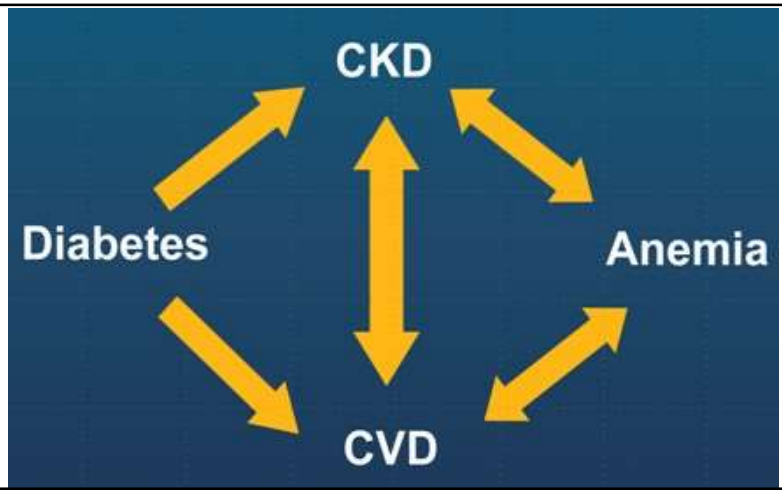
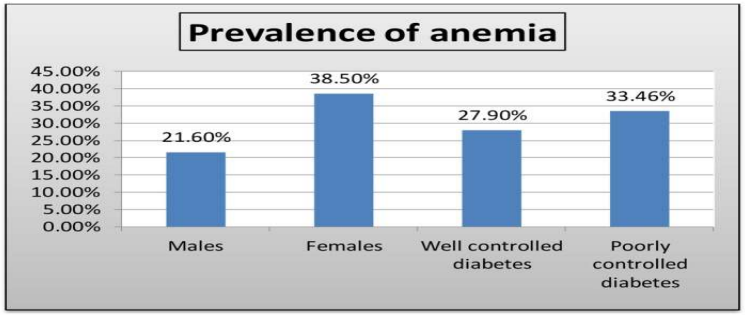
CKD - related Anemia Management. Is there any difference between Original Brand & Biosimilars?

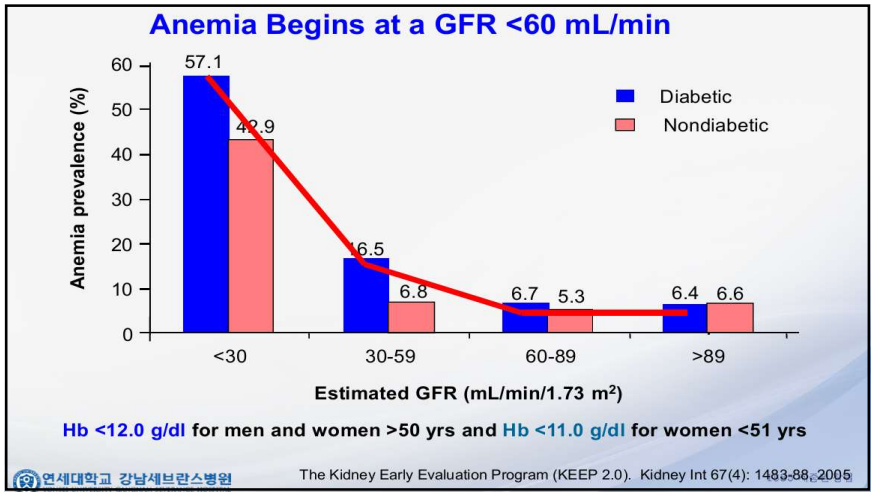
Prof Pham Van Bui
Univ. of Medicine Pham Ngoc Thach
Nguyen Tri Phuong Hospital
President, Society of the Nephrology-Dialysis Therapies
Invited Professor, Liege Univ. of Medicine, Belgium



