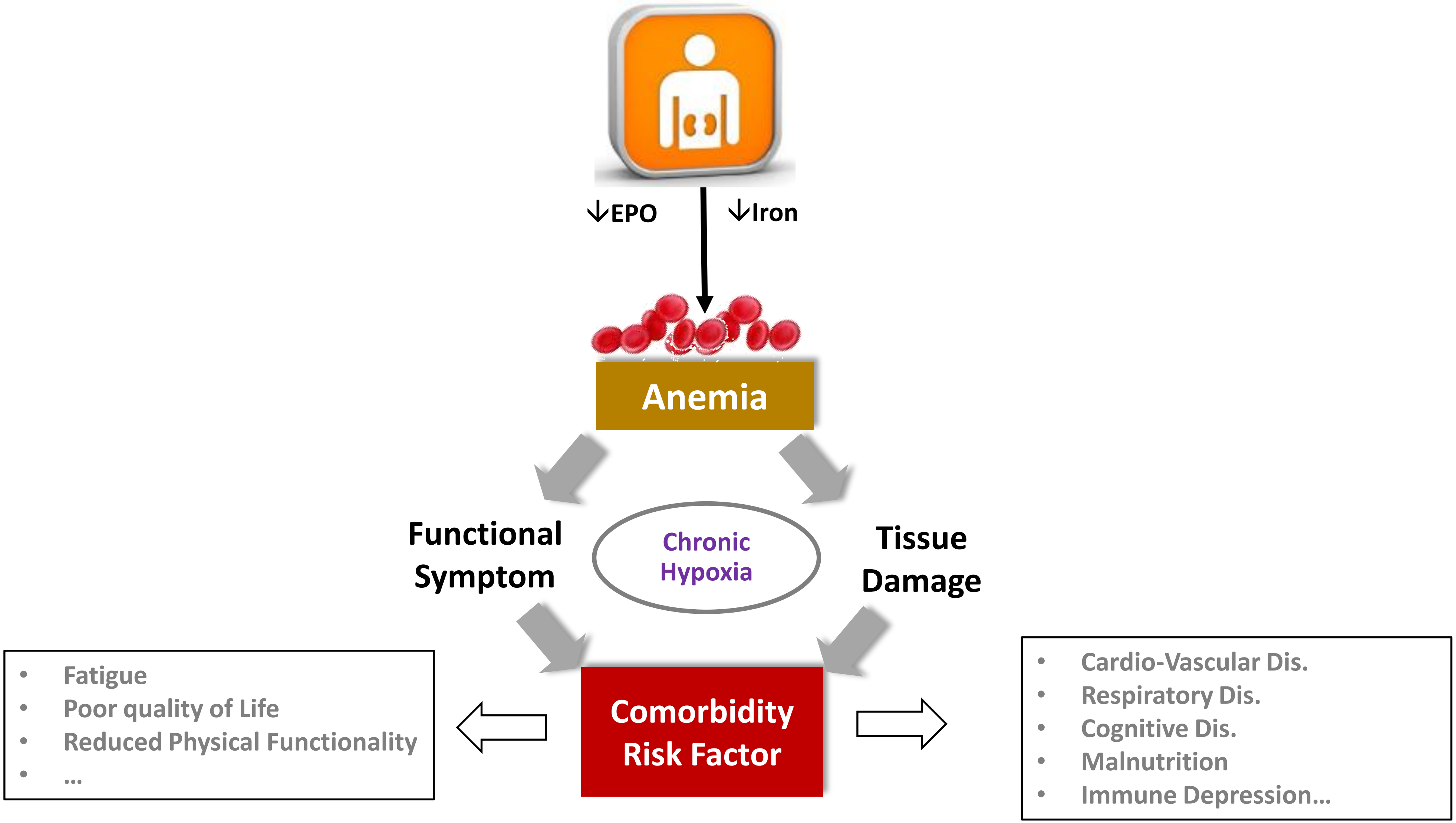




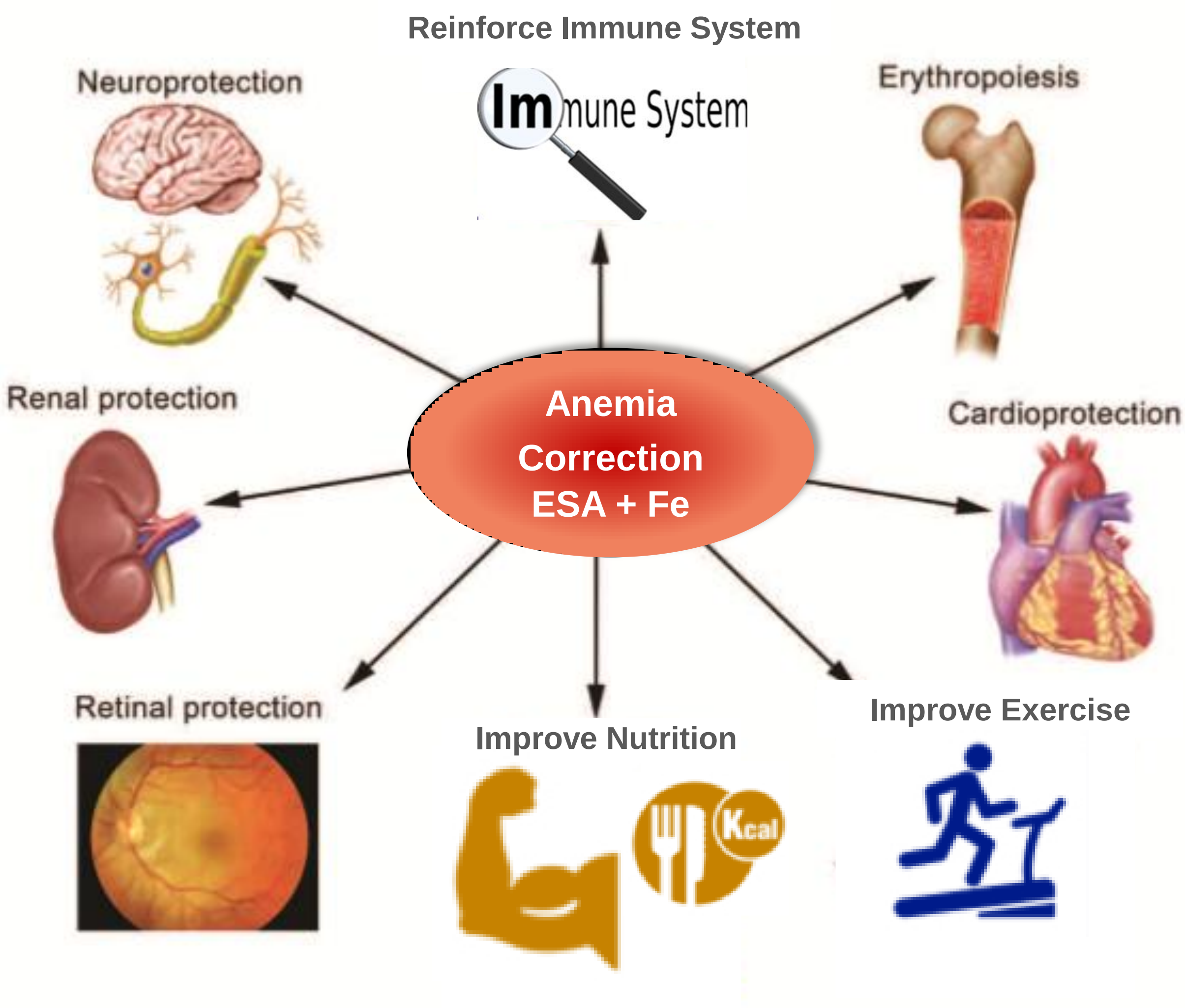
Renal Anemia has Multiple Effects in CKD5D Patients



Anemia is an Additional Pathogenic Factor (Hypoxia) in HD Patients



Correction of Anemia is Associated with Biological and Clinical Benefits in HD Patients



Improve patient outcomes

↑ Patient perception (HRQOL)

↓ Morbidity

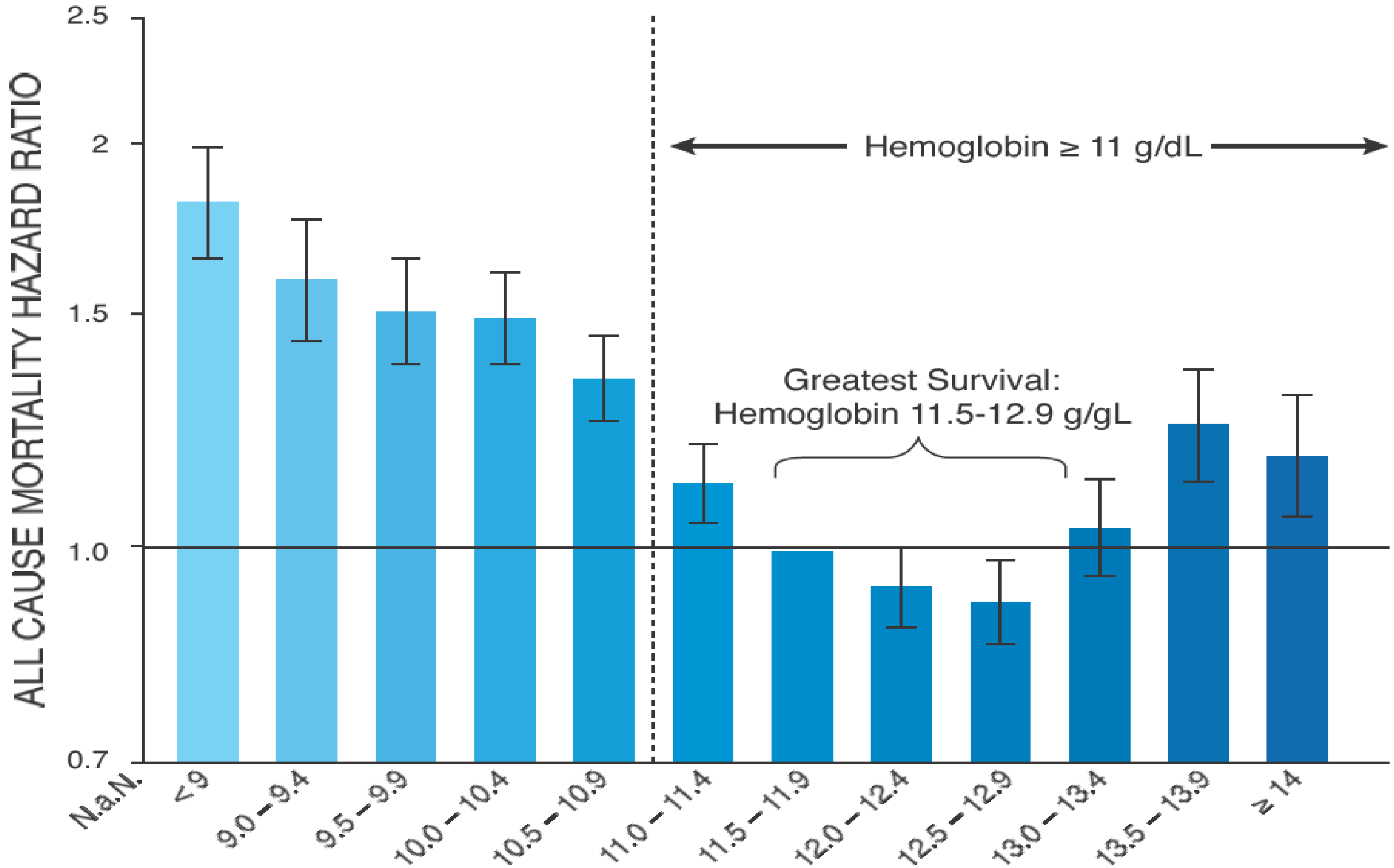
↓ CV Mortality

Value based care

- Cost-Effective
- QALY

Arcasoy MO. *Haematologica* 2010; 95(11):1803-1895

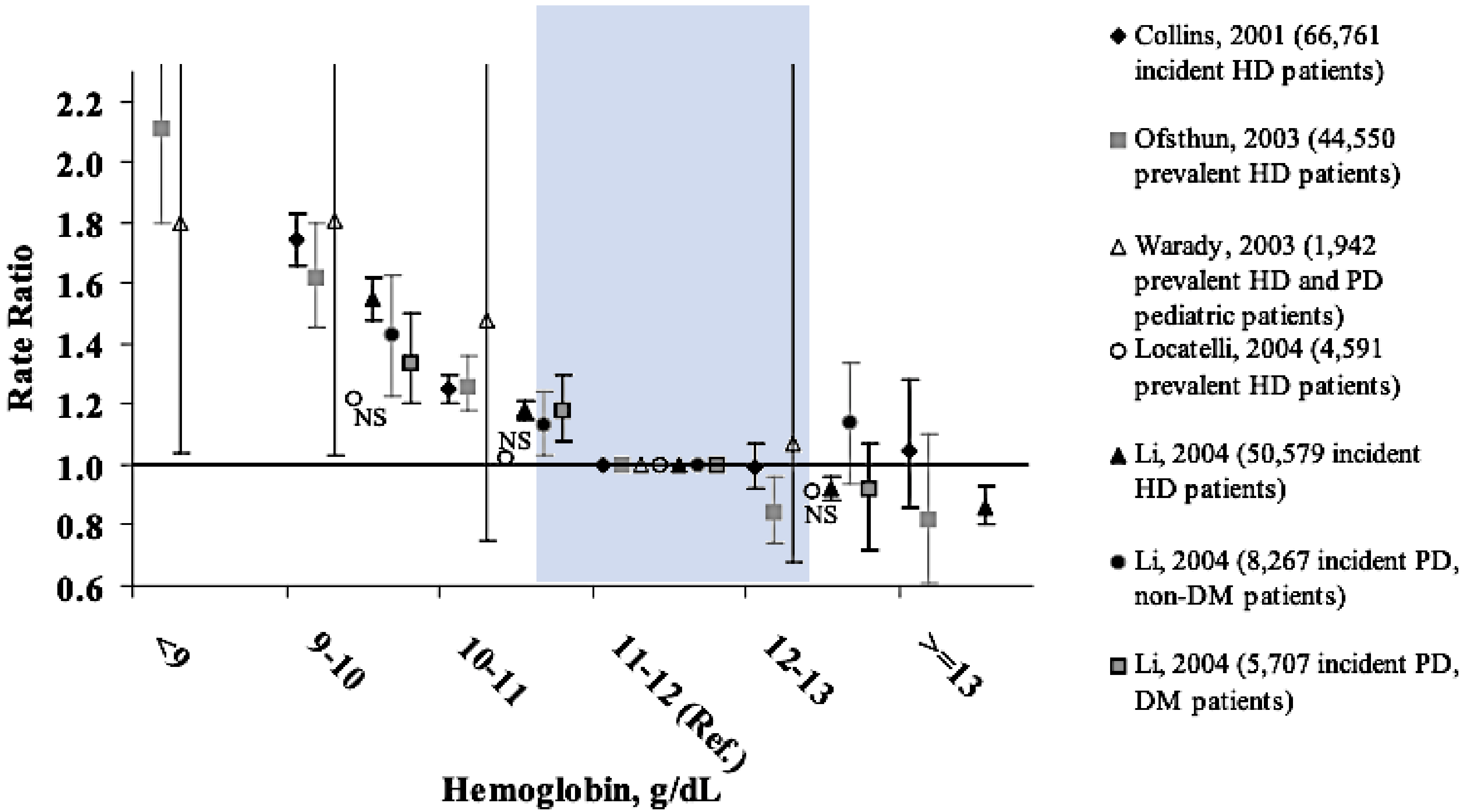
Hazard Ratio for All-Cause Mortality Based On Time-Dependent Hb Levels Over 8 Calendar Quarters in a LDCP



Retrospective Cohort Study
(July 2001 to June 2003)
58,058 MHD patients
DaVita dialysis clinics US

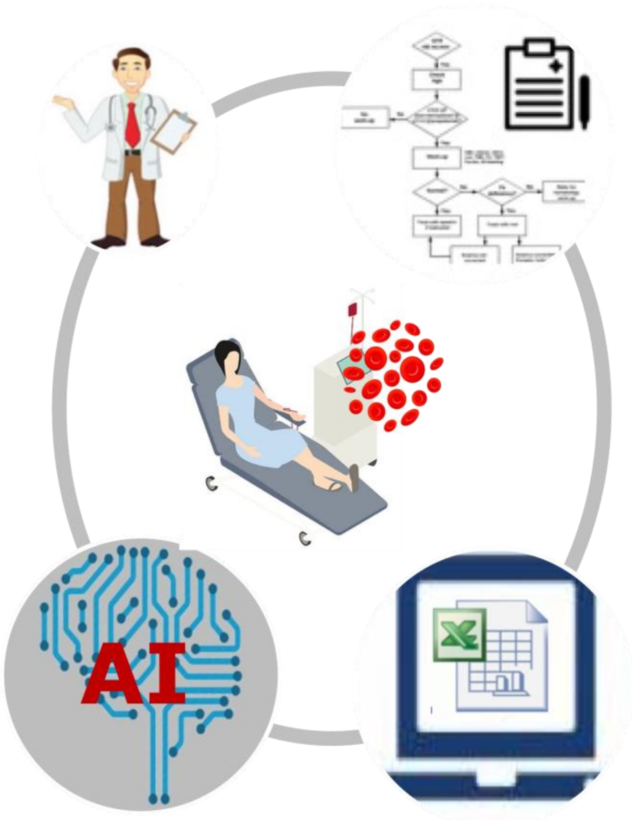
Kalantar-Zadeh K et al, *J Am Soc Nephrol.* 2005;16(10):3070-80.

Evidence-Based Systematic Literature Review of Hemoglobin and All-cause Mortality In Dialysis Patients



Volkova N et al, *Am J Kidney Dis.* 2006;47(1):24-36.

Agenda: From Algorithm to Artificial Intelligence



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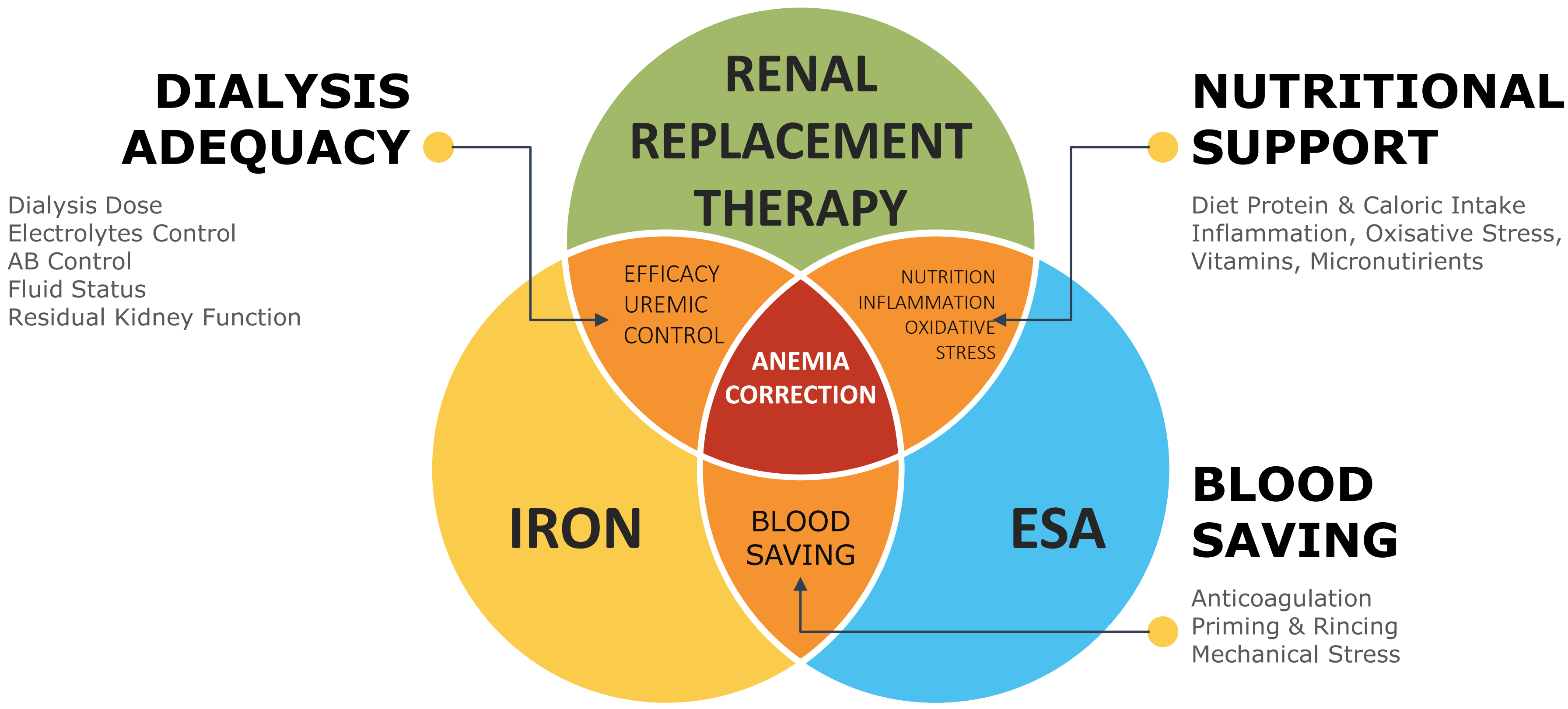
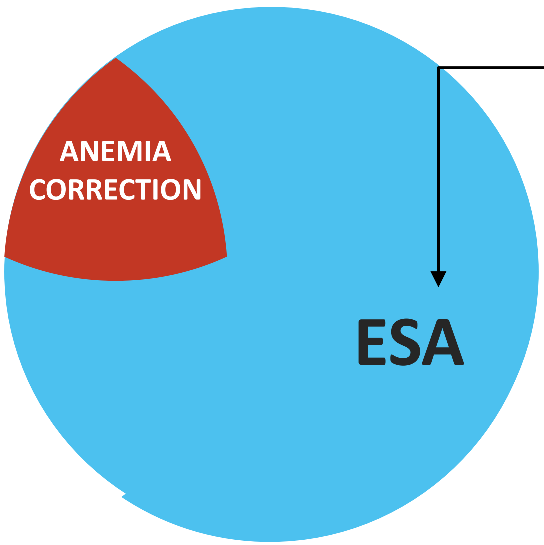
Factors Involved in Anemia Correction of CKD5 Dialysis



Erythropoietic Stimulating Agents



ERYTHROPOEITIC STIMULATING AGENTS

- Human Recombinant Erythropoietin
  - Epoetinα (Eprex, Orthobiotech; Epoetin, Amgen)
  - Epoetinβ (Neorecormon, Roche)
- Erythropoietin Biosimilar

IV/SC Short Acting ESA

  - Epoetin α, β, δ…
- Engineered Erythropoietin
  - Darbepoetin α (Aranesp, Amgen)
  - Methoxy Polyethylene Glycol-Epoetin β, (Mircera, Roche)
- EPO Mimetic Peptides (Withdrawn from market)
  - Hematid, Affymax

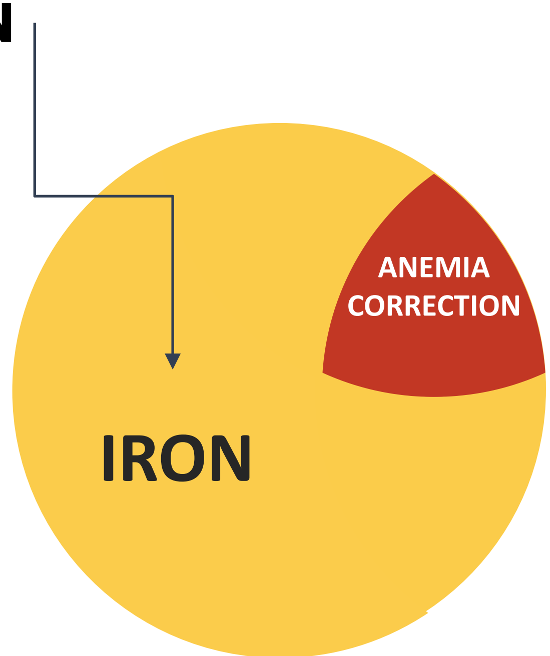
IV/SC Long Acting ESA

- HIF Prolyl-Hydroxylase Inhibitors (Ongoing studies)
  - Roxadustat (FibroGen, Astellas, AstraZeneca)
  - Vadadustat (Akebia Therapeutics)
  - Daprodustat (GlaxoSmithKline)
  - Molidustat (Bayer)

Oral Administration

Iron Supplementation

IRON SUPPLEMENTATION



Major Oral Iron Supplements

Supplement	Elemental iron per dosage unit	Frequency
Ferrous sulfate	65 mg/tablet[a]	1 tablet, 1–3 times per day
Ferrous gluconate	38 mg/tablet [a]	1 tablet, 1–3 times per day
Ferrous fumarate	106 mg/tablet [a]	1 tablet, 1–3 times per day
Ferric maltol	30 mg/tablet	1 tablet, twice per day
Ferric citrate	210 mg/tablet	1-2 tablets, 3 times per day
Liposomal iron	30 mg/tablet	1 tablet per day

[a]For 325-mg tablets.