Prevalence of Anemia in Type 2 Diabetic Patients

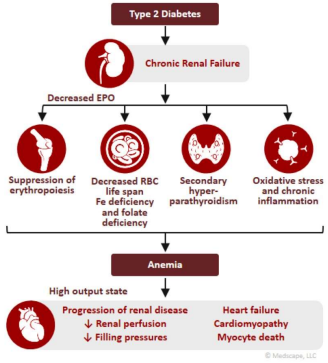


Salma M. AlDallal & Nirupama Jena(2018). *J Hematol* 2018 May; 7(2): 57–61



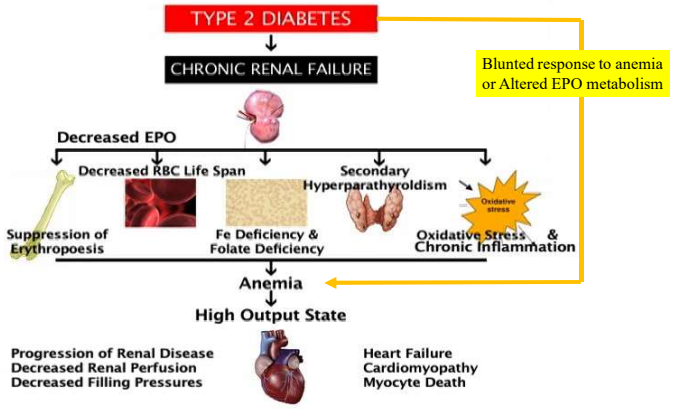
The Link Between T2D/CKD/CVD

- Patients with CKD = at risk for CV events
  - Patients with CVD = at risk for developing kidney disease progression
  - **If both conditions present: patients are at especially high risk**

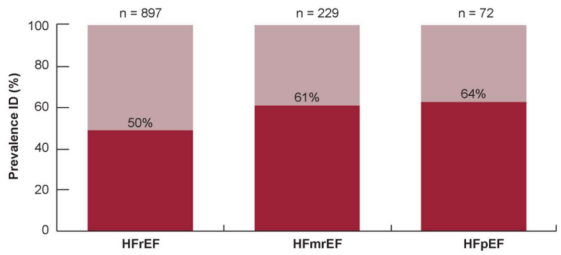


The risk of CVD and kidney disease is particularly high among patients with T2D

Forte V, et al. *IntechOpen*. 2011:273-282.



Prevalence of ID Across EF Spectrum of HF



ID is common in patients with HF, regardless of the type of EF

Martens P, et al. *Acta Cardiol*. 2018:73:115-123.

ID vs Anemia in CHF

ID ≠ Anemia

- ID defined as[a]
  - Serum ferritin < 100 µg/L or
  - Serum ferritin 100 to 299 µg/L and TSAT < 20%
- ID is a distinct clinical condition from anemia[b]
- Many patients with CHF have ID and anemia[b,c]
- But ID can exist in the absence of anemia[b,c]

a. Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-2200; b. Cappellini MD, et al. *Am J Hematol*. 2017;92:1068-1078; c. Klip IT, et al. *Am Heart J*. 2013;165:575-582.

Anemia in HF Patients

- Anemia and iron deficiency (ID) in patients with HF :
  - 2 important comorbidities common
  - Associated with poor clinical status & worse outcomes.
- Prevalence of anemia (Hb <13 g/dL/ ♂ & <12 g/dL/♀), regardless of HFrEF or HFpEF
  - ≈30% in stable and
  - ≈50% in hospitalized patients,

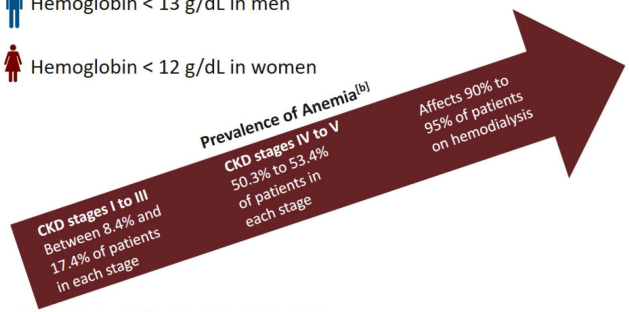
Inder S. Anand. Circulation. Anemia and Iron Deficiency in Heart Failure, Volume: 138, Issue: 1, Pages: 80-98, DOI: (10.1161/CIRCULATIONAHA.118.030099)