Major Intravenous Iron Formulations

Formulation	Dosage	Frequency
Iron sucrose	200 mg	5 doses over 2 weeks
Ferumoxytol	510 mg	2 doses, 3-8 days apart
Ferric gluconate in sucrose complex	250 mg	4 doses weekly
Ferric carboxymaltose	750 mg	2 doses, 1 week apart
Iron isomaltoside	1000 mg	1 dose
Iron dextran (low molecular weight)	500 to 1000 mg	Variable

Water-Soluble Dialysate Iron Formulation

Ferric pyrophosphate citrate (FPC)

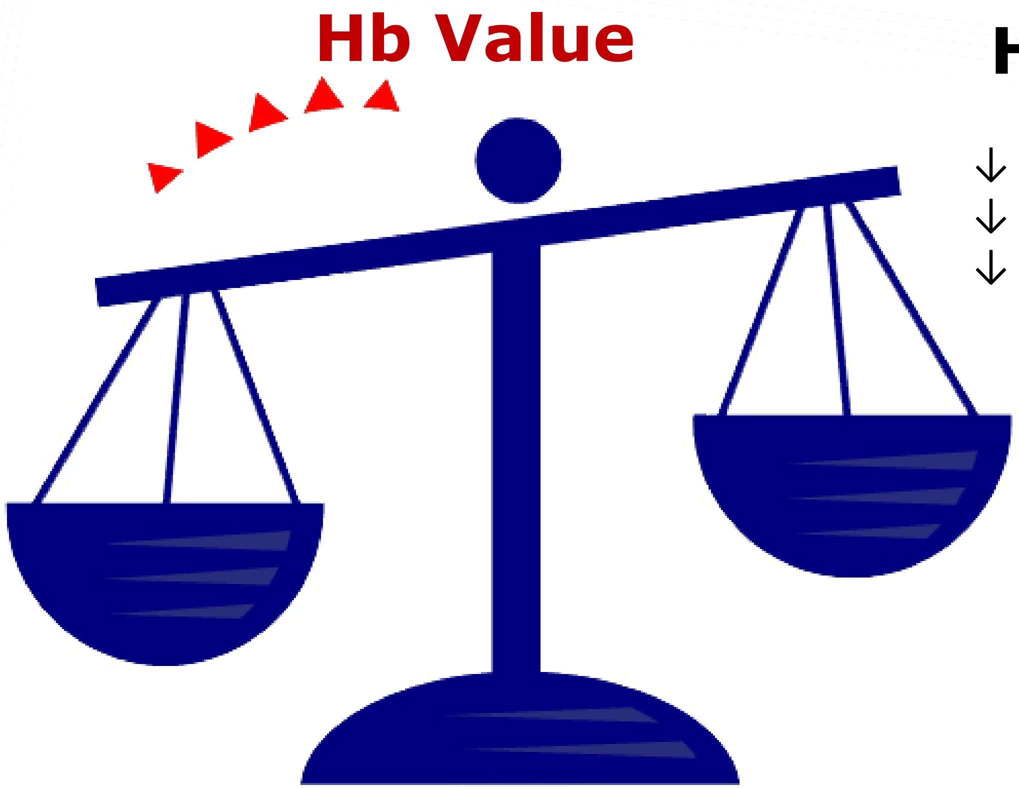
Gutiérrez OM. *Kidney Int Rep.* 2021 ;6(9):2261-2269.

Anemia Correction is Still a Challenge in HD Patients

Balance of Benefits and Harms

BENEFITS

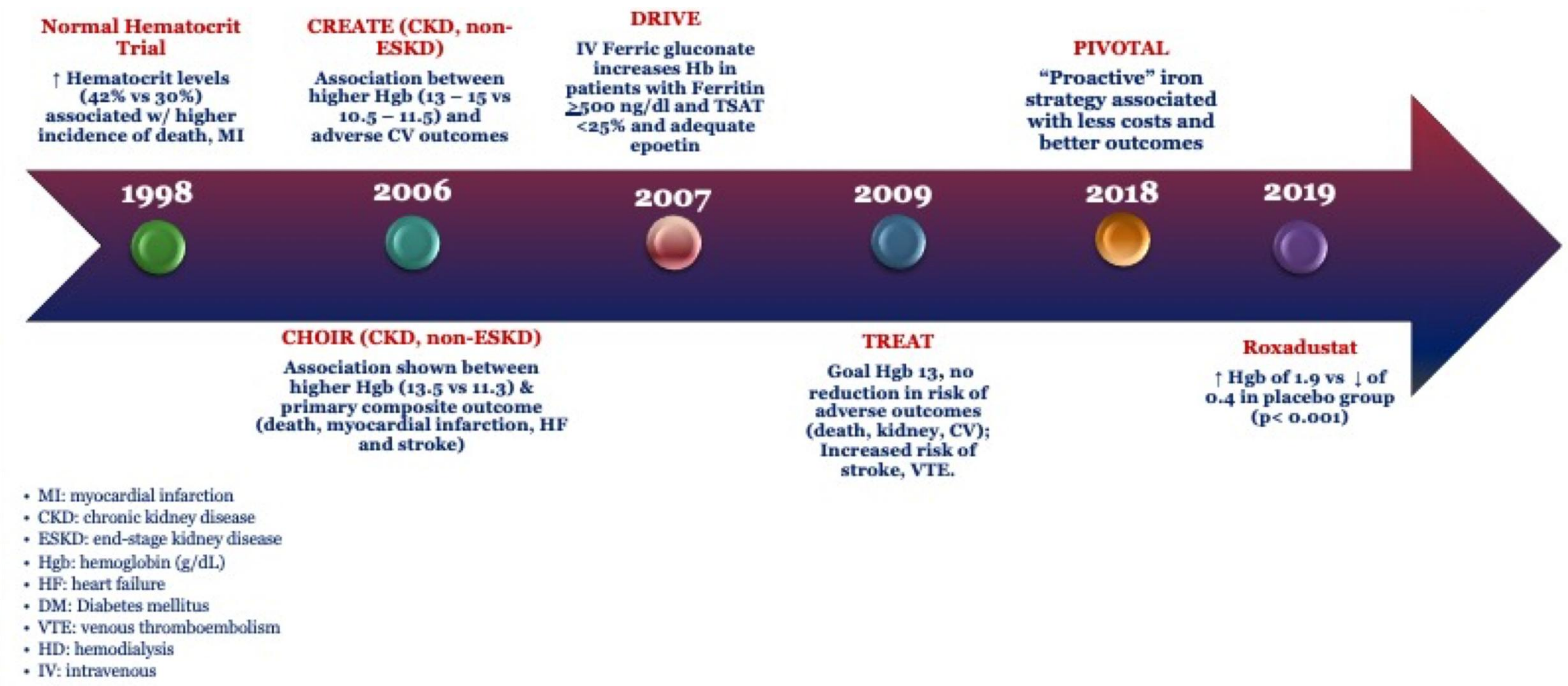
↑ Quality of life
↑ Physical and social function
↑ Cognitive function
↑ Nutrition
↑ Cardiac function
↑ Patient outcomes



HARMS

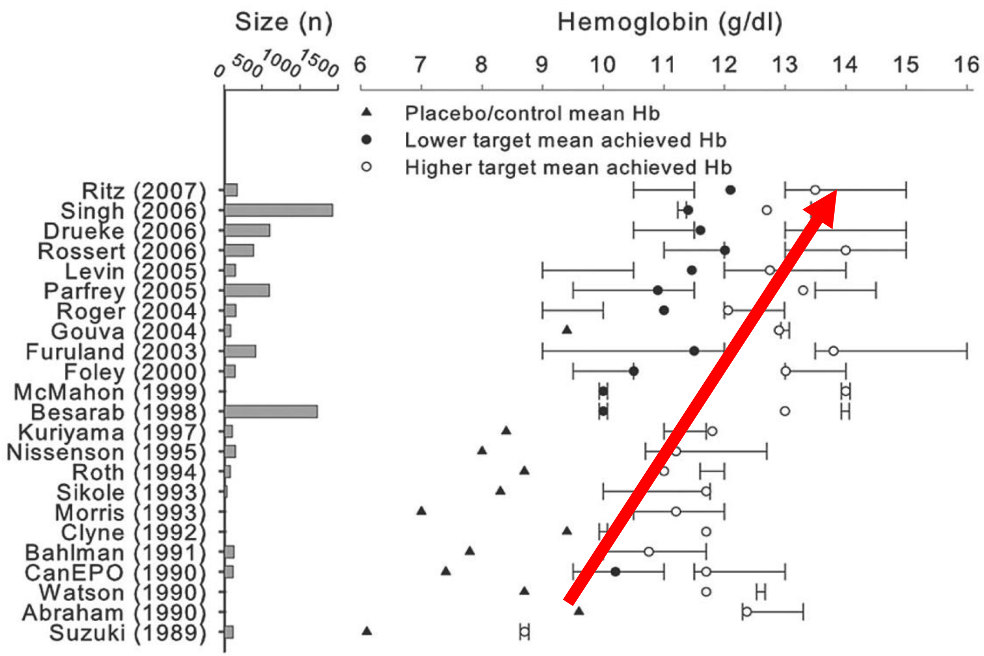
↓ Hazards/Risks
↓ Side effects
↓ Cost

Landmark Trials in Anemia Treatment in Kidney Disease



Hb Target Has Changed Over Time and Results

1989 → 2007 2007 → 2009 - - - → 2022



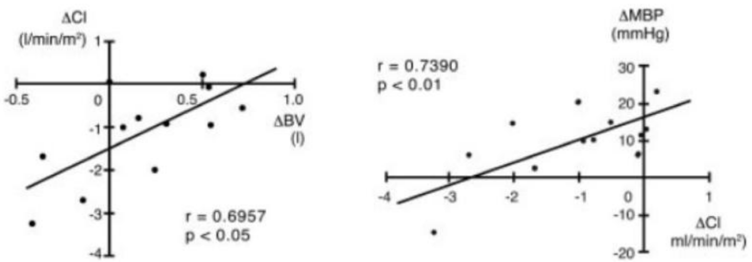
CHOIR, Correction of Hemoglobin and Outcomes in Renal Insufficiency
CREATE, Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta
EMP, Erythropoiesis Stimulating Agent monitoring program - FDA, Food Drug Administration
NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative
TREAT, Trial to Reduce Cardiovascular Events with Aranesp Therapy

KDOQI: 2007 update of hemoglobin target. Am J Kidney Dis. 2007; 50: 471-530

Spiegel DM et al, *Am J Kidney Dis.* 2009; 55:113-120

Drawbacks Reported with Anemia Management…

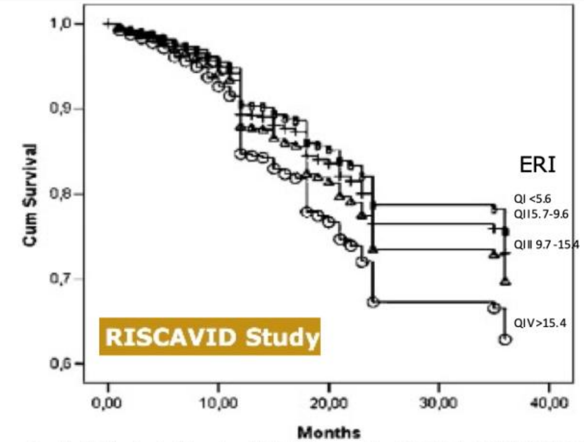
Arterial Hypertension Induced by Erythropoietin and Erythropoiesis-Stimulating Agents (ESA)



Krapf R et al, *Clin J Am Soc Nephrol.* 2009;4(2):470-80.

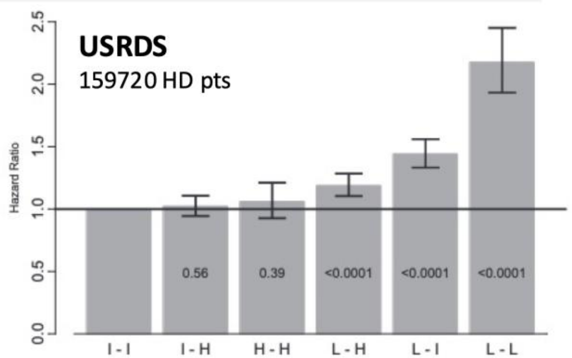
…

High ERI is Associated with Higher Risk of Death



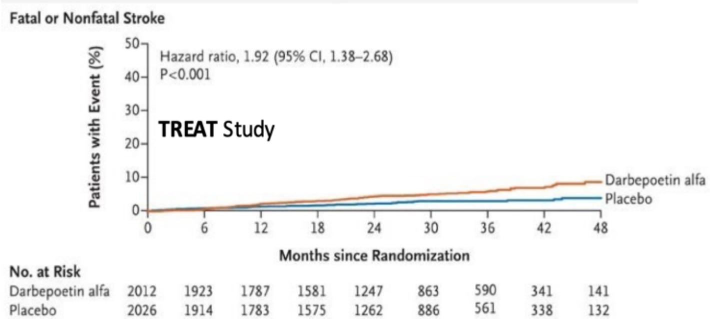
Panichi V et al, *Nephrol Dial Transplant,* 2011;26(8):2641-8

Large Variability of Monthly Hb Values are Associated with Higher Risk of Death



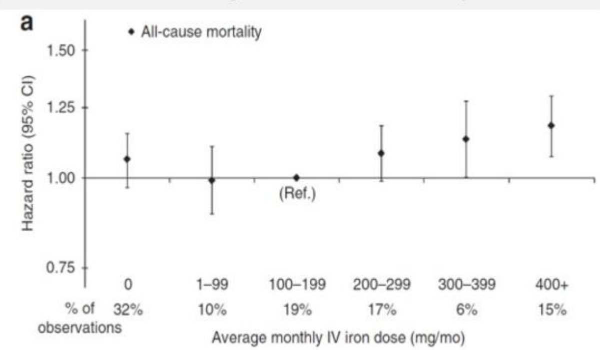
Gilbertson DT et al, *Clin J Am Soc Nephrol.* 2008;3(1):133-8.

Normal Hb (14g/dl) is Associated with Higher Incidence of Stroke in DM HD Patients



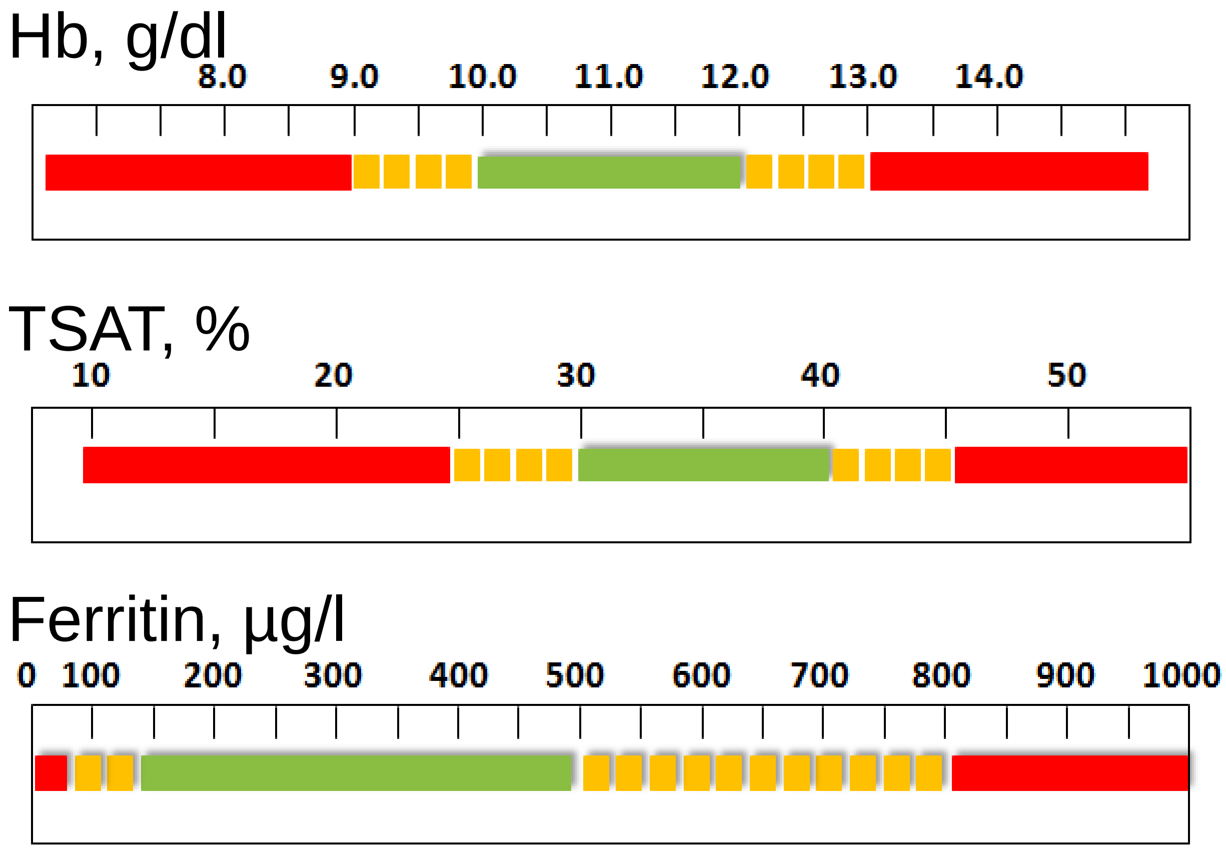
Pfeffer MA et al, N Engl J Med. 2009;361(21):2019-32.

IV Iron Administration >200mg/mo. is Associated with a Higher Risk of Mortality



DOPPS Bailie GR et al, *Kidney Int.* 2015;87(1):162-8.

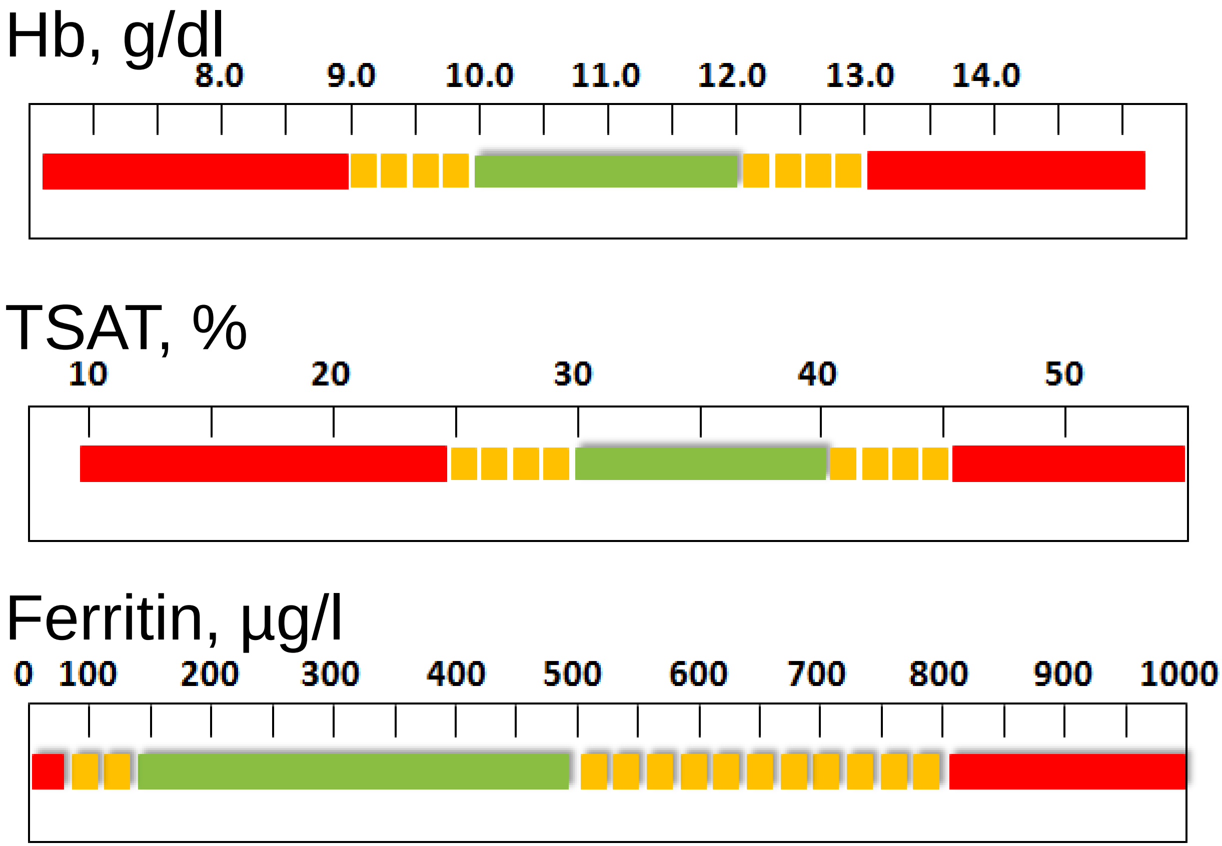
Optimal Targets in CKD HD Patients



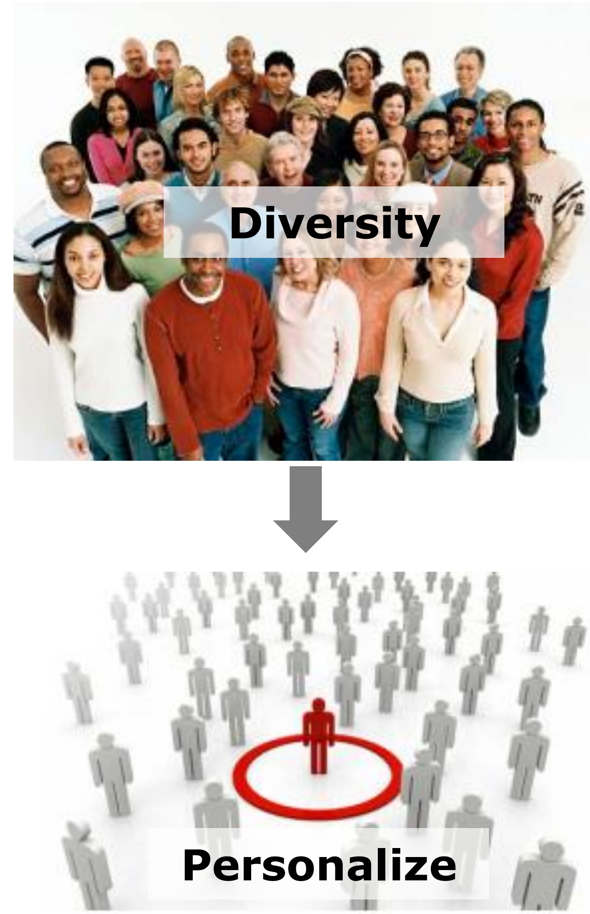
KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int.* 2012; 2(Sup 4):331–335