Anemia in CKD

World Health Organization definition of anemia[a]

Hemoglobin < 13 g/dL in men

Hemoglobin < 12 g/dL in women



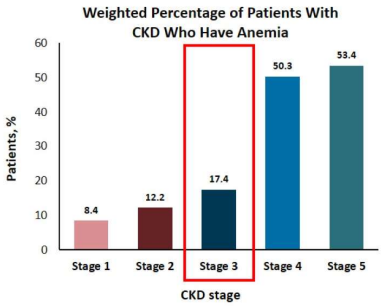
a. WHO. 2011; b. Stauffer ME, et al. *PLoS One*. 2014;9:e84943.

Anemia and CKD

31.4 million people in the United States have CKD[a]

4.8 million also have anemia[a]

- Prevalence 15.4% in patients with CKD and 6.3% in non-CKD
- Prevalence increases with CKD stage



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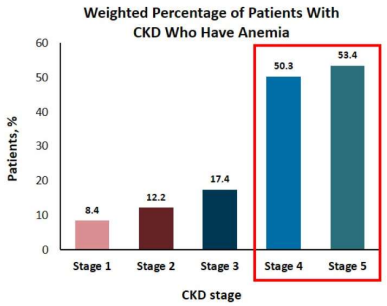

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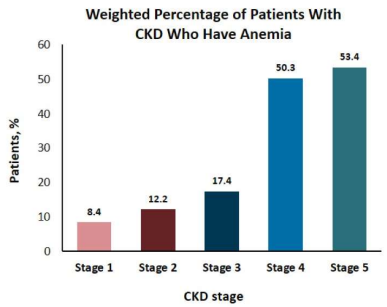
Anemia doubles mortality risk[b]

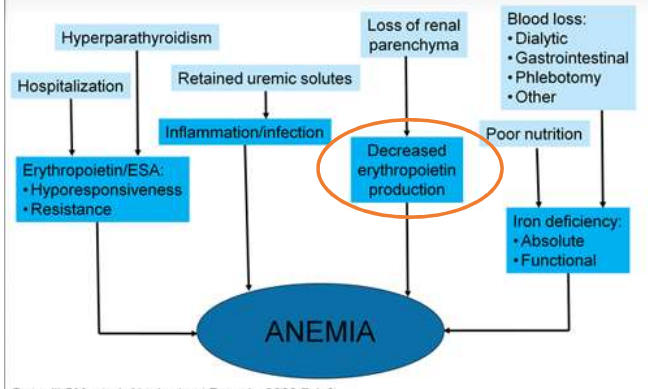
Severe anemia (Hb < 10.5 g/dL) increases risk for[c]:

- Mortality (HR 5.27)
- Cardiovascular hospitalization (HR 2.18)
- End-stage renal disease (HR 5.46)



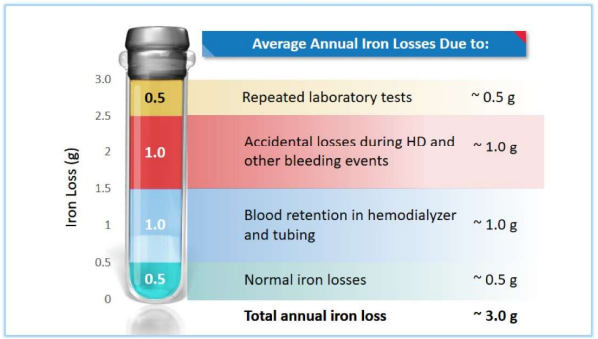
a. Stauffer ME, et al. *PLoS One*. 2014;9:e84943; b. Sato Y, et al. *Clin Exp Nephrol*. 2018;22:388-394;
c. Thorp ML, et al. *Nephrology (Carlton)*. 2009;14:240-246.