Optimal Targets in CKD HD Patients

Customization is Suitable according to Patient Profile*



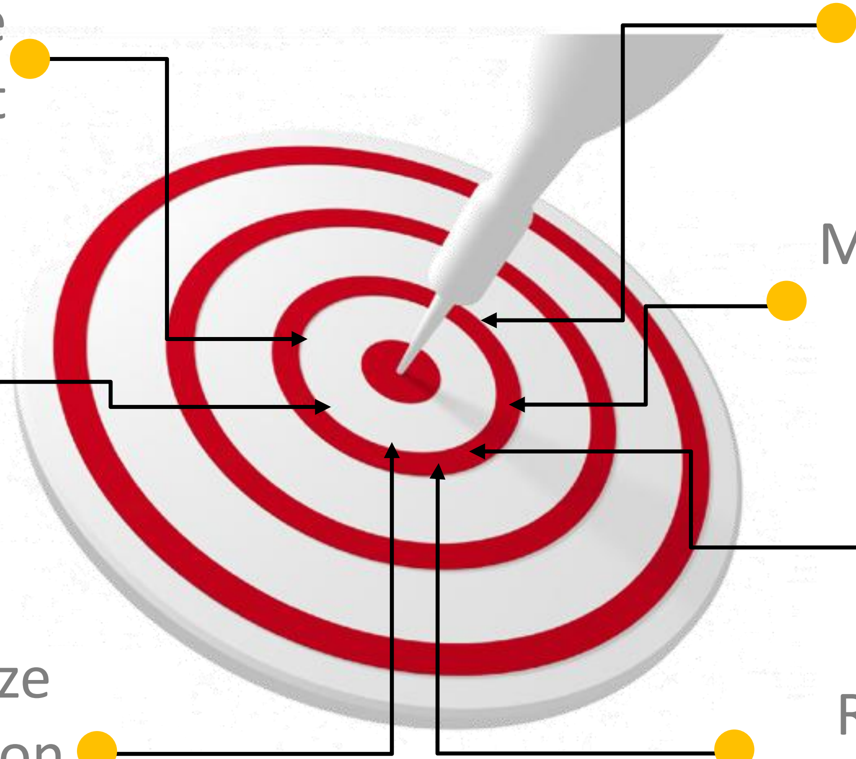
***ERBP**



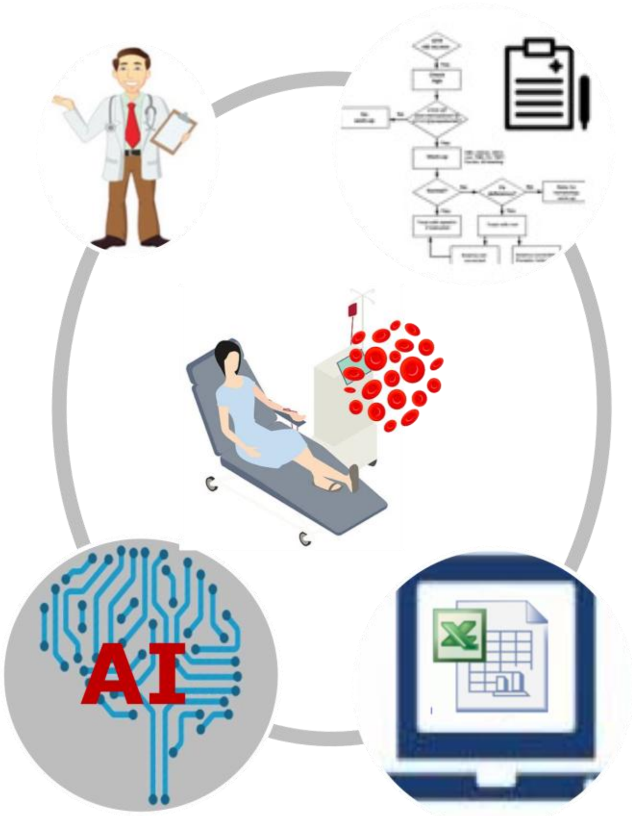
KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int.* 2012; 2(Sup 4):331–335

Anemia Correction in HD Patients Has Multiple Targets

Targets of Anemia Correction



Agenda: From Algorithm to Artificial Intelligence



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Anemia Management in HD Patients

From Pure Clinical Decision to AI Support-Decision

1

Clinician Decision

Anemia Treatment Prescription & Management

Anemia Management at Patient and Facility Level

Collection of Data – Storage and Analysis (XLS)

Patient Name	Code	Hb previous month	Hb current month	OH/ECW pre HD	ERI	Darbo Alpha	Alpha, Beta EPOs	Theta Epo	Bio-similars	MPG-E beta	ESA Therapy		Ferritin	Transfer. Saturat.	C-Reac. Protein	MCV	MCHC	Iron IV	Iron IV
				%	IU/kg/week/g x 100 ml	µg/Kg/month	IU/Kg/month	IU/Kg/month	IU/Kg/month	µg/Kg/month	Total / Month	Frequency		%	mg/L	fl	g/L	mg/month	µg/Kg/month
				≤ 15	≤ 15	≤ 1,75	≤ 350	≤ 350	≤ 350	≤ 1,75			≥ 200 ≤ 800	≥ 20 ≤ 50	≤ 20	≥ 90 ≤ 105	≥ 32 ≤ 36		
	[illegible]	11	11	-10,2									226	16	51,4	87	32	300	4,31
	[illegible]	10,4	11,4	12,1	12,7					2,53	MPGE: 200	20;	638	49	13,6	98	33	500	6,31
	[illegible]	13,2	13,7	10,7	2,9					0,7	MPGE: 50	13;	306	48	3,6	101	36	100	1,39
	[illegible]	12	10,9	-2,9	6,9					1,32	MPGE: 100	21; 28;	486	30	77,4	70	31	100	1,32
	[illegible]	12,4	12,7	15,8	3,5					0,78	MPGE: 50	27;	925	42	2,8	93	34		
	[illegible]	9,4	9,4	11,8	6,8	1,27					Darbo: 80	Monday;	761	64	18,2	101	36		
	[illegible]	11	10,3	19,1	33,5					6,01	MPGE: 250	Tuesday; (every 4 weeks);	588	23	0,2	87	34	100	2,4

Folic Acid	Vitamin B12	Carnitine	Age	Female	Dry Body Weight	Time On Dialysis	Effective weekly treatment time	Blood Volume Processed	Effective Infusion Volume Total	OCM Kt/V	V.A.	Alb.	Mean Arterial BP Pre	Cardio-circolatory therapy (" ACEi/ARB)	iPTH	iPTH Correct.	aaCCI score	Probability mortality 1 year	Diabetes	Tumors	White cells	Platelets
n	n	n	Year		Kg	monthr	min	L/weekly	L/weekly		n	g/dl	mmHg	n	pg/mL	pg/mL		%	n	n	no./mm³	no./mm³/1000
			> 10 < 100		> 35 < 130		≥ 720	≥ 240	≥ 60	≥ 1,4			> 60 < 106		≥ 50 ≤ 550	≥ 50 ≤ 550						≥ 100 ≤ 300
			68		69,6	61	683	322	70	2,04	AVF	3,9	89	1	237	237	4	11			9900	239
			81		79,2	50	784	334	78	1,73	AVF	3,7	68		99	99	8	25	X		7200	240
		X	50		71,9	26	787	415	95	2,08	AVF	4,0	96		189	189	4	11			4400	164
X			86		76,0	24	735	329	68	1,82	AVF	3,8	87		193	193	11	25	X	X	8400	191
			73		64,0	64	813	291	77	1,94	TC	3,6	79	2	659	659	9	25			4000	96
			67		62,8	49	460	196	56	2,25	AVF	2,7	47	1	216	216	5	27			4500	74
			31		41,6	42	726	328	68	3,00	AVF	3,7	91		30	30	5	11	X		10200	229

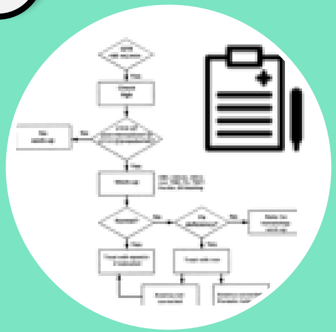
Anemia Management in HD Patients

From Pure Clinical Decision to AI Support-Decision

1

Clinician Decision

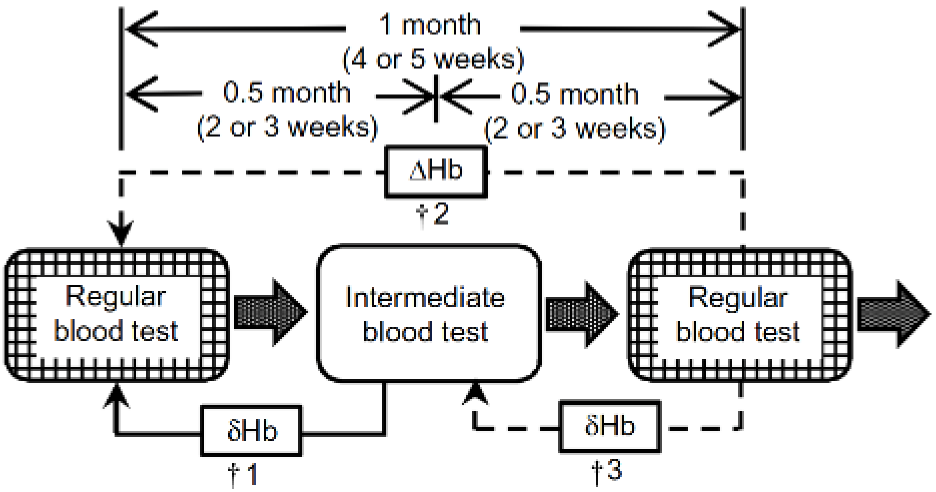
2

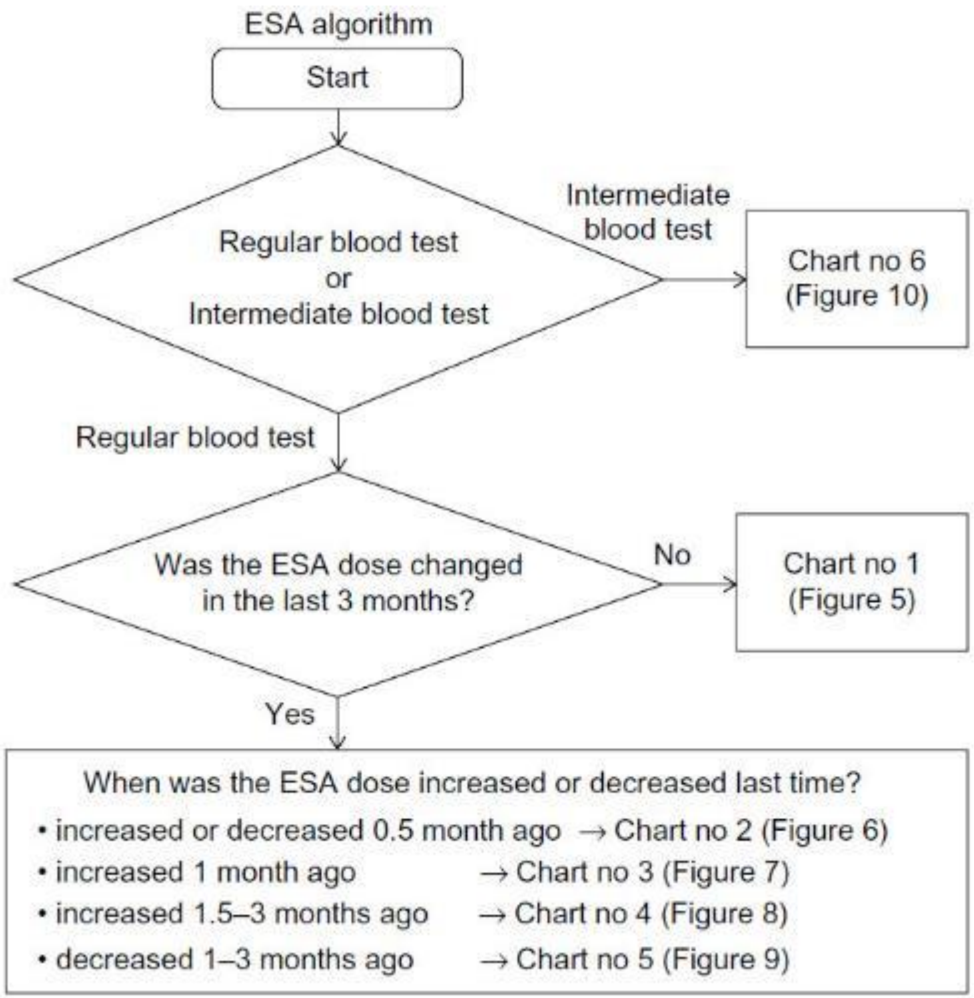


Paper Algorithm

Anemia Treatment Prescription & Management

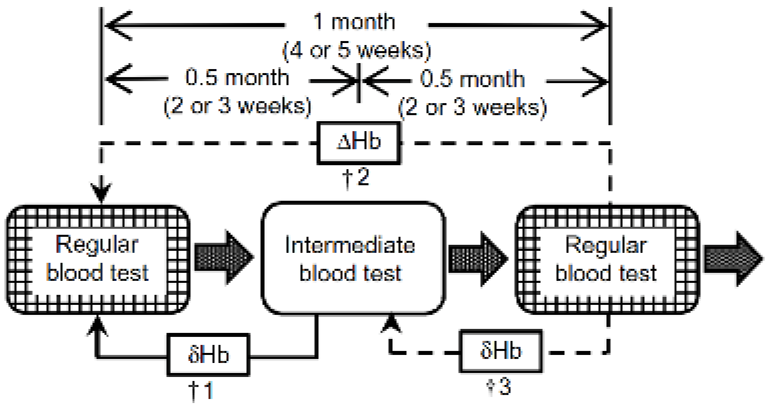
Creation of an Anemia Management Algorithm
ESA Administration



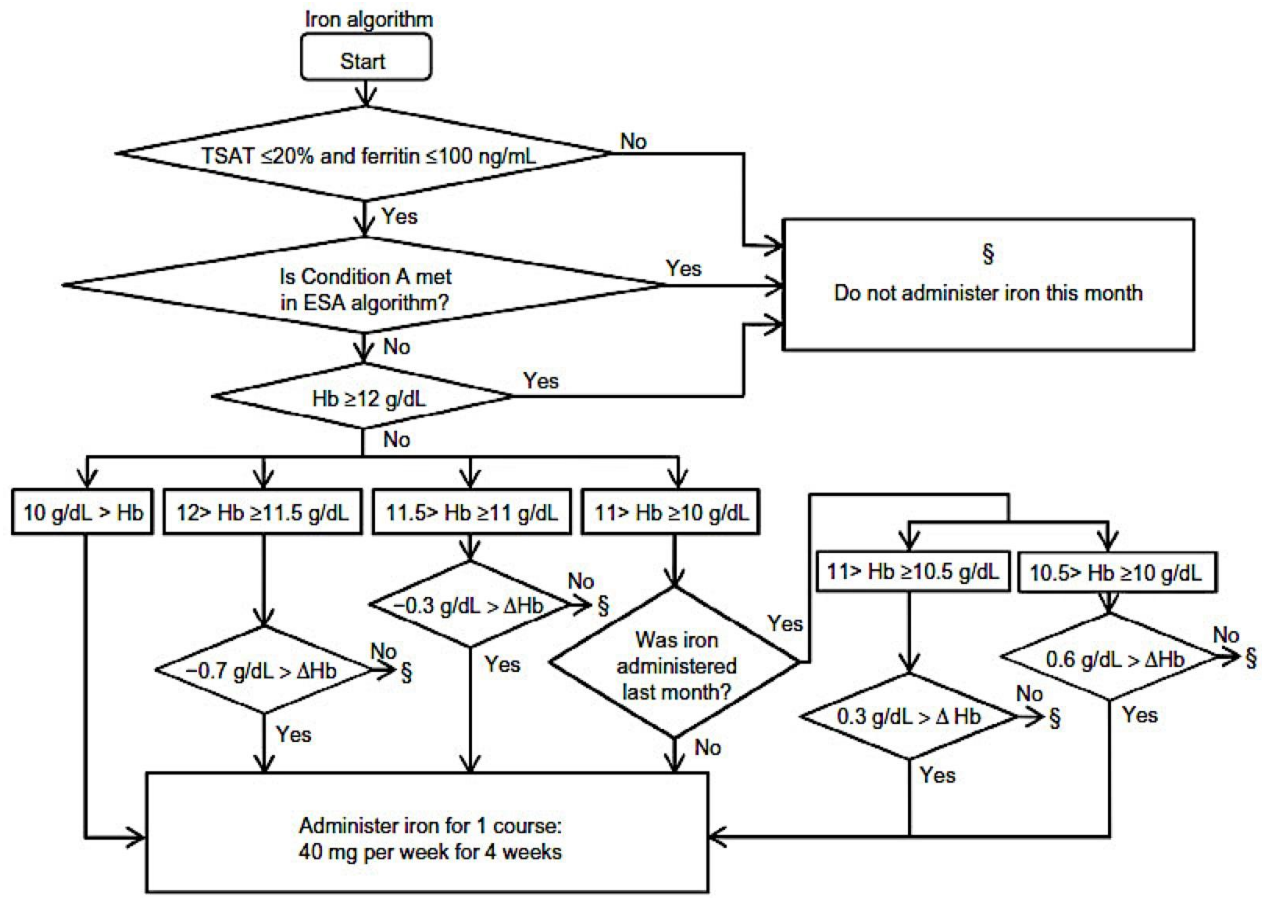


Mizutani Y et al, Int J Nephrol Renovasc Dis. 2015;8:65-75.

Creation of an Anemia Management Algorithm
Iron Supplementation

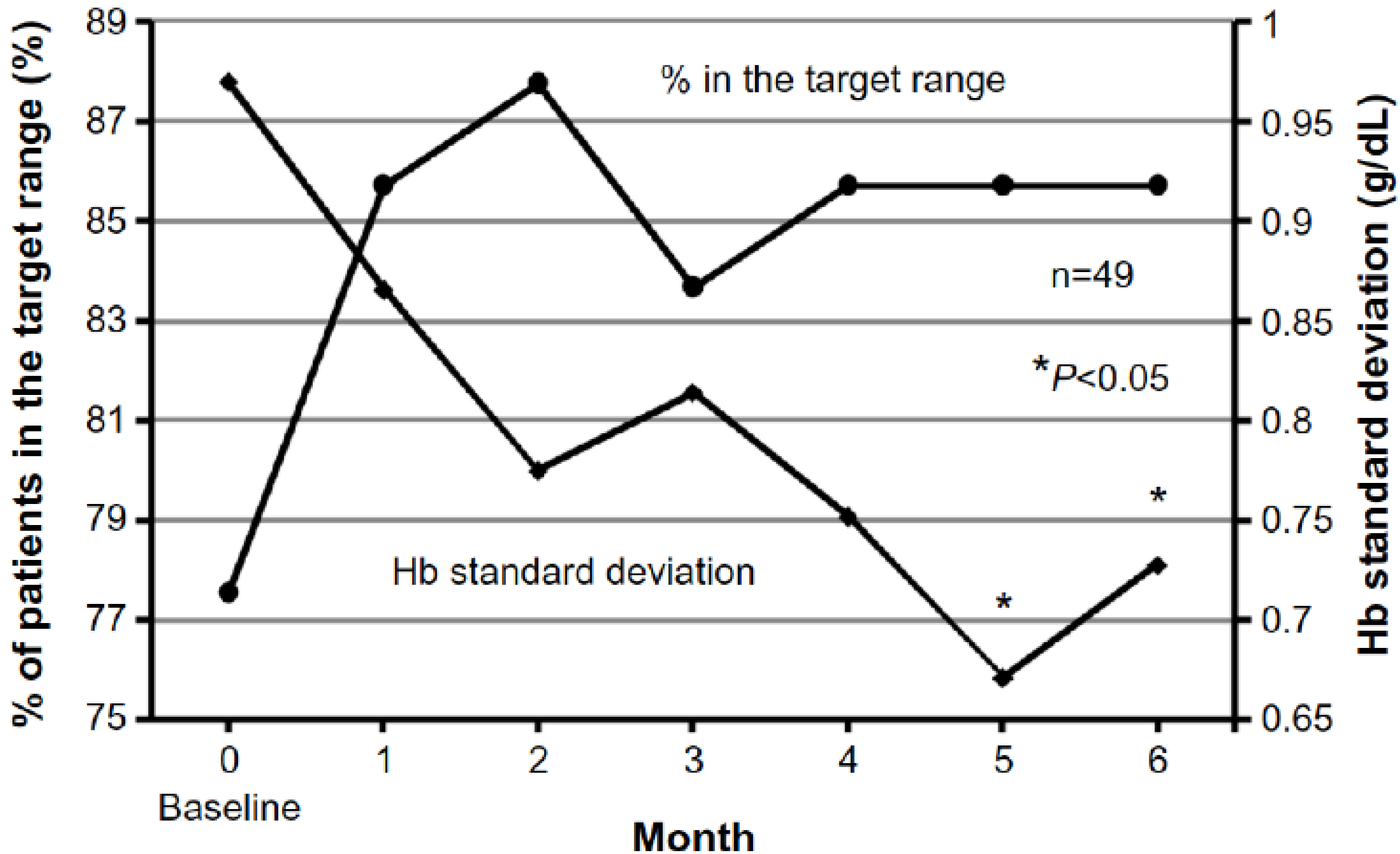


+ Iron parameters:
Ferritin/TSAT



Mizutani Y et al, Int J Nephrol Renovasc Dis. 2015;8:65-75.

Anemia Algorithm Increases Patients in Target and Reduces Hb Fluctuation



Prospective Study
Algorithm implementation
49 patients - 6 months

Mizutani Y et al, Int J Nephrol Renovasc Dis. 2015;8:65-75.

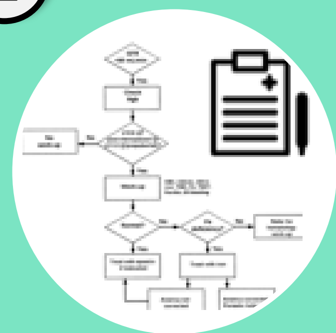
Anemia Management in HD Patients

From Pure Clinical Decision to AI Support-Decision

1

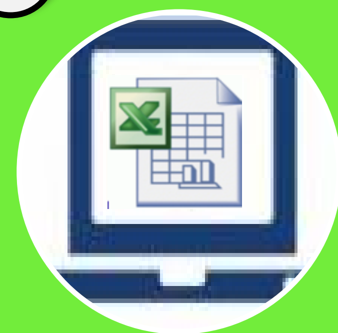
Clinician Decision

2



Paper Algorithm

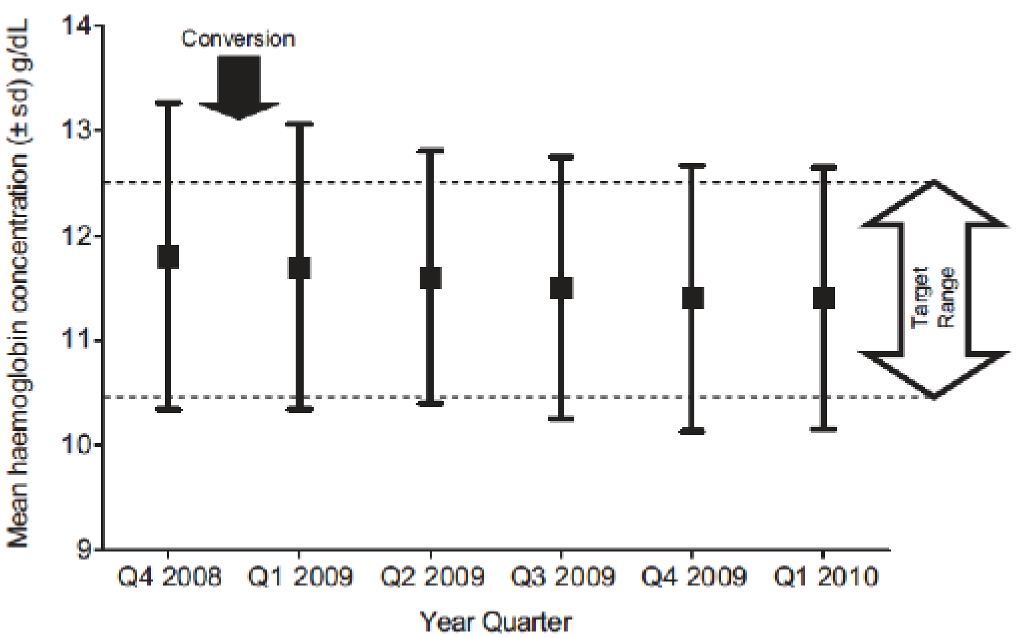
3

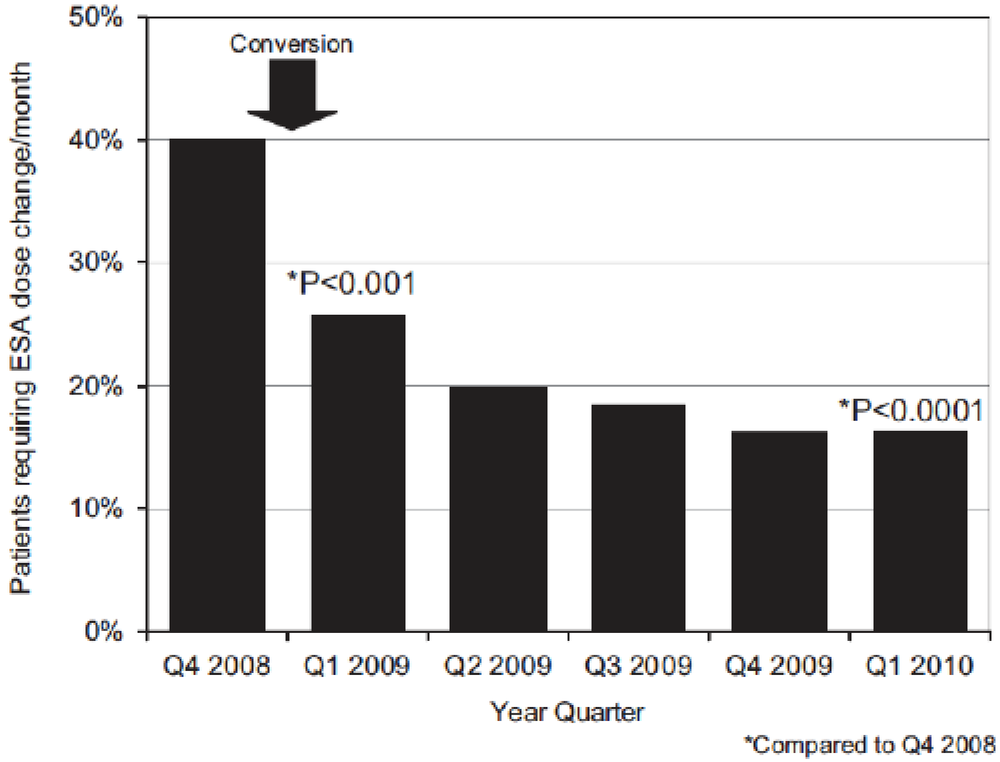


Digital Assisted

Anemia Treatment Prescription & Management

Algorithm for Computed-Supported Anemia Management in HD Patients
Better Results For Less Work