Anemia of CKD: Pathogenesis



Brunelli SM, et al. *Nephrology Rounds*. 2009;7:1-6.

Substantial Iron Losses in Patients Undergoing Hemodialysis



Kalantar-Zadeh K, et al. *Adv Chronic Kidney Dis*. 2009;16:143-151.

Reprinted from Advances in Chronic Kidney Disease, 16(2), Kalantar-Zadeh, K., et al., Intravenous Iron Versus Erythropoiesis-Stimulating Agents: Friends or Foes in Treating Chronic Kidney Disease Anemia?, pp. 143-151, Copyright (2009), with permission from Elsevier.

Anemia and CKD Associated With New-Onset AF

- 1232 AF/ 132 250 , mean F-U 13,8 năm → lower both the eGFR(<60 mL/min/1.73m^2) as well as [Hb], the greater the risk of AF.

Hemoglobin (g/dL)	Multivariable HR (95% CI)	*P*
≥15 to <18	2.11 (1.53–2.90)	<0.0001
≥13 to <15	3.00 (1.67–5.38)	<0.0001
<13 (anemia)	3.22 (2.43–4.19)	0.0003

*Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, body-mass index, total cholesterol, triglycerides, HDL cholesterol, smoking, alcohol consumption, and diabetes

Xu DZ et al(2014). *Am J Cardiol*

Anemia in the Elderly a Potential Dementia Risk Factor

- Among older adults, anemia is associated with an increased risk of developing dementia
- if there was anemia at baseline, the risk of dementia was increased by about 60%.

Yaff K. et al(2013) *Neurology*.81:528-533. Abstract

Vlagopoulos P. et al: cohort analysis(Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study and Framingham Offspring Study,)

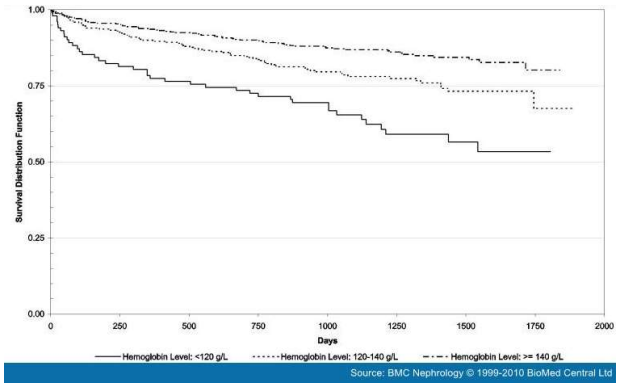
2770 pts with DM but No Anemia
245 pts with DM and Anemia
14% of the cohort had CKD
Mean follow-up: 8.6y

End point	DM+ ANEMIA+CKD	DM+ ANEMIA+ No CKD	DM+ CKD+ No ANEMIA	DM+ NoANEMIA + No CKD
Composite end point(%)	75	36	60	37
MI/fatal CAD(%)	35	13	30	19
Stroke(%)	23	7	15	9
All cause mortality(%)	68	28	52	24

Clinical outcomes in the overall cohort of subjects with DM +/- Anemia and/or CKD

Vlagopoulos P. et al(2005), JASN

Anemia and Chronic Kidney Disease are Potential Risk Factors for Mortality in Stroke Patients



Health Risks of Anemia in CKD

Compared with patients without anemia, those with severe anemia (Hb < 10.5 g/dL) have[a]

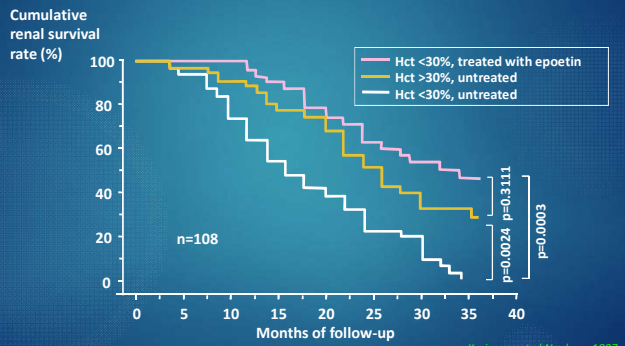
> 5× increased risk of dying

> 2× increased risk of cardiovascular hospitalization

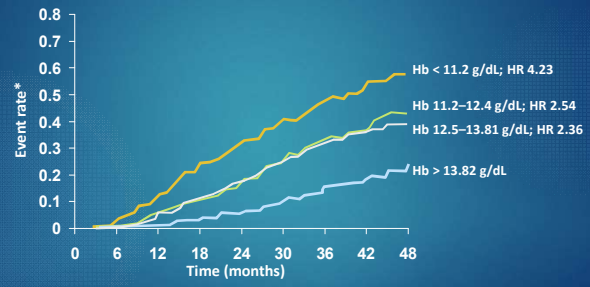
> 5× increased risk of end-stage kidney disease

Thorp ML, et al. *Nephrology (Carlton)*. 2009;14:240-246.

Anemia treatment can slow the progression of CRF



The RENAAL study



*Doubling of serum creatinine or ESRD.

HR = hazard ratio

Keane WF, et al. Kidney Int. 2003;63:1499-507

-In diabetic nephropathy: Anemia starts earlier and is more profound than other CKD

-Effects of EPO:

- **-Antioxidant**
- **-Antihypoxic**
- **-Anti-apoptotic**

-Hb < 10g/l and GFR < 60ml/min →↑CV, LVH, CHF

Early Epo treatment prevents:

- **-CV mortality – morbidity**
- **-Tubular lesions and interstitial fibrosis**
- **-Progression of CKD**

Dimkovic N (2003), *Med Pregl; 56(11-12): 529-535*
Murpey ST, Parfrey PS (2000), *Semin Nephrol 20(4): 350-355*

TREATING ANEMIA EARLY IN RENAL FAILURE PATIENTS SLOWS THE DECLINE OF RENAL FUNCTION: A RANDOMIZED CONTROLLED TRIAL.

- RCT: early versus deferred initiation of erythropoietin in nondiabetic predialysis patients with sCr 2 to 6 mg/dL and Hb 9 to 11.6 g/dL
  - Early treatment arm(n= 45): immediately started on 50 U/kg/wk of erythropoietin alpha
  - Deferred treatment arm(n= 43): start erythropoietin only when Hb decreased to <9 g/dL
- Primary end point: composite of doubling of creatinine, renal replacement, or death
- F-U: median of 22.5 months

Gouva C. Kidney International, Vol. 66 (2004), pp. 753–760

TREATING ANEMIA EARLY IN RENAL FAILURE PATIENTS SLOWS THE DECLINE OF RENAL FUNCTION: A RANDOMIZED CONTROLLED TRIAL.

Table 1. Baseline characteristics

	Early arm $N = 45$	Deferred arm $N = 43$	P value[a]
Female/male	20/25	18/25	0.98
Age, mean (SD), *years*	66.7 (10.4)	64.2 (12.2)	0.44
Weight, mean (SD), *kg*	72.3 (8.9)	70.4 (9.4)	0.44
Hemoglobin, mean (SD), *g/dL*	10.1 (0.5)	10.1 (0.6)	0.72
Hematocrit, mean (SD), %	30.8 (1.4)	31.0 (1.1)	0.58
Serum creatinine, mean (SD), *mg/dL*	3.27 (0.99)	3.39 (0.82)	0.27
Creatinine clearance, mean (SD), *mL/min*	25.7 (9.1)	22.3 (6.0)	0.14
History of hypertension, *N* (%)	42 (93)	36 (84)	0.19
24-hour protein, mean (SD), *g*	0.66 (0.39)	0.57 (0.36)	0.28

[a]Based on Mann-Whitney *U* test and chi-square test with continuity correction, as appropriate.