Predictive algorithm anemia management
214 Prevalent HD Patients UK

Lindsey E et al, *Nephrol Dial Transplant* 2012;27: 2425–2429

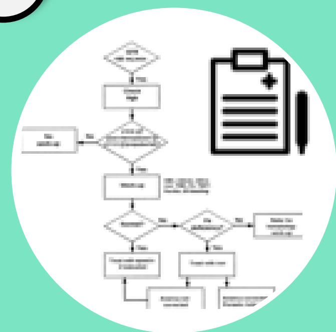
Anemia Management in HD Patients

From Pure Clinical Decision to AI Support-Decision

1

Clinician Decision

2

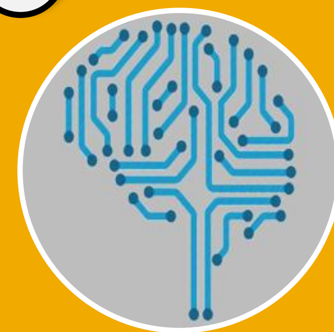


Paper Algorithm

3

Digital Assisted

4

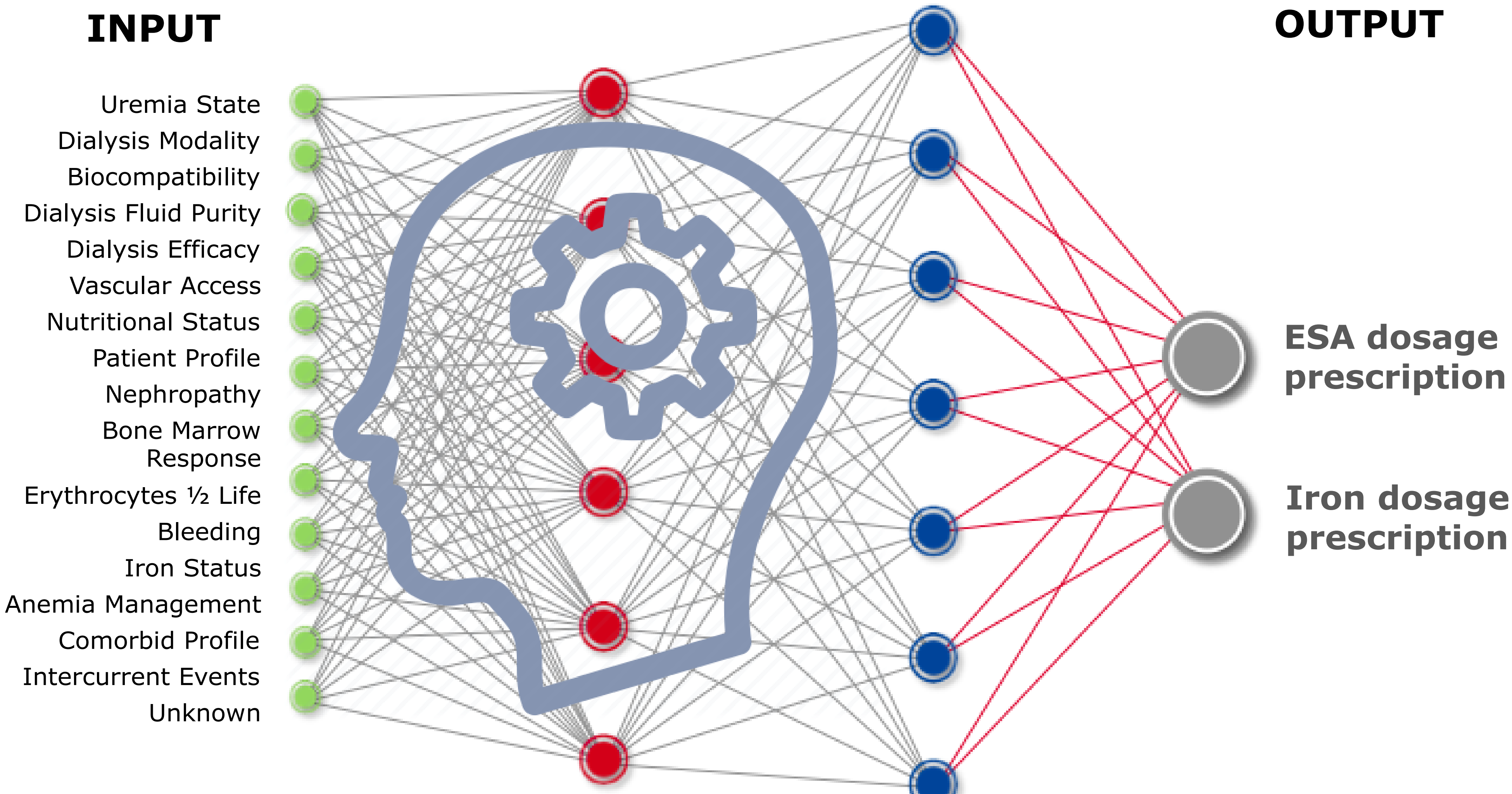


Artificial Intelligence Support

Anemia Treatment Prescription & Algorithm

Anemia Management

Conventional Way Based on Human Intelligence



Math Should not be a Burden for Clinicians….

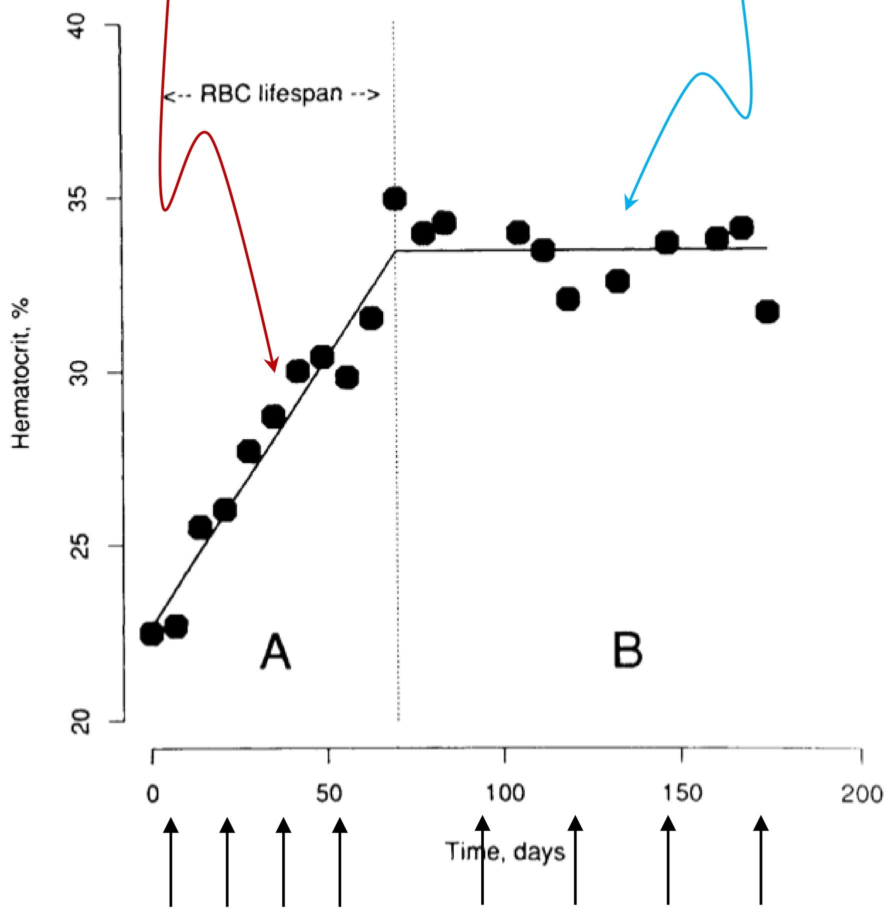
"The essence of math is not to make simple things complicated, but to make complicated things simple."

— STAN GUDDER

Pharmacodynamic Model of EPO Therapy in HD Patients

Sensitivity to EPO (S)

RBC Lifespan (τ)



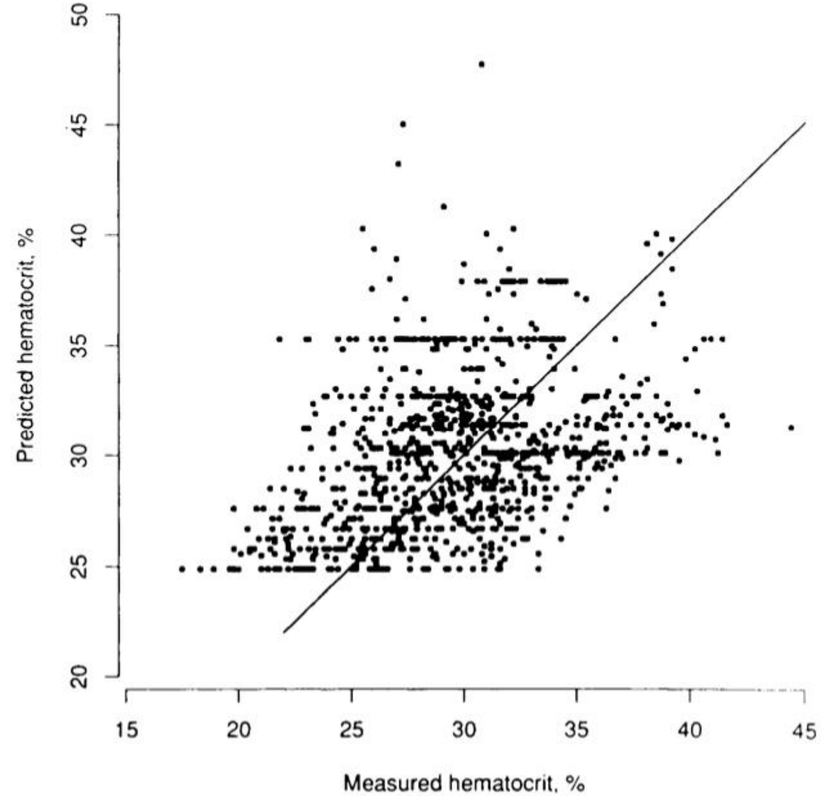
54 HD Pts

EPO

EPO

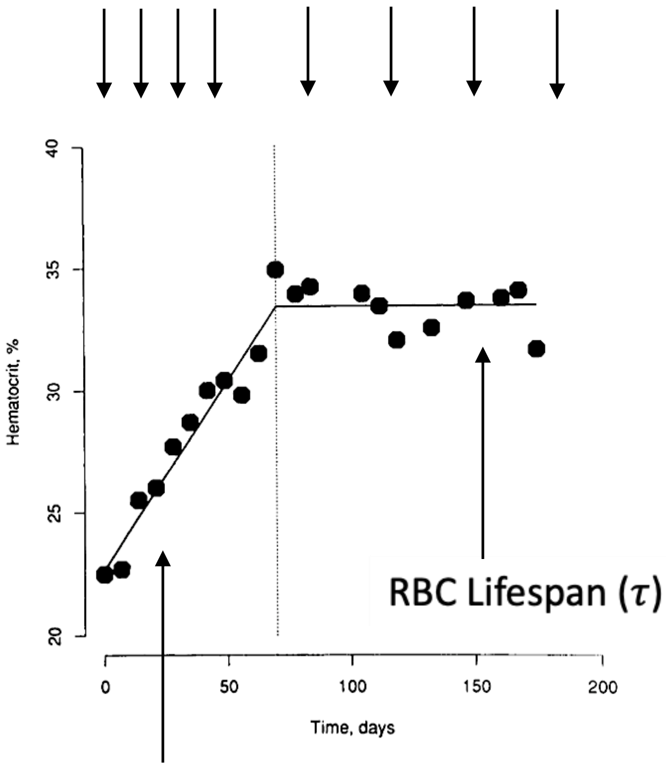
S= pseudo-linear dose response (ERI)

τ 64±18 d

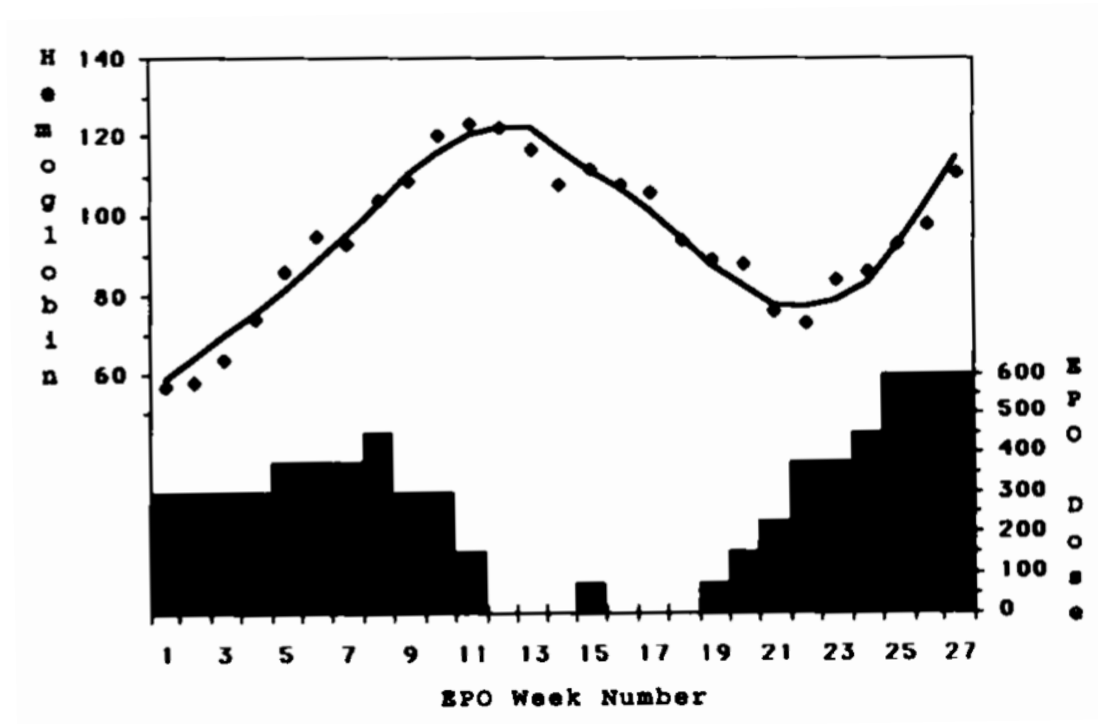


Uehlinger DE et al, *Clin Pharmacol Ther.* 1992;51(1):76-89.

Mathematical Modeling of EPO Therapy



S, slope dose response ESA/Hb (ERI)
IU/Kg/Wk



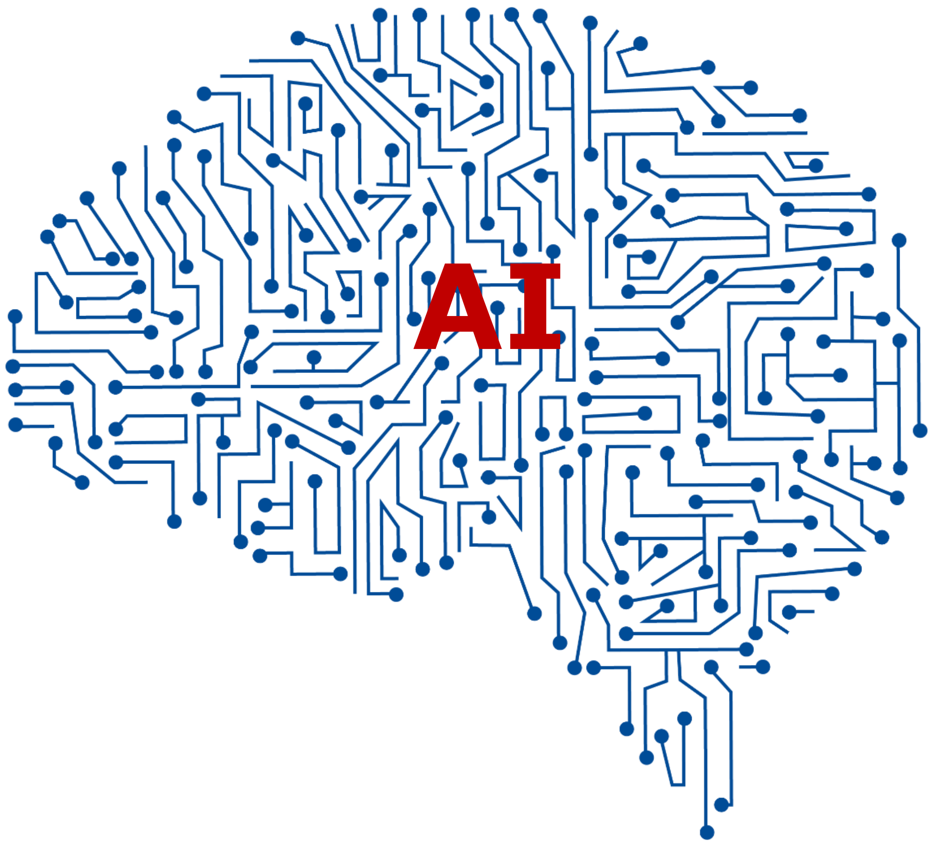
S = 0.015 $\pm$ 0.06 IU/Kg/wk

$\tau = 14 \pm 4.1$ d

67 HD Pts
Canadian EPO Study

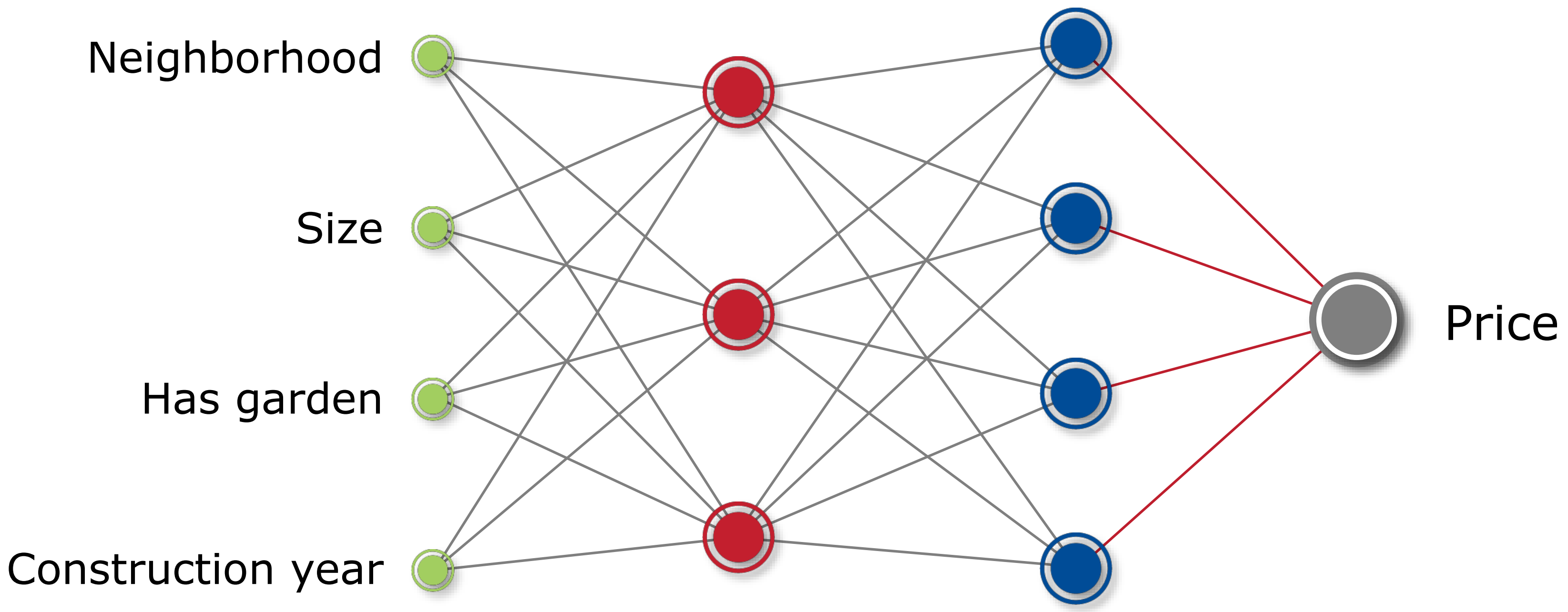
Garred LJ et al, ASAIO Trans. 1991;37(3):M457-9.

Artificial Intelligence is Everywhere
Invades our Daily Life



- ✓ GPS
- ✓ Search engines
  - e.g., Google search
- ✓ Image recognition
- ✓ Amazon selling process
- ✓ Games
  - e.g., PS4
- ✓ Watson, IBM
- ✓ Robotic surgery
  - e.g., «da Vinci»
- ✓ ...

Artificial Neural Networks
A Practical Example: Buying a House (Real Estate)



The **more pairs** of input-output data you collect,
the **more accurate** the outcome will be

Artificial Neural Networks

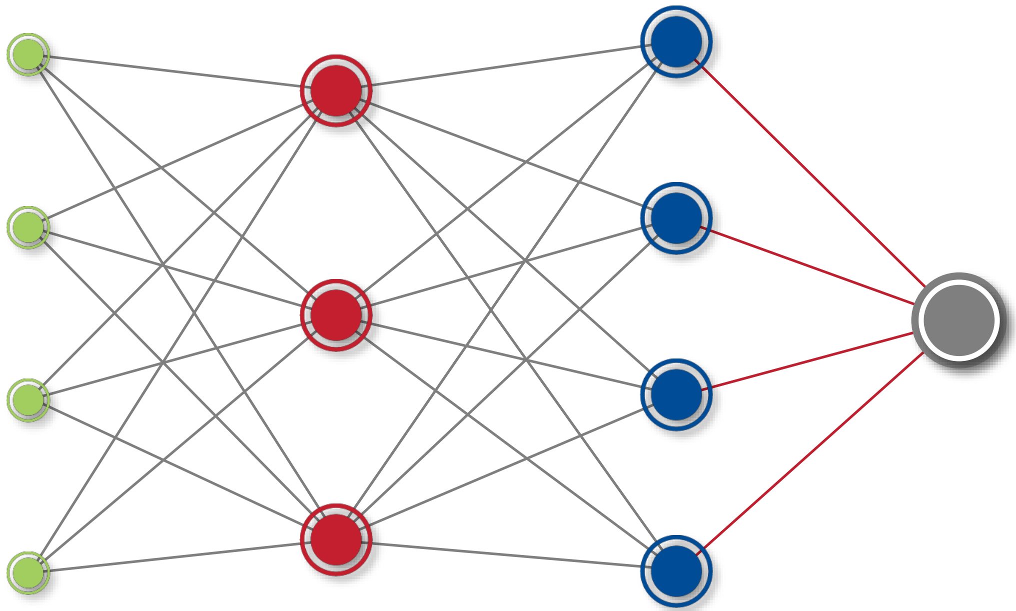
A Practical Example: Buying a House (Real Estate)

Manhattan

120 m^2

No garden

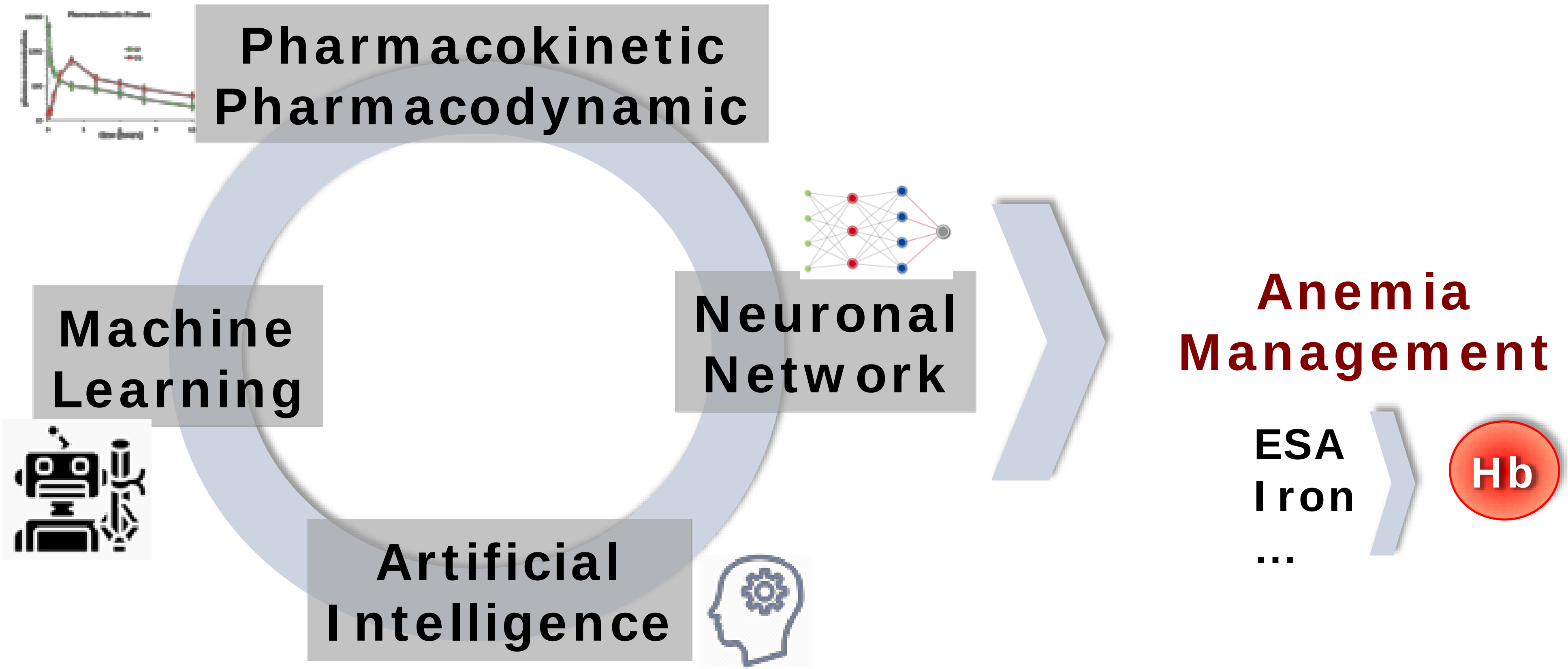
1999



USD 832,514

Once you have **a trained model**, you can use it for prediction.
That is, **on fresh new data**!

Artificial Intelligence Applied to Anemia Management in HD Patients



Artificial Intelligence as Support of Clinical Decision Making in Anemia Management

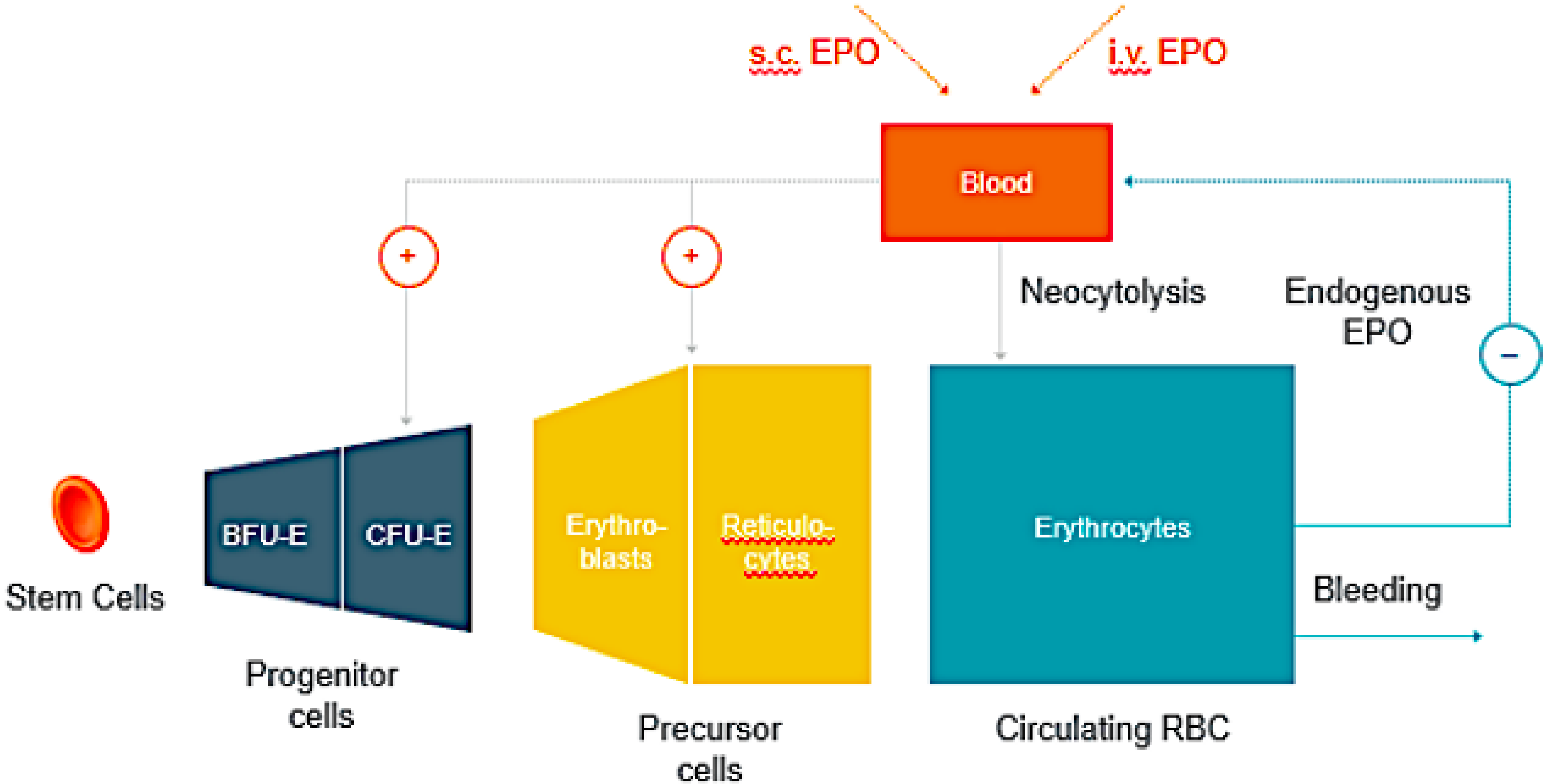
Mathematical Modeling

- Knowledge of physiologic process
- Knowledge of pharmacokinetic/dynamic characteristics
  – ESA sensitivity
  – Erythrocytes life span
  – Reticulocytosis
  – Neocytolysis
  – Iron availability
  – Other parameters
- Formulate mathematical model
- Validate model (internal/external)
  – Bigdata – Advanced analytic
  – Create avatar or twin-patient
- Clinical trial /superiority
  – RCT versus traditional care

Machine Learning

- No specific knowledge
  – Bigdata input
  – Machine learning
  – Advanced analytics
  – Training large dataset
- Validate model
  – Internal/external
  – Agreement predicted/observed
  – Retrieve pharmacokinetic
- Clinical trial/superiority
  – Prospective study

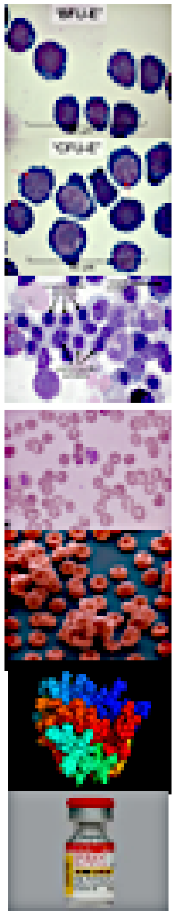
A Model of Erythropoiesis in Adults with Sufficient Iron Availability



Fuertinger DH et al, *J Math Biol.* 2013;66(6):1209-40

Formulate the Mathematical Model

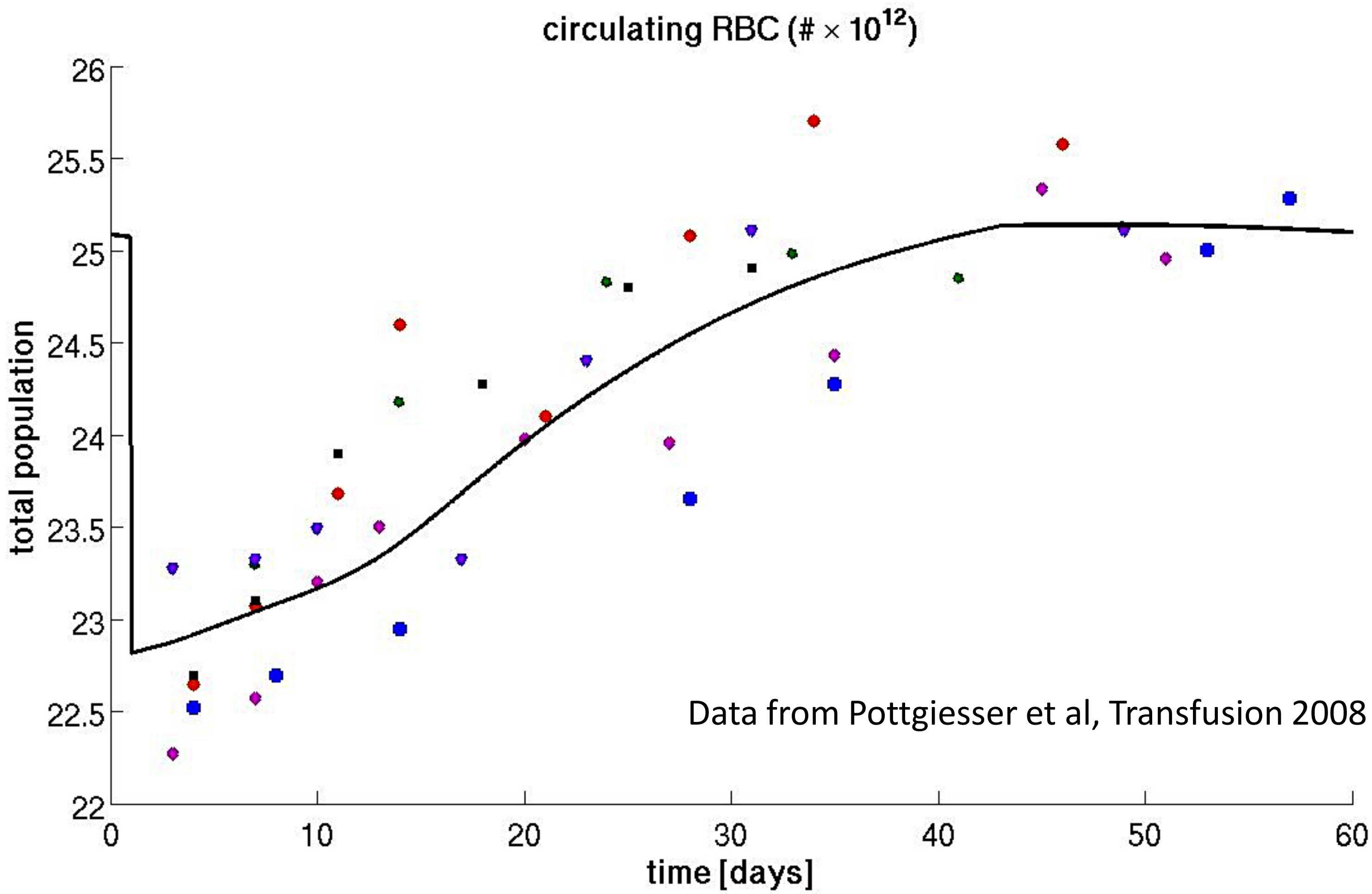
Cell proliferation, maturation velocity and apoptosis of erythroid cells are influenced by erythropoietin (EPO)



BFU-E	$\frac{\partial}{\partial t}p(t,x^p)+\frac{\partial}{\partial x^p}p(t,x^p)=\beta^p p(t,x^p),$
CFU-E	$\frac{\partial}{\partial t}q(t,x^q)+\frac{\partial}{\partial x^q}q(t,x^q)=(\beta^q-\alpha^q(E(t)))\,q(t,x^q),$
Erythoblasts	$\frac{\partial}{\partial t}r(t,x^r)+\frac{\partial}{\partial x^r}r(t,x^r)=\beta^r r(t,x^r),$
BM Reticulocytes	$\frac{\partial}{\partial t}s(t,x^s)+v^s(E(t))\frac{\partial}{\partial x^s}s(t,x^s)=-\alpha^s s(t,x^s),$
Erythrocytes	$\frac{\partial}{\partial t}m(t,x^m)+\frac{\partial}{\partial x^m}m(t,x^m)=-\alpha^m(E(t),x^m)\,m(t,x^m),$
endogenous Epo	$\frac{d}{dt}E^{\mathrm{end}}(t)=\frac{1}{TBV}E^{\mathrm{end}}_{\mathrm{in}}(t)-c^{\mathrm{end}}_{\mathrm{deg}}E^{\mathrm{end}}(t),$
exogenous Epo	$\frac{d}{dt}E^{\mathrm{ex}}(t)=\frac{1}{TBV}E^{\mathrm{ex}}_{\mathrm{in}}(t)-c^{\mathrm{ex}}_{\mathrm{deg}}E^{\mathrm{ex}}(t),$

Fuertinger DH et al, *J Math Biol.* 2013;66(6):1209-40

Model Validation in Blood Donation Subjects



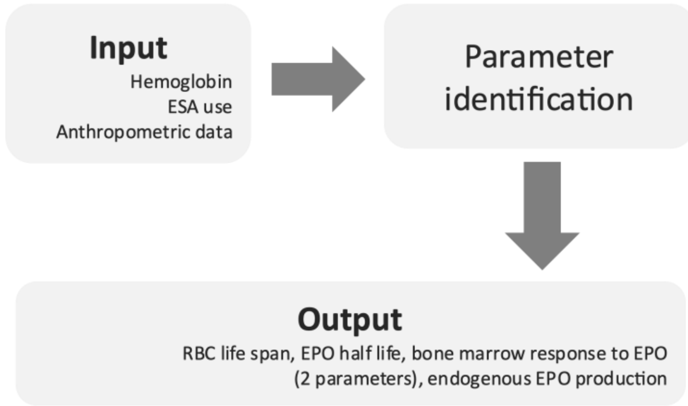
Fuertinger DH et al, *J Math Biol.* 2013;66(6):1209-40

A Numerical Method for Structured Population Equations Modeling Control of Erythropoiesis

Model Adaptation to Individual Patients using Parameter Estimation: Avatar Generation

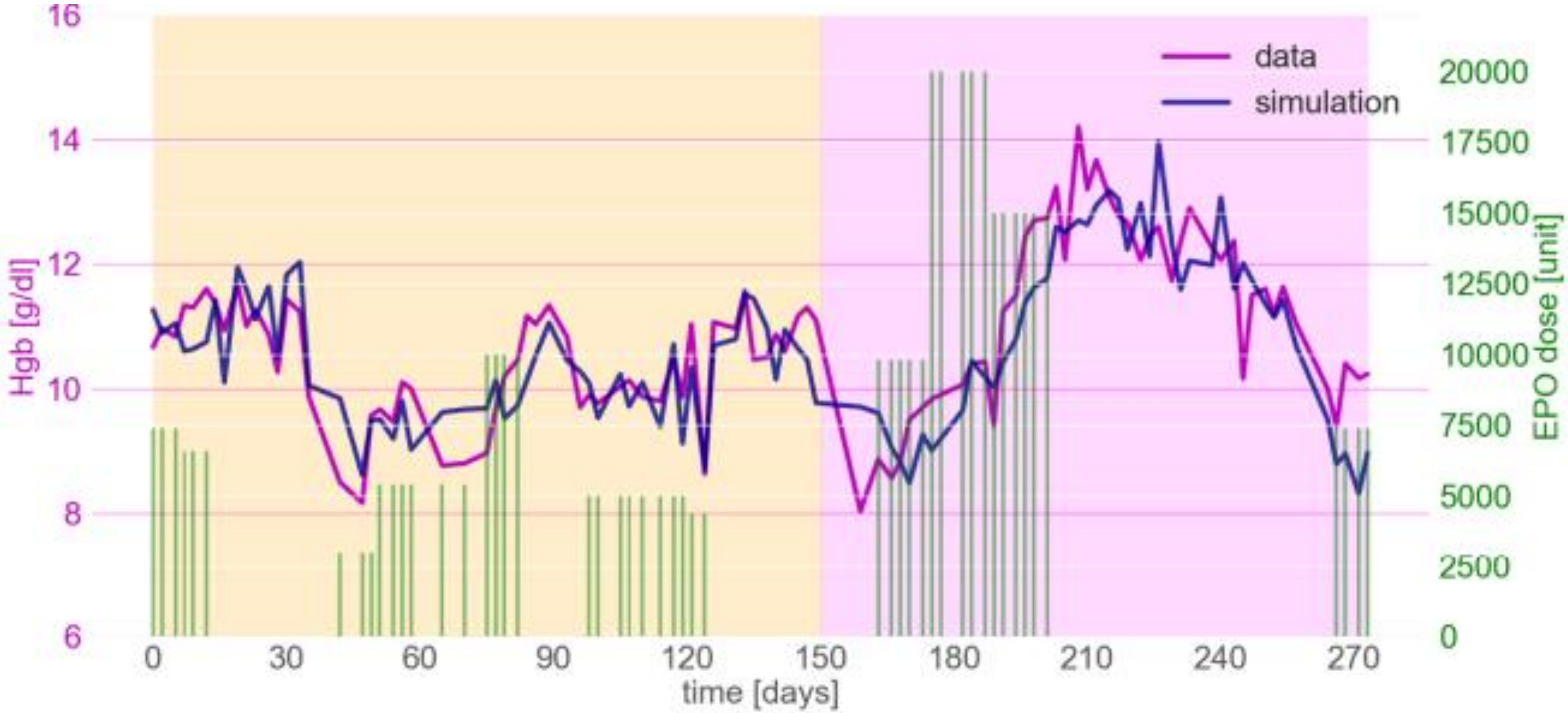
- Model includes 30 parameters
- 2 parameters are adjusted using empirical formulas
  - Data: gender, height, weight
- 5 parameters are inferred from data
  - Data: hemoglobin levels, ESA administration; anthropometric data
- Minimize a weighted least square cost functional
- Model was adapted to 60 ESRD patients

$$J(p_1, \ldots, p_n) = \sum_{j=1}^{N} w(t_j)\left(y\left(t_j\right) - \phi\left(\theta, t_j\right)\right)^2$$



Fuertinger DH et al. *IFAC Proceedings Volumes* 2013;46(26):93-96

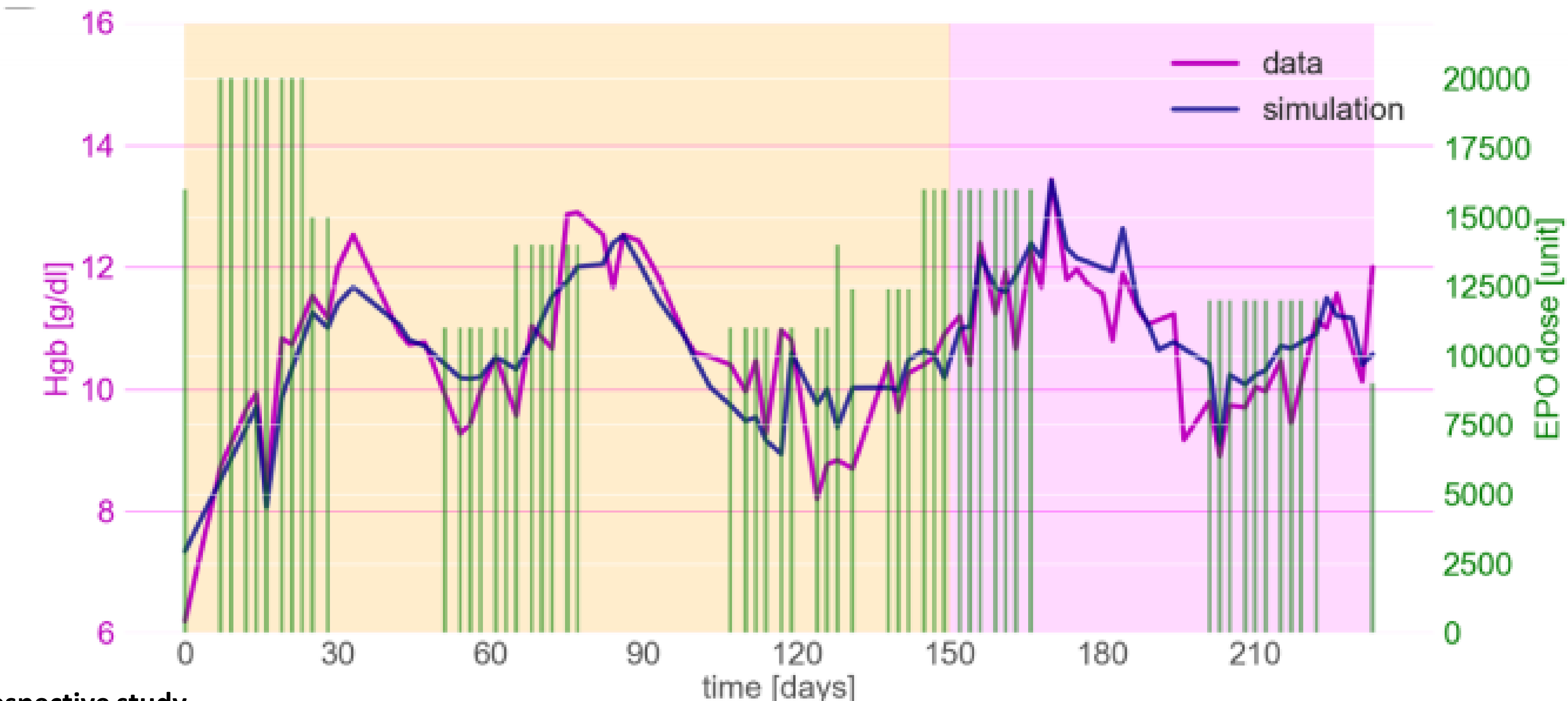
Comparison of Model Simulations (blue) and Empirical Data (magenta) – Selected Patient #1



Prospective study
60 HD pts receiving ESA
Key parameters temporal
Hb data Crit-Line monitor
150d baseline period

Fuertinger DH et al. *PLoS One.* 2018;13(4):e0195918.

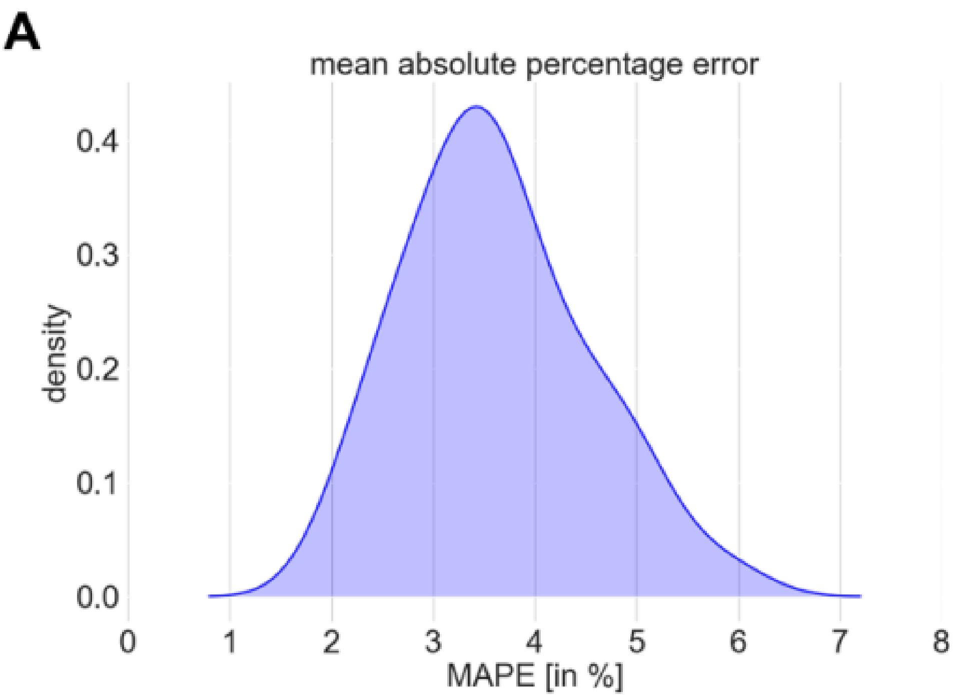
Comparison of Model Simulations (blue) and Empirical Data (magenta) – Selected Patient #2

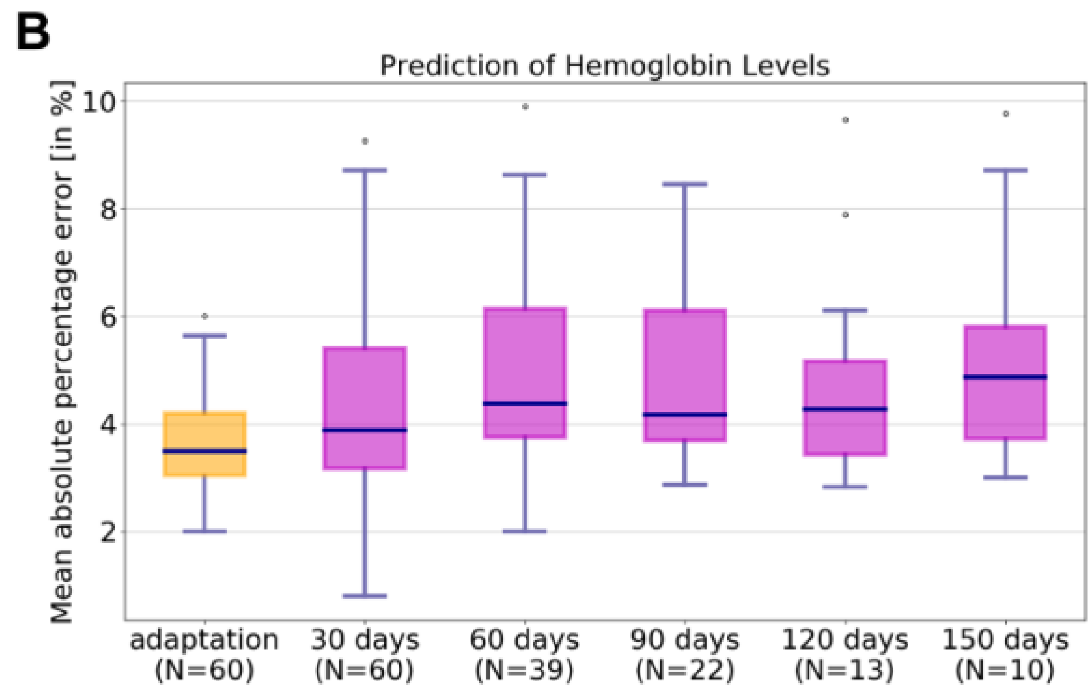


Prospective study
60 HD pts receiving ESA
Key parameters temporal
Hb data Crit-Line monitor
150d baseline period

Fuertinger DH et al. *PLoS One.* 2018;13(4):e0195918.