Gouva C. Kidney International, Vol. 66 (2004), pp. 753–760

TREATING ANEMIA EARLY IN RENAL FAILURE PATIENTS SLOWS THE DECLINE OF RENAL FUNCTION: A RANDOMIZED CONTROLLED TRIAL

Table 2. Hematologic and renal parameters at 12 months

	Early arm	Deferred arm	P value[a]
Hemoglobin, mean (SD), *g/dL*	12.9 (0.4)	10.3 (1.0)	<0.001
Hematocrit, mean (SD), %	38.4 (1.5)	31.4 (2.6)	<0.001
Serum creatinine, mean (SD), *mg/dL*	3.81 (1.43)	5.07 (2.39)	<0.001
Creatinine clearance, mean (SD), *mL/min*	21.9 (9.4)	16.1 (6.3)	<0.001

[a]*P* values are based on analysis of covariance adjusting for the baseline values. Last observation carried forward has been applied in the analyses, as described in **Methods**.

Gouva C. Kidney International, Vol. 66 (2004), pp. 753–760

TREATING ANEMIA EARLY IN RENAL FAILURE PATIENTS SLOWS THE DECLINE OF RENAL FUNCTION: A RANDOMIZED CONTROLLED TRIAL

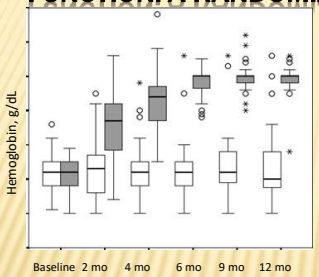


Fig. 1. Hemoglobin levels at baseline and during follow-up (at 2, 4, 6, 9, and 12 months) in the deferred (white boxes) and early (gray boxes) treatment groups. The box plots show the median (horizontal line), interquartile range (box), and range (whiskers), unless there are also outliers and/or extreme values with 1.5 to 3 and >3 box lengths, respec- tively, away from the edge of the box, in which case these are shown by circles and asterisks.

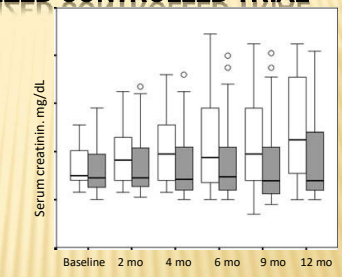


Fig. 2. Serum creatinine levels at baseline and during follow-up (at 2, 4, 6, 9, and 12 months) in the deferred (white boxes) and early (gray boxes) treatment groups. The box plots show the median (horizontal line), interquartile range (box), and range (whiskers), unless there are also outliers and/or extreme values with 1.5 to 3 and >3 box lengths respectively, away from the edge of the box, in which case these are shown by circles and asterisks. Not shown are two creatinine values above 10 mg/dL

Gouva C. Kidney International, Vol. 66 (2004), pp. 753–760

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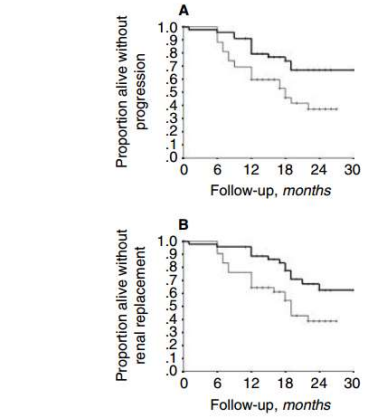


Fig. 3. Kaplan-Meier plots for doubling of creatinine, renal replacement, or death (*A*), and renal replacement or death (*B*) in the early (thick line) versus deferred (thin line) treatment arms.

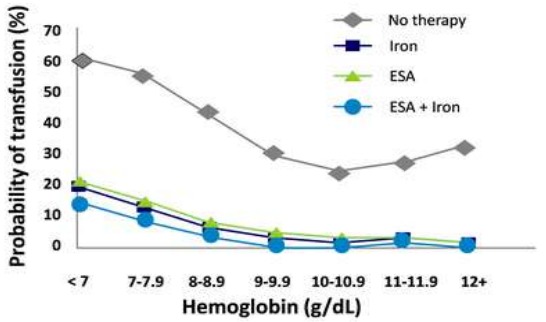
ESA Use for Anemia in CKD and CV Outcomes Trials