Prediction of Hb Values in Virtual Dialysis Clinic Avatars

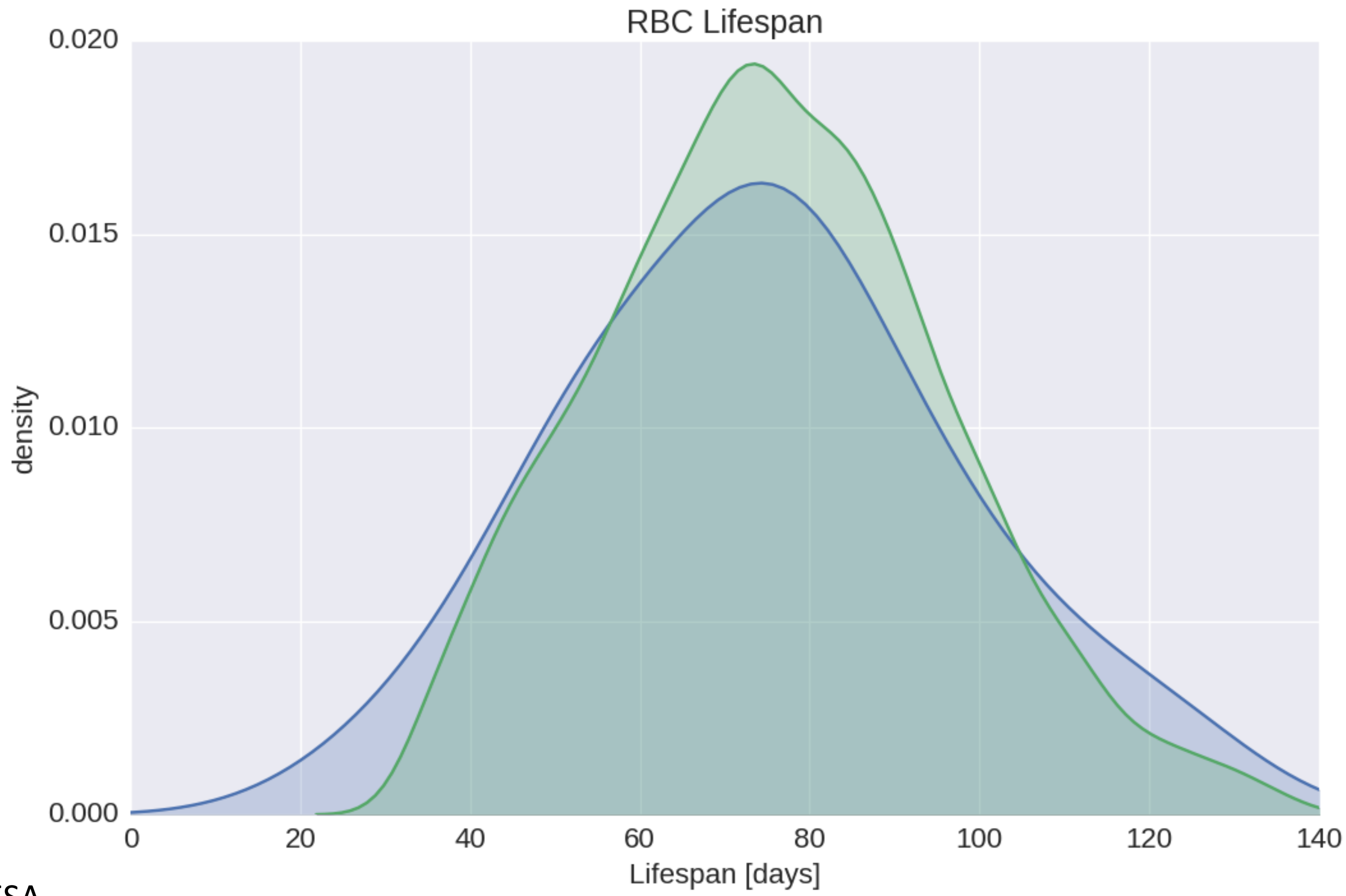




Prospective study
60 HD pts receiving ESA
Key parameters temporal
Hb data Crit-Line monitor
150d baseline period

Fuertinger DH et al. *PLoS One.* 2018;13(4):e0195918.

Prediction of RBC Life Span In Virtual Dialysis Clinic Avatars



Prospective study
60 HD pts receiving ESA
Key parameters temporal
Hb data Crit-Line monitor
150d baseline period

Fuertinger DH et al. *PLoS One.* 2018;13(4):e0195918.

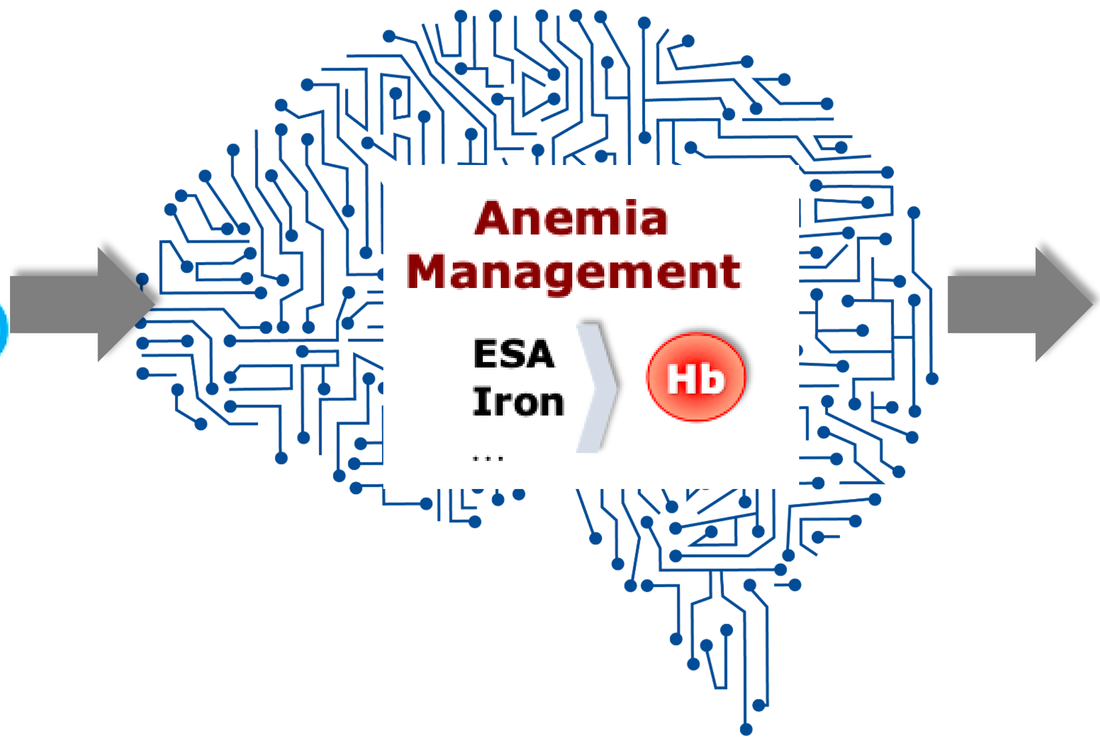
Artificial Intelligence in HD Patient Management

Anemia Control Model

>800 FMC clinics
>30 countries
>30 000 users
>100 000 patients

EuClID

European Clinical Data System



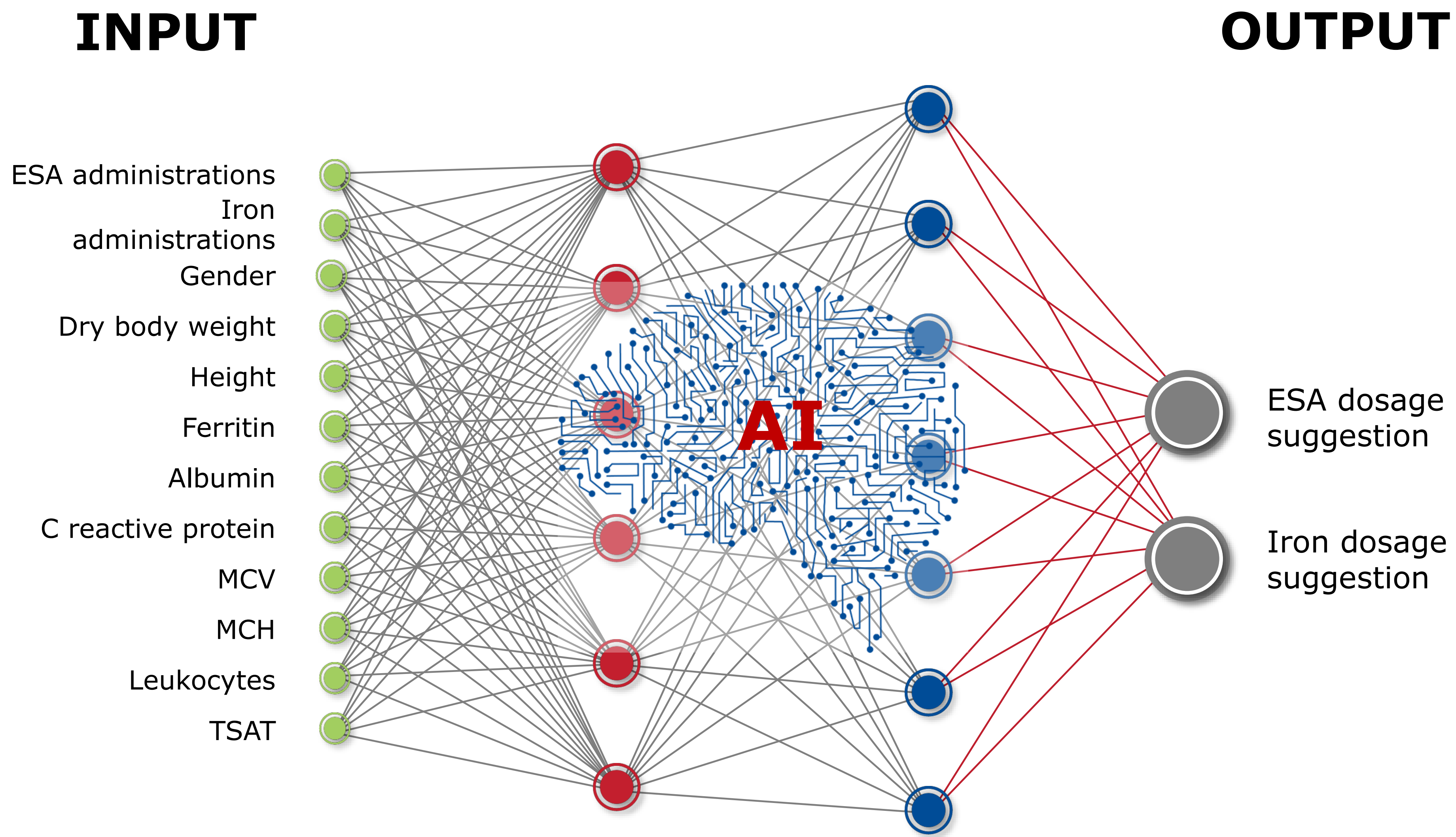
Anemia Control Model (ACM)

ANEMEX

Anemia Control Model® (ACM) from FMC

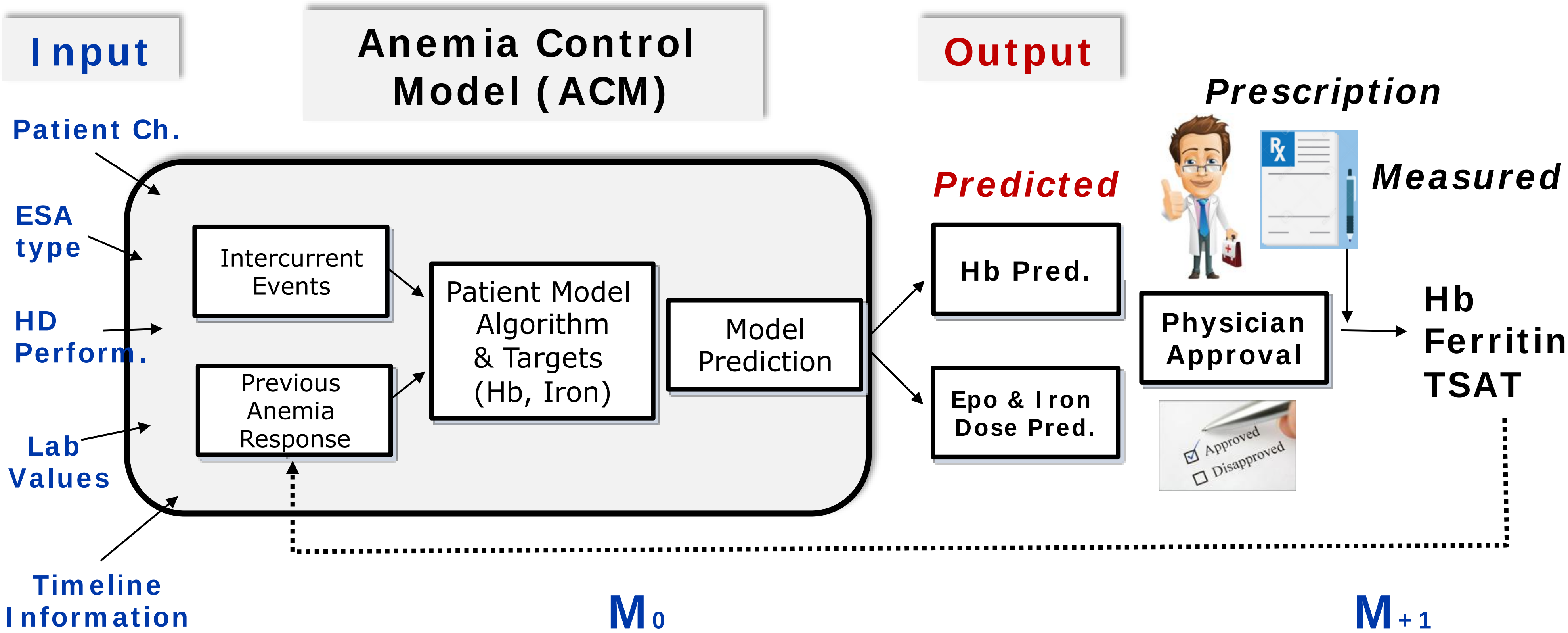
ACM, Euclid Dataset of FMC Clinics

Trained on 950.000 Patients Records



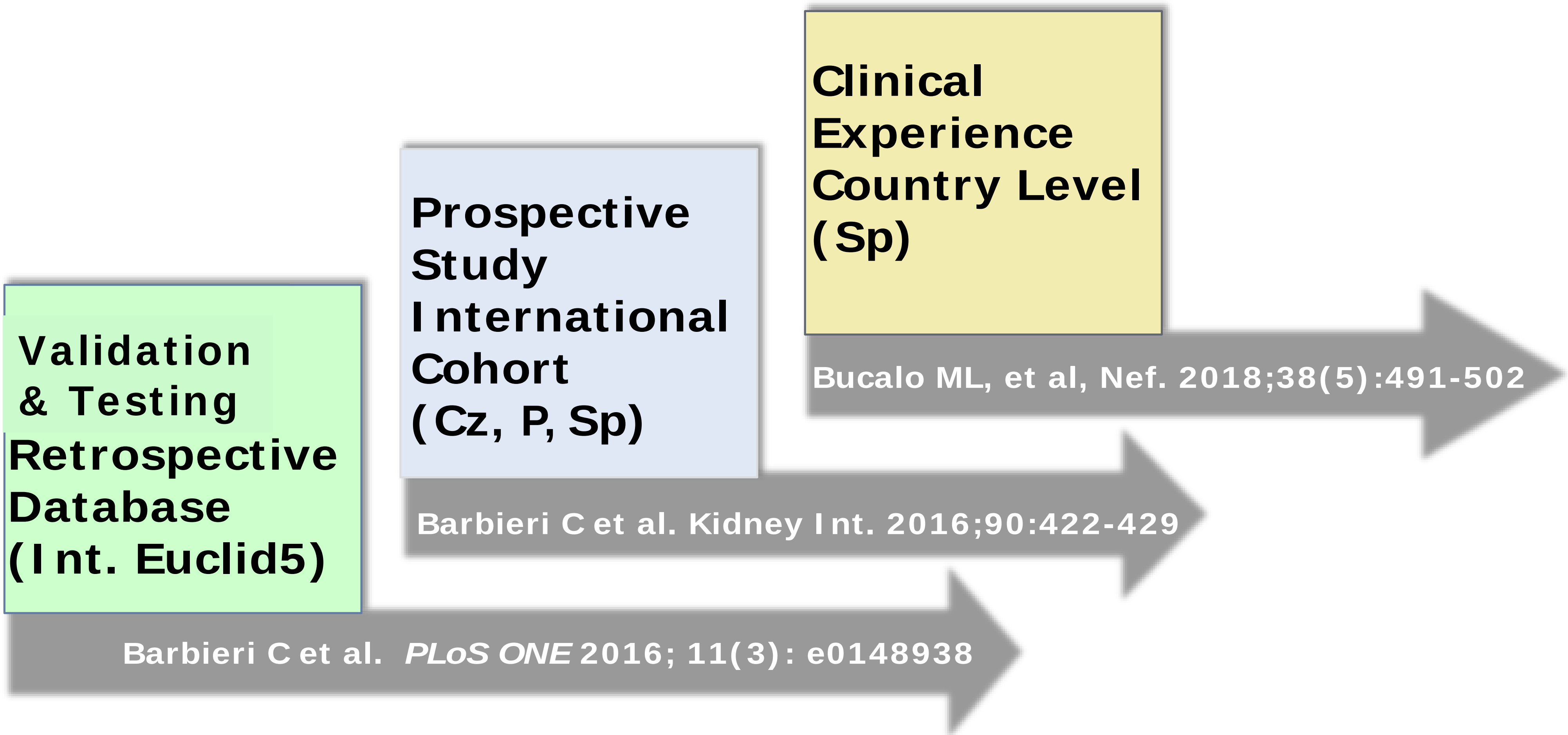
Development of Anemia Control Model

Artificial Intelligence, Neuronal Network, Algorithm & ESA Kinetic

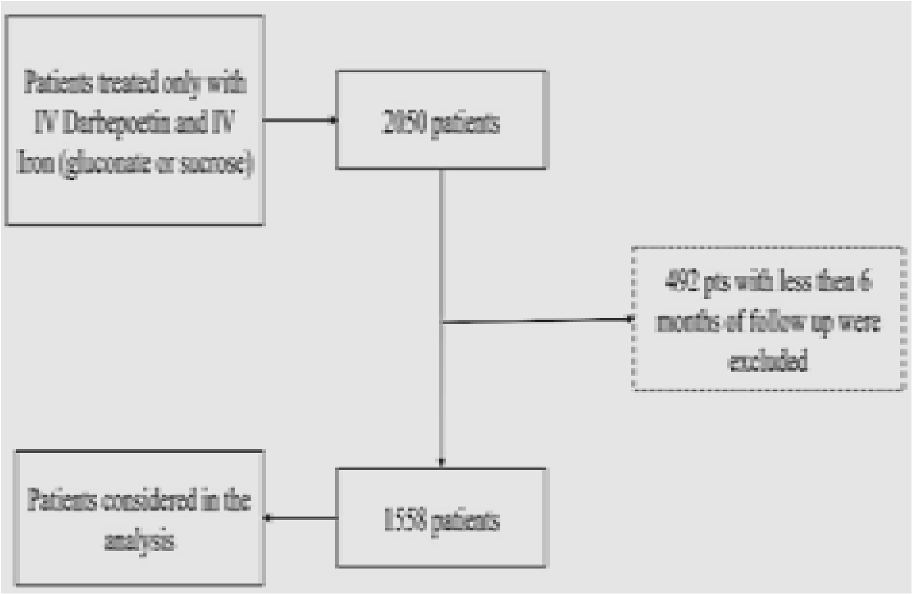


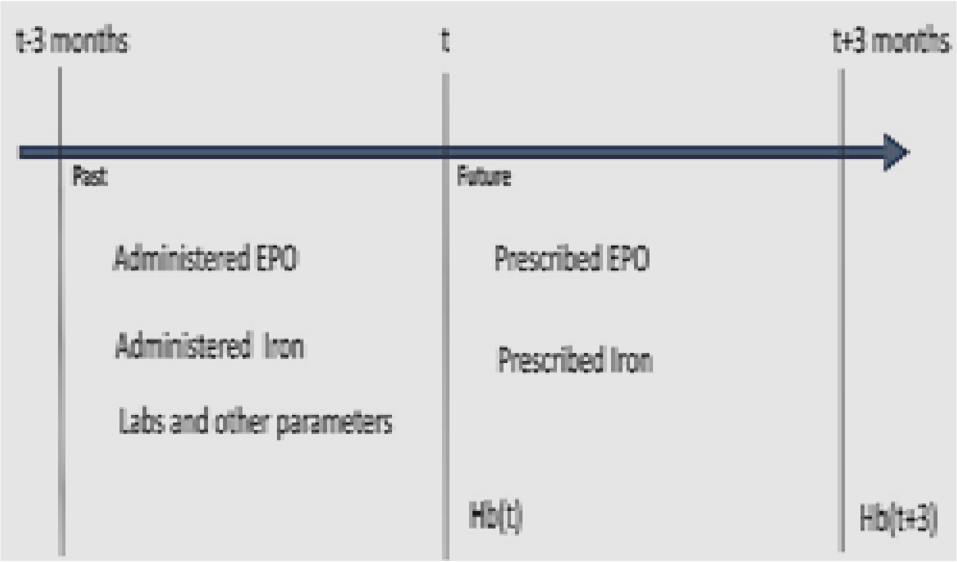
Anemia Control Model (ACM)

Scientific Roadmap : Validation, Testing, Implementation



ACM – Model Validation
Retrospective Database Cohort





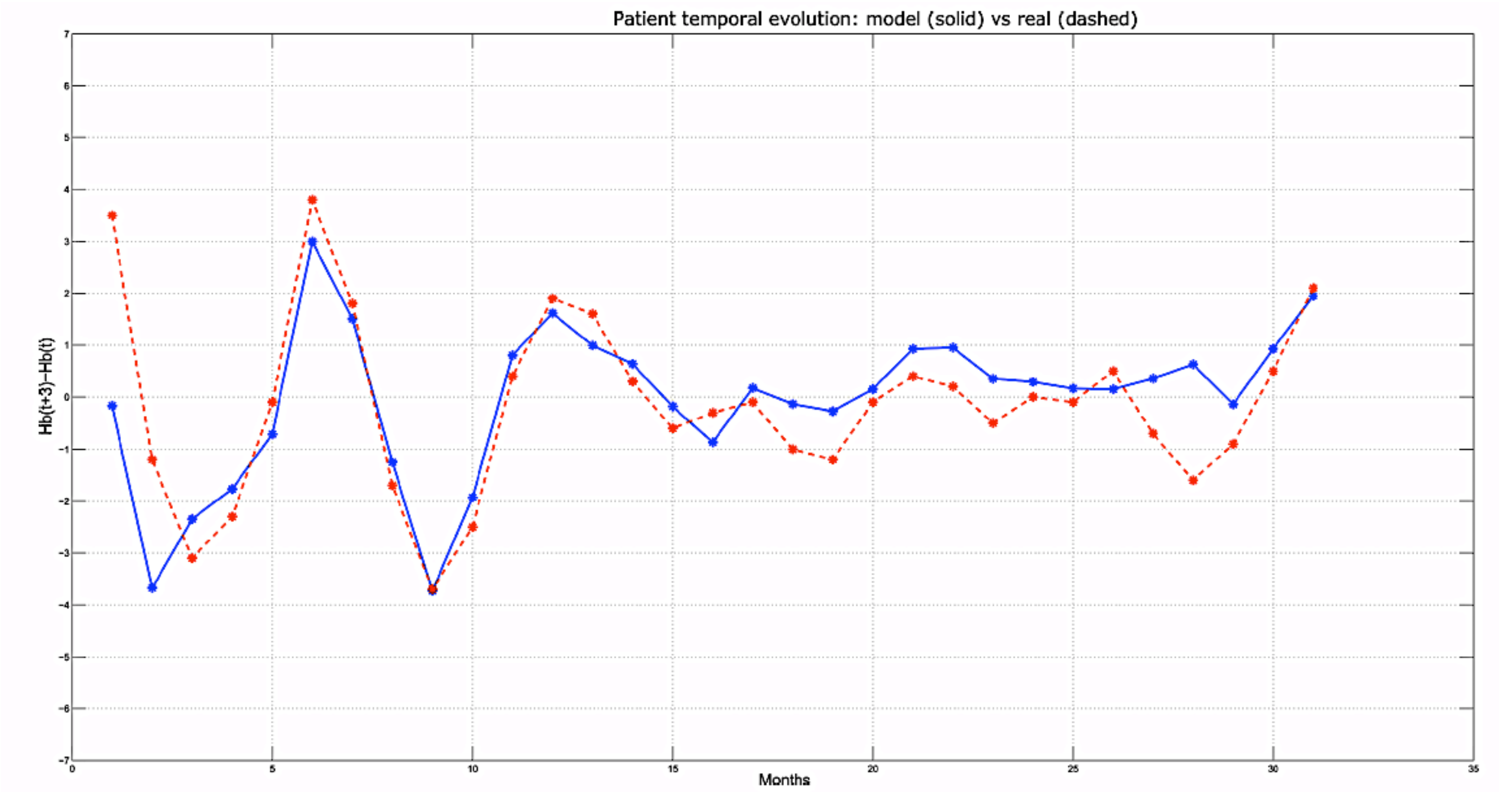
ACM
Anemia Control Module

Barbieri C et al. *PLoS ONE* 2016; 11(3): e0148938

ACM – Model Validation

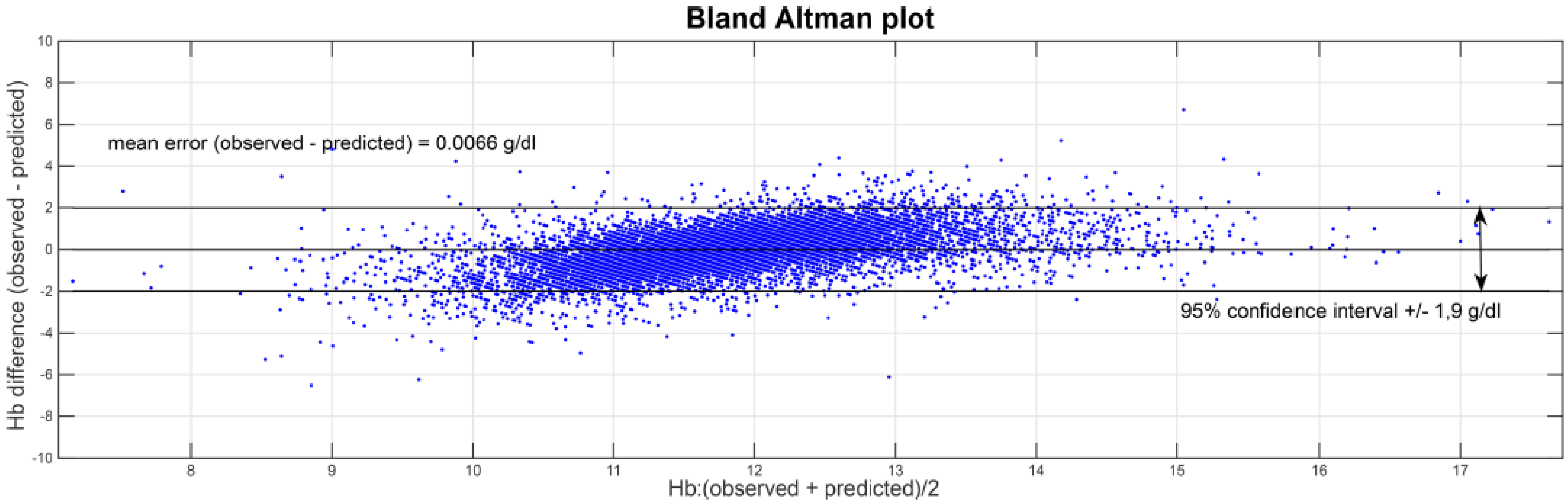
Observed versus Predicted Hb in a Typical Patient

Predicted vs. actual Hb variations for a typical patient characterized by a prediction error close to the mean absolute error on test set



Barbieri C et al. *PLoS ONE* 2016; 11(3): e0148938

ACM – Model Validation
Bland-Altman Analysis of Observed/Predicted Hb Values



ACM
Anemia Control Module

Barbieri C et al. *PLoS ONE* 2016; 11(3): e0148938

Anemia Control Model (ACM) to Anemex

Scientific Roadmap : Validation, Testing, Implementation

Clinical Experience Country Level (Sp)

Bucalo ML, et al, Nef. 2018;38(5):491-502

Prospective Study International Cohort (Cz, P, Sp)

Barbieri C et al. Kidney Int. 2016;90:422-429

Validation & Testing Retrospective Database (Int. Euclid5)

Barbieri C et al. *PLoS ONE* 2016; 11(3): e0148938

Barbieri Study
Design

2012/06 — 2013/05 — 2013/06 — 2014/05

Control Phase

Standard Anemia Care

All Patients (n=653)

Observational Phase

ACM Guided Anemia Care

All Patients (n=383)
ACM Compliant Patients (n=313)

Facility-Level Analysis
Patient-Level Analysis

- **ESA Used**: Darbepoetin α
- **Prevalent** HD Patients (n = 752)
- **EuCliD**
- **Study Clinics:** NephroCare
  - Motol Prague Cz
  - Cartagena & San Pedro del Pinatar, Sp
  - Lumiar, P

ERBP
Hb target 10-12 g/dl
TSAT >30% - Ferritin 150-600µg/l

Barbieri C et al. Kidney Int. 2016;90:422-429

Barbieri & al study
Patient Characteristics

Patient characteristics in study

Characteristics	All patients
No. of patients	383
Follow-up period, mo, mean ± SD	22.12 ± 2.40
Age, yr, mean ± SD	65.18 ± 14.89
Male, no. (%)	231 (60.3)
Comorbidities at ACM entrance, no. (%)	
Coronary artery disease	33 (8.6)
Congestive heart failure	82 (21.4)
Peripheral vascular disease	114 (29.8)
Cerebrovascular disease	71 (18.5)
Chronic pulmonary disease	58 (15.1)
Diabetes	87 (22.7)
Charlson Comorbidity Index, mean ± SD	6.98 ± 3.30

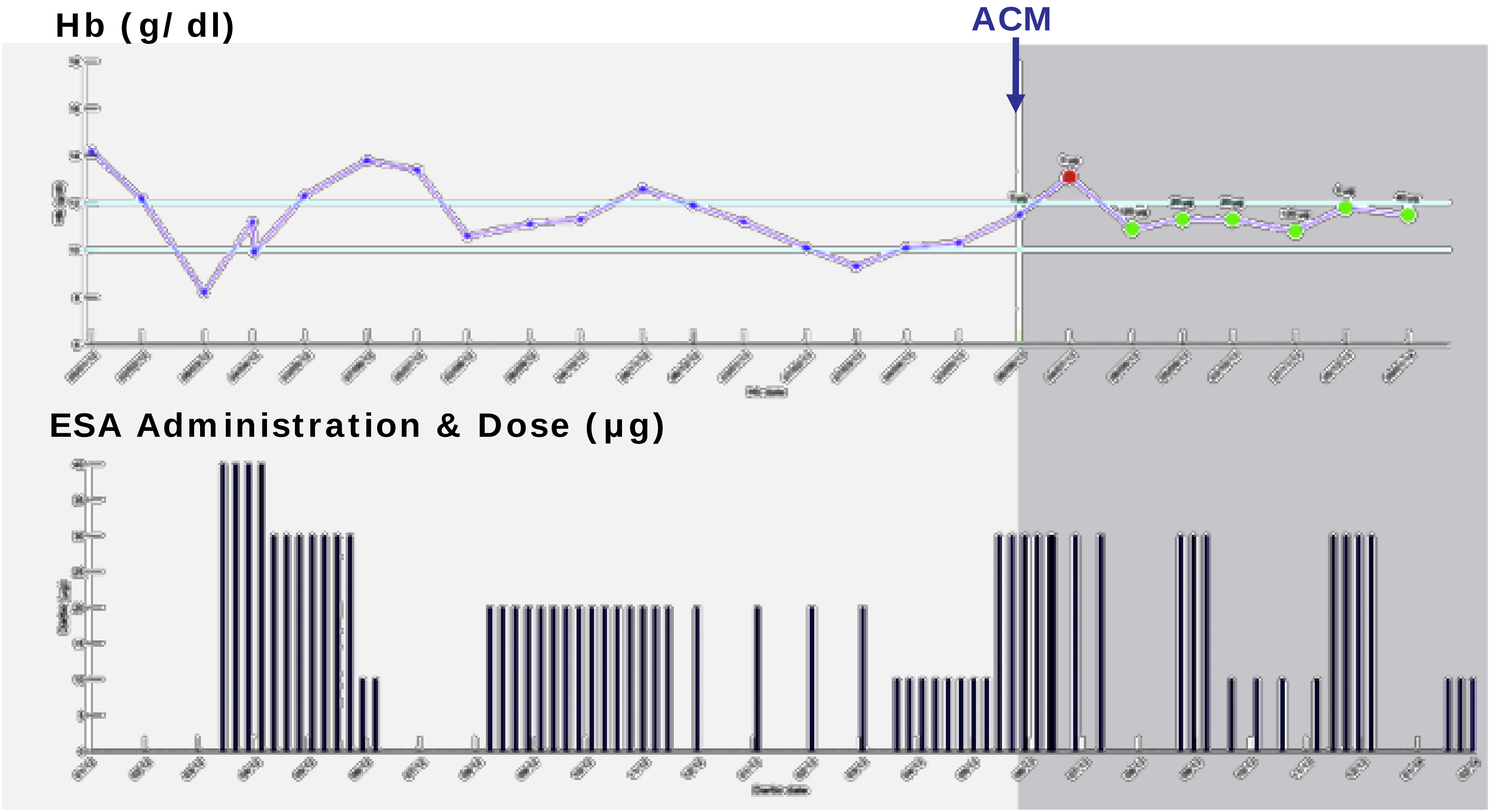
Characteristics	All patients
Causes of kidney disease, no. (%)	
Diabetes	75 (19.6)
Hypertension	69 (18.0)
Chronic glomerulonephritis	88 (23.0)
Urinary obstruction/chronic interstitial nephritis	10 (2.6)
Polycystic kidney disease	25 (6.5)
Other	116 (30.3)
Vascular access, no. (%):	
Fistula	261 (68.1)
Catheter	59 (15.4)
Graft	63 (17.2)
Treatment modality, no. (%)	
HDF online	361 (94.3)
High-flux HD	14 (3.7)
Other	7 (1.8)

HD, hemodialysis; HDF, hemodiafiltration.

ESA Used : Darbepoetin α

Barbieri C et al. Kidney Int. 2016;90:422-429

Hb Behavior over Time pre and post-ACM
Example of a Typical Patient



ESA: Darbepoetin alfa

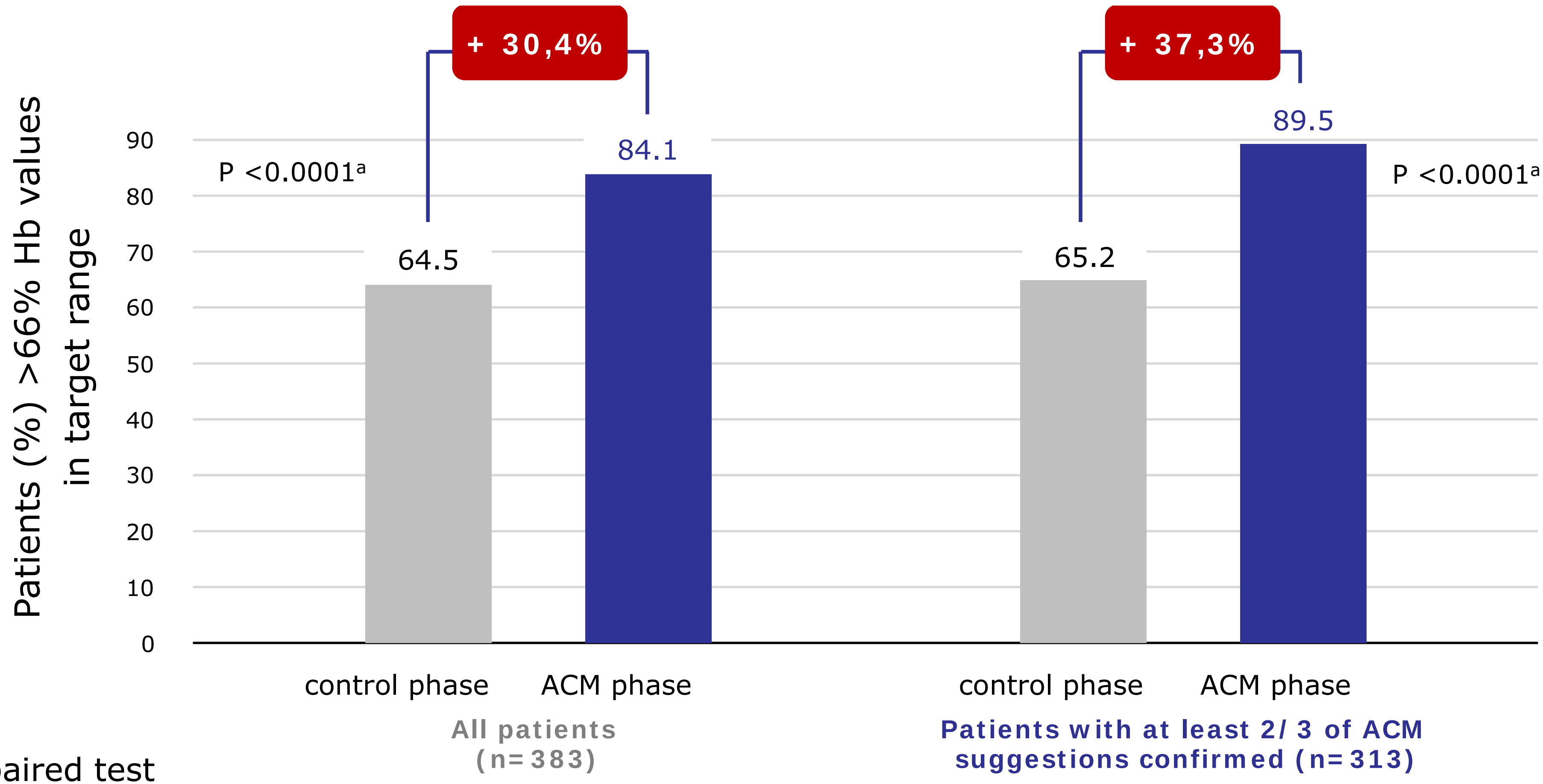
Accepted suggestion

Rejected suggestion

Barbieri C et al, *Kidney Int.* 2016;90:422-429

ACM Use Increased Percentage of Patients in Target

Patients with at least two-thirds of their Hb values on target increased significantly



[a]. paired test

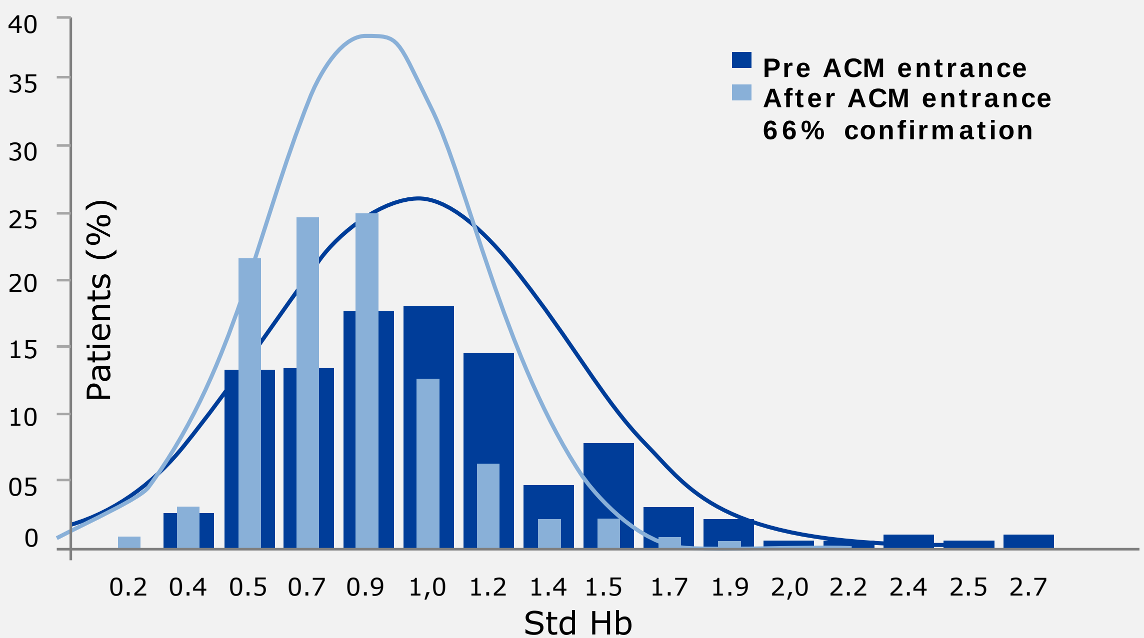
ESA Used : Darbepoetin α

Barbieri C et al. Kidney Int. 2016;90:422-429

ACM Use Reduced Hb Variability

After ACM deployment, Hb variability decreased

Histogram of Hb SDs before and after ACM introduction



313 patients with **66,6%** confirmation of ACM suggested dosages

- Histogram shows the distribution of Hb standard deviations in the study phases (pre ACM entrance & after ACM entrance).
- The change in skewness, kurtosis and the distribution shift confirm that Hb variability decreased after ACM deployment.

ESA Used : Darbepoetin α

Barbieri C et al. Kidney Int. 2016;90:422-429

Anemia Management Supported by ACM Reduces ESA Consumption and Improves Outcomes

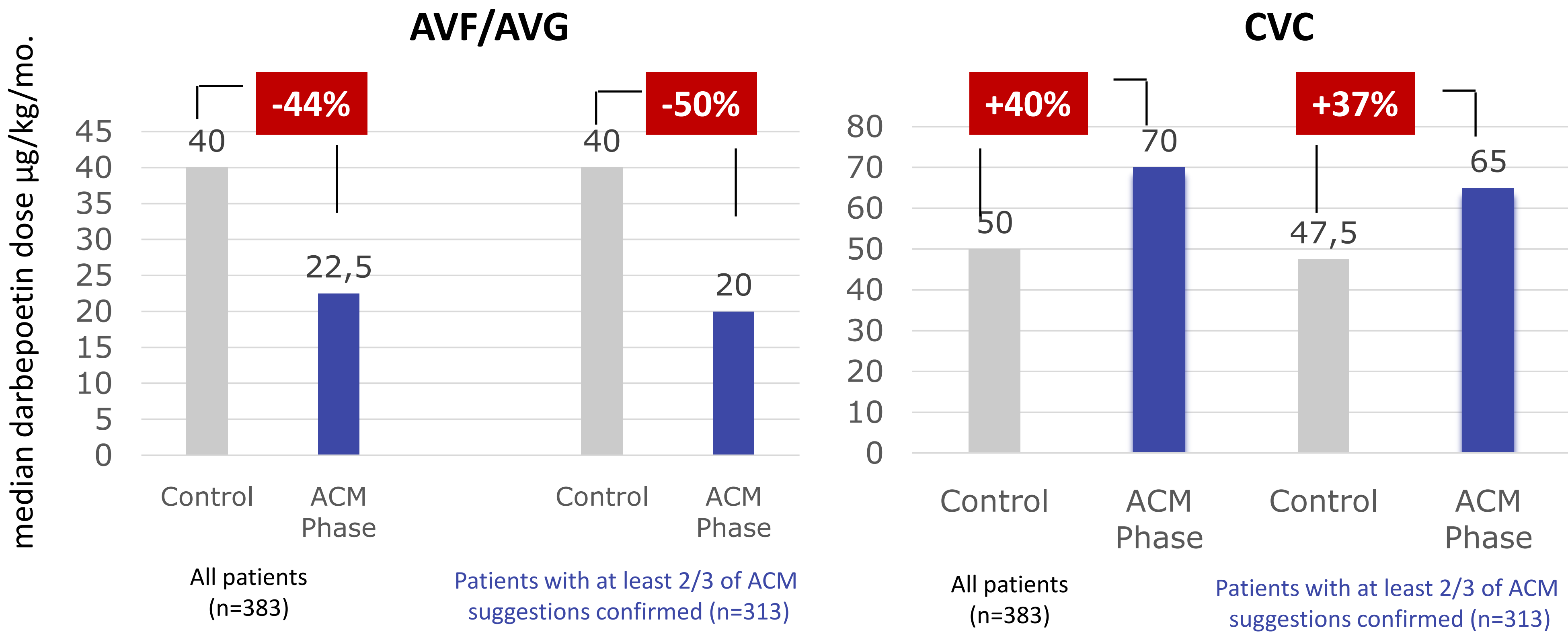
	Control phase	Observation phase	P-value
ACM-compliant patients (n = 313)			
Anemia outcomes			
Hb SD, g/dl, mean ± SD	0.97 ± 0.41	0.80 ± 0.29	<0.001[a]
Patients with >66.6% Hb within target range, no. (%)	204 (65.2)	280 (89.5)	<0.001[b]
Median darbepoetin dose, µg, median (IQR)	40.00 (80.00)	20.00 (70.00)	0.001[c]
Median absolute delta darbepoetin dose, µg, median (IQR)	10.00 (25.00)	10.00 (40.00)	0.24[c]
Adverse events			
Patients with cardiovascular events, no. (%)	64 (20.4)	39 (12.5)	0.009[b]
Cardiovascular events (incidence/ 1000 patient-years)	276.36	191.15	0.002[d]
Hospitalization days (incidence/ 1000 patient-years)	3319.69	3348.67	0.42[d]
Patients with transfusion events, no. (%)	7 (2.2)	0 (0)	0.02[b]
Transfusion events (incidence/ 1000 patient-years)	54.59	0	<0.001[d]

ESA Used : Darbepoetin α

Barbieri C et al, *Kidney Int.* 2016;90:422-429

Effect of Vascular Access Type on Anemia Correction

Catheters Increase ESA Consumption & Hb Variability

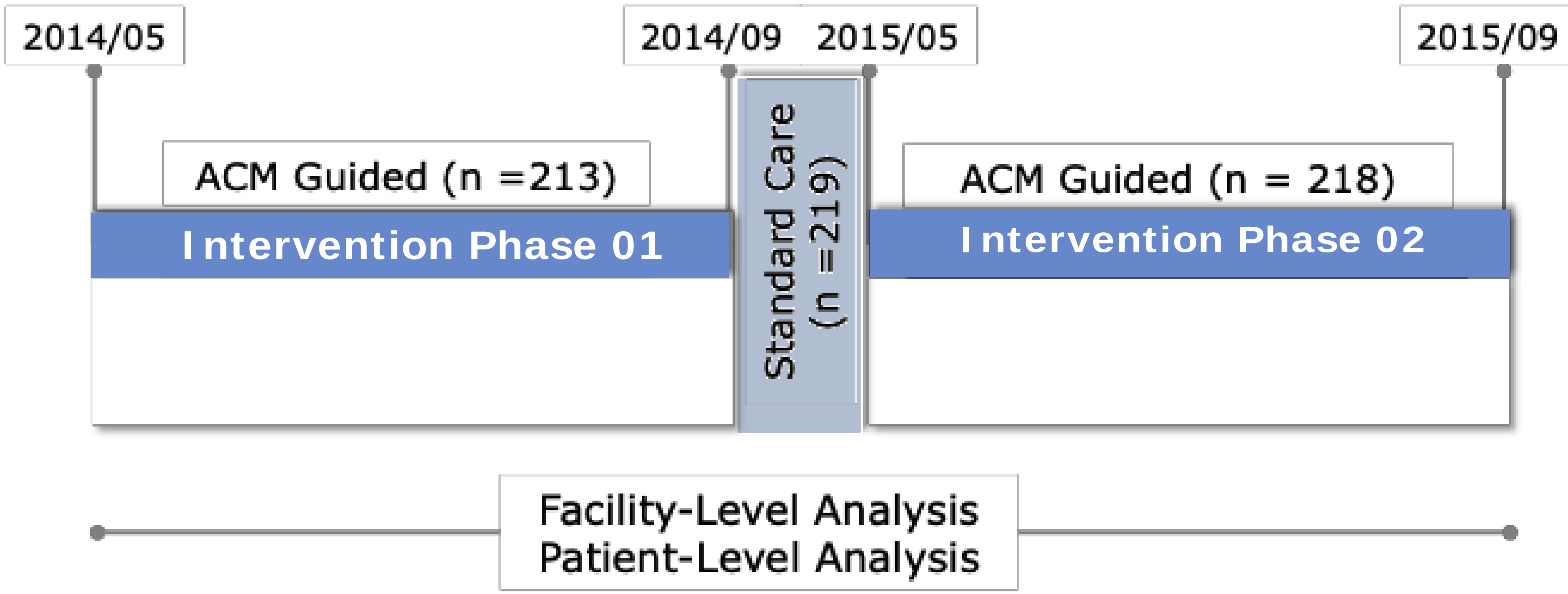


ESA Used : Darbepoetin α

Barbieri C et al. Kidney Int. 2016;90:422-429

ACM Used In Daily Clinical Life

Example of Spain – Study Design



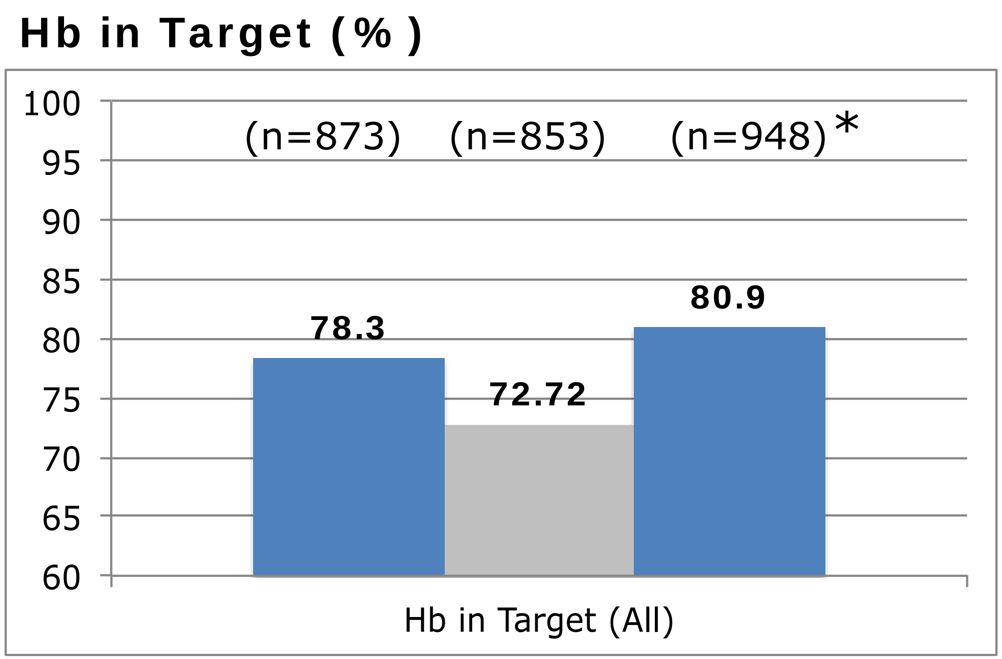
- **ESA Used**: Darbepoetin α
- **Prevalent** HD Patients (n =219)
- **EuClID**
- **Study Clinics:** NephroCare

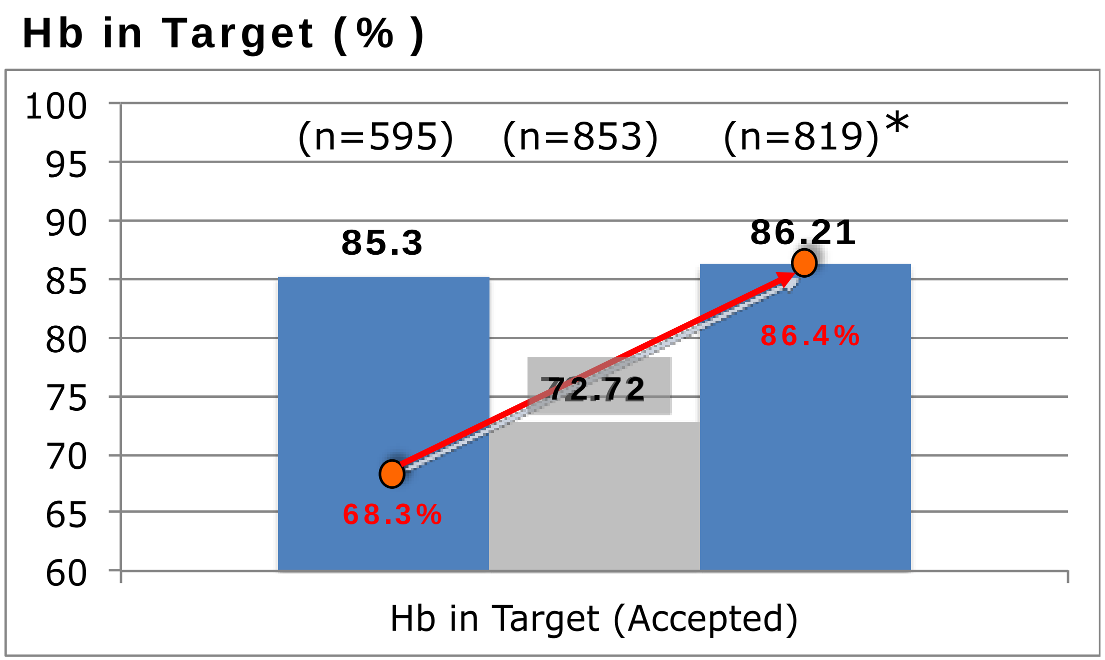
Spain

- Murcia, Cartagena
- San Pedro del Pinata

Bucalo ML et al, *Nefrol*. 2018;38(5):491–50

Primary Outcome
Hb in Target

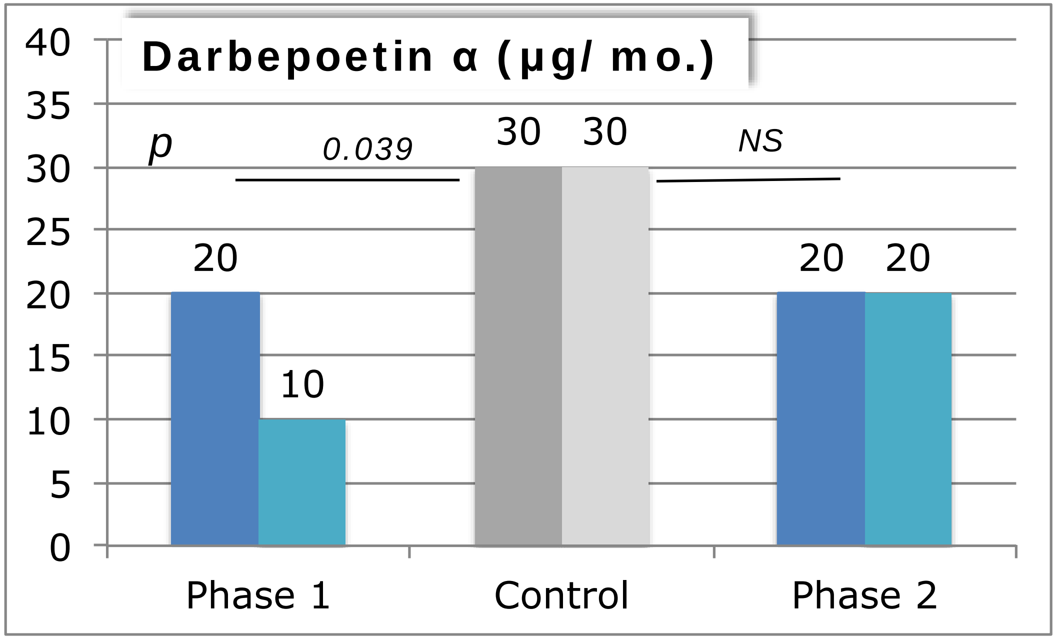


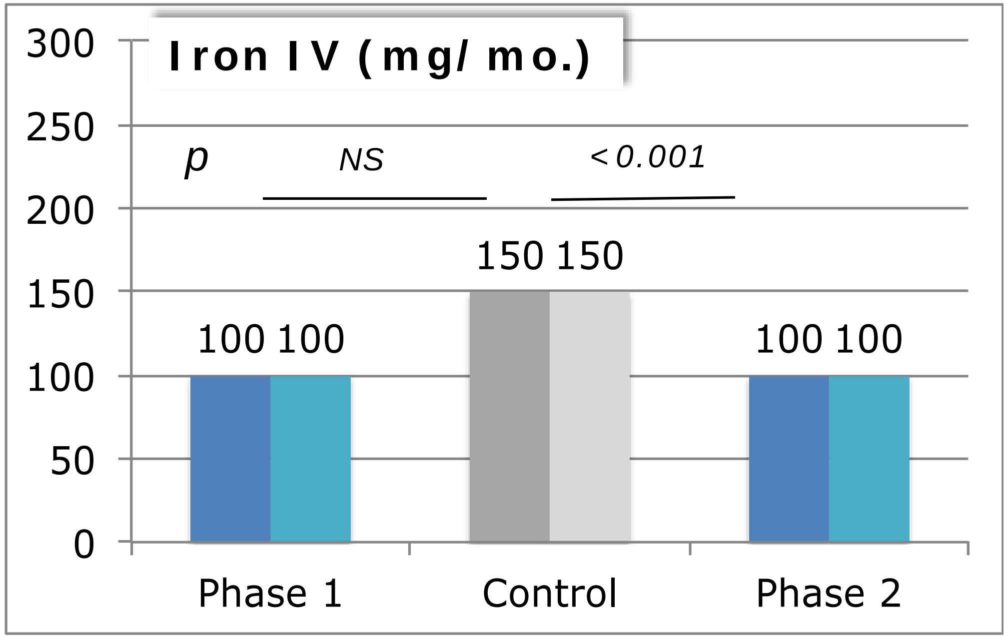


* Number of Hb measurements

Bucalo ML et al, Nefrol. 2018;38(5):491–50

Secondary Outcome
ESA and Iron Consumption

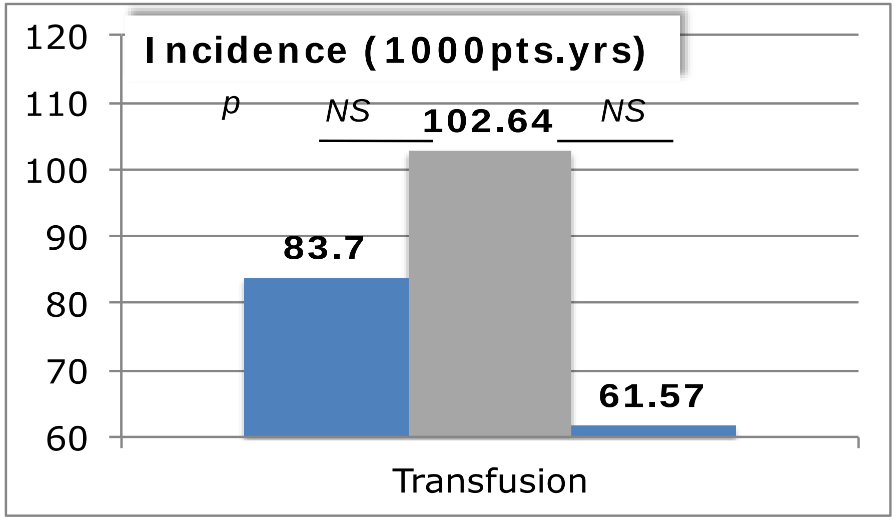


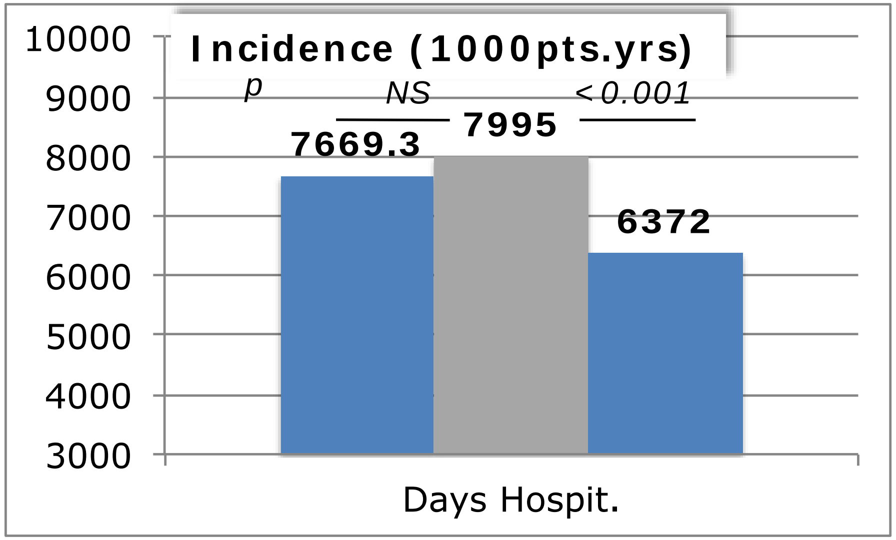


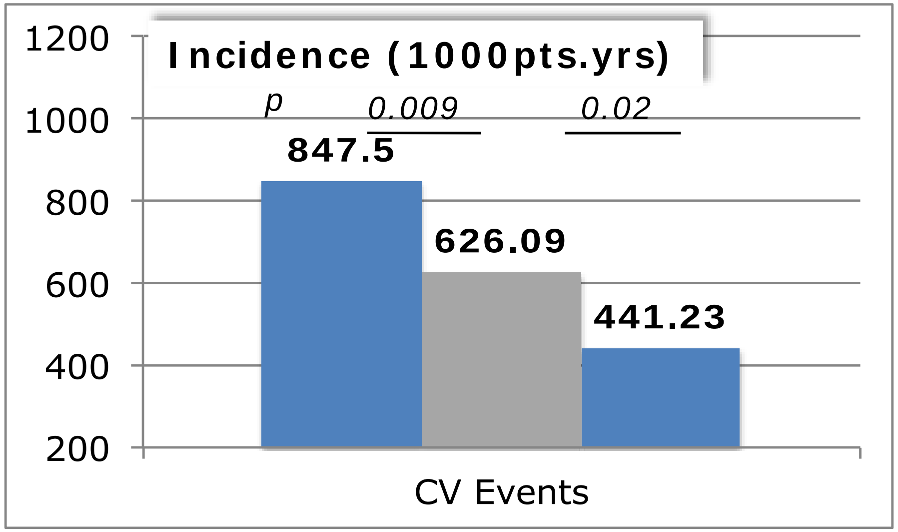
Bucalo ML et al, *Nefrol*. 2018;38(5):491–50

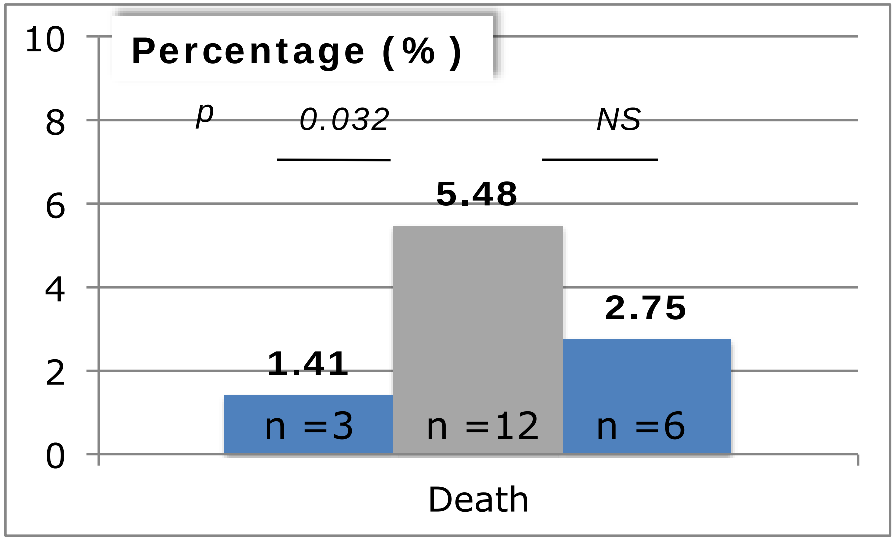
Secondary Outcome

Transfusion – Morbidity - Mortality



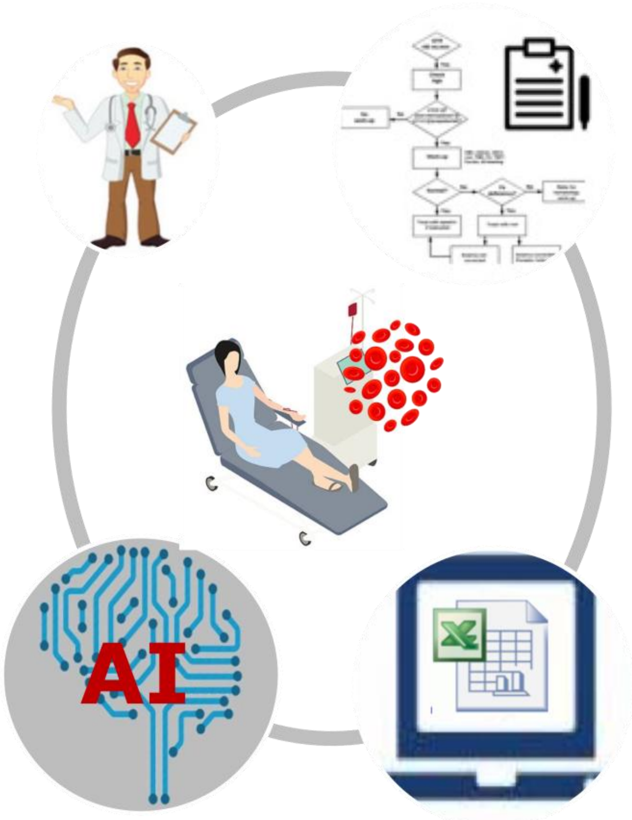






Bucalo ML et al, *Nefrol*. 2018;38(5):491–50

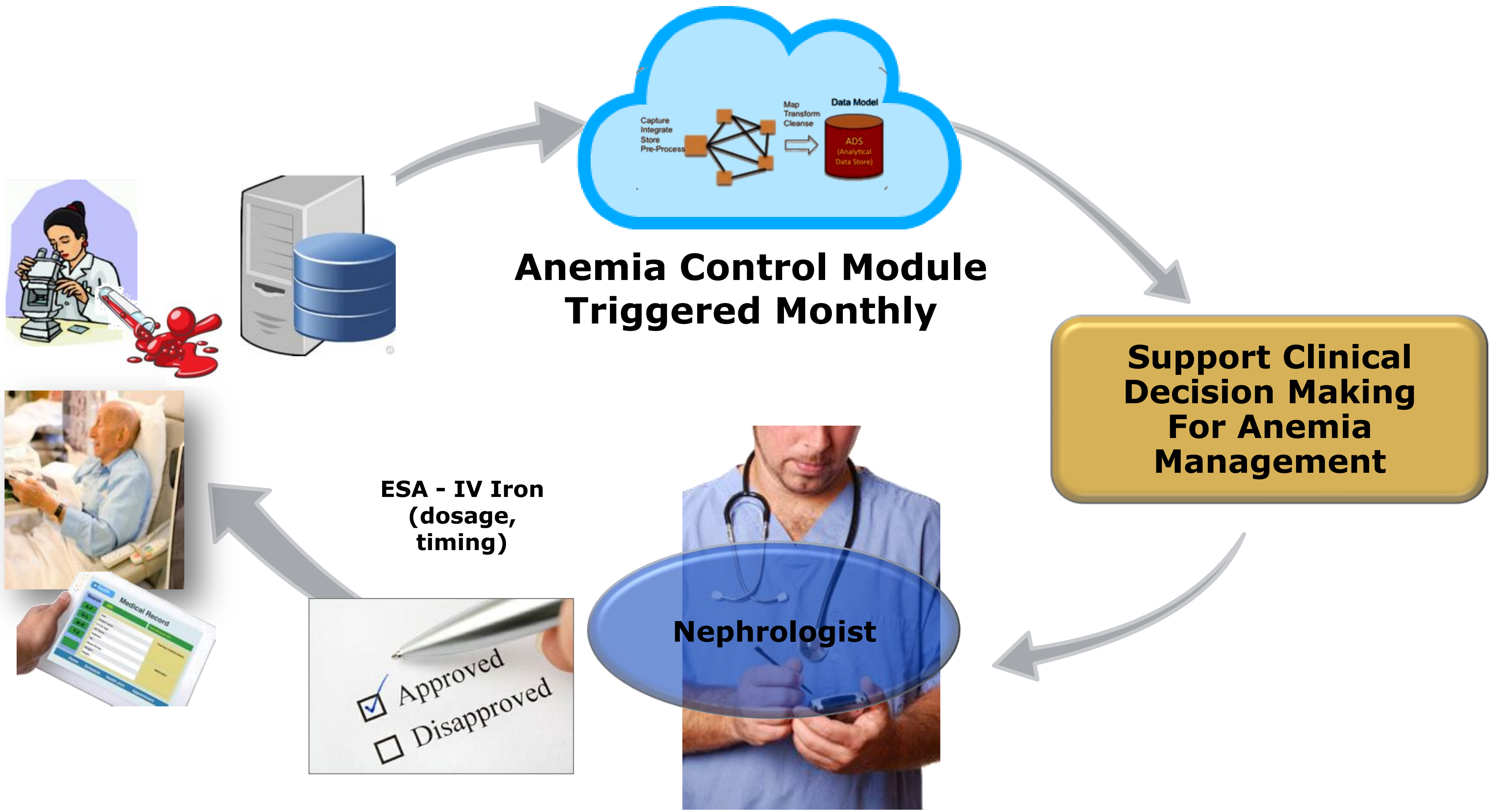
Agenda: From Algorithm to Artificial Intelligence



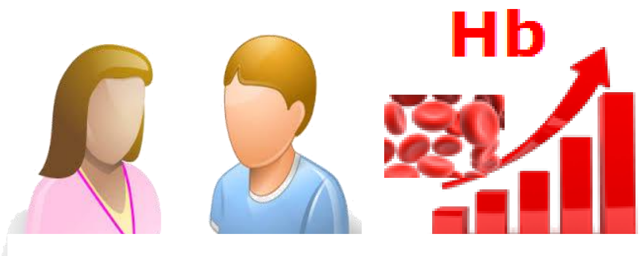
- Renal anemia: lesson learned in few decades
- Anemia correction: ESA, as a disruptive treatment in CKD treatment
- Anemia management: from clinical to artificial intelligence support
- **Take home message: what's next**

Anemia Control Module

Feedback Control Loop to Support Clinical Decision Making



AI is a Tool that Add Value to Care of HD Patients



$$\textbf{Value Based Care} = \frac{\textbf{Outcome}}{\textbf{Cost}}$$

Porter ME. *N Engl J Med.* 2010;363(26):2477-81.

In Brief… Benefits of AI in the Management of Anemia in HD Patients

- Increase number of patients in targets for Hb and iron markers
- Minimize Hb fluctuations over time
- Reduce significantly ESA and iron consumption
- Reduce variations in ESA/iron prescription
- Permit to identify potential causes of ESA resistance
- Provide information on ESA activity (sensitivity) and RBC life span (days)
- Prevent iron use imbalance (hemosiderosis) or ESA
- Reduce significantly cost associated with ESA/iron use
- Tend to reduce morbidity/mortality associated with anemia correction

Remaining Questions and Next Steps to be Validated

- Software and medical device require CE certification
- Software should complying with drug prescription
- Generalizability and extension to others erythropoietic stimulating agents needs to be validated
- Economical model has to be created since it is currently out of dialysis fees
- Liability of prescription (user/software) is a new concern