Four Randomized Controlled Trials of Hemoglobin-Raising in Chronic Kidney Disease

	NHCT[a,b]	CHOIR[c]	CREATE[d]	TREAT[e]
Population	Patients with chronic heart failure and end-stage renal disease on dialysis	Chronic kidney disease	Chronic kidney disease	Chronic kidney disease with diabetes
Hemoglobin target	10 vs 14 g/dL	13.5 vs 11.3 g/dL	> 13 vs 11 g/dL	> 13 vs 9 g/dL
Target achieved?	No	No	Yes	Yes
Primary outcomes	Time to death or first myocardial infarction	Composite of death, myocardial, infarction, hospitalization for chronic heart failure, stroke	Time to first cardiovascular event	Composite of death or a cardiovascular event and death or end-stage renal disease
Risks with higher hemoglobin level	Trend toward increased risk of primary outcome resulted in early study interruption	Increased risk of primary outcome	Trend toward risk increase that was nonsignificant: no benefits	No risk increase or reduction
Other results	Higher rate of thrombosis in high-target group		Improved quality of life	Higher rate of stroke

a. Besarab A, et al. *N Engl J Med*. 1998;339:584-590; b. Epogen® (epoetin alfa) PI 1989;
c. Singh AK, et al. *N Engl J Med*. 2006;355:2085-2098; d. Drüeke TM, et al. *N Engl J Med*. 2006;355:2071-2084; e. Pfeffer MA, et al. *N Engl J Med*. 2009;361:2019-2032.

Transfusion Rates by Hgb Level According to Treatment Status



Lawler EV, et al. *Clin J Am Soc Nephrol*. 2010;5:667-672.

Erythropoietin
IV vs Subcutaneous

- Retrospective cohort study of 62,710 adults on hemodialysis
- Treated with either erythropoietin IV vs subcutaneous administration
- Higher erythropoietin doses needed with IV vs subcutaneous (on average, 25%)
- Risk of early death or hospitalization for CHF or myocardial infarction higher with IV-administered erythropoietin

Wright DG, et al. *Clin J Am Soc Nephrol*. 2015;10:1822-1830.

FDA Warning on Use of ESAs

- Using ESAs to target a Hb > 11 g/dL increases the risk of serious adverse CV events and does not provide additional benefit
  - No clinical trial has identified a Hb target level, ESA dose, or dosing strategy that does not increase these risks

Patients with CKD

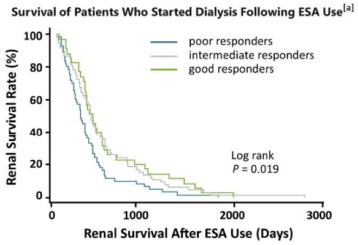
If Hb > 10 g/dL, reduce or interrupt the dose of ESA and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions

Patients with CKD on dialysis

If Hb approaches or exceeds 11 g/dL, reduce or interrupt the dose of ESA

FDA.gov. FDA Drug Safety Communication 2017.

ESA Hyporesponsiveness



- High-dose ESA can overcome hyporesponse[c]

Poor ESA response associated with poorer survival[a]
Poor responsiveness may be acute or chronic[b]

a. Kuwahara M, et al. *Clin Exp Nephrol*. 2015;19:598-605; b. Sibbel SP, et al. *BMC Nephrol*. 2015;16:144; c. Locatelli F, et al. *Am J Nephrol*. 2017;45:187-199.

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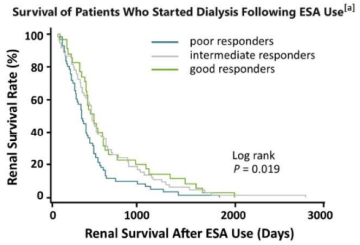

- High-dose ESA can overcome hyporesponse[c]
- High-dose ESA associated with increased risk of[c]:
  - Hypertension
  - Seizures
  - Thrombosis
  - Stroke
  - Heart failure

Poor ESA response associated with poorer survival[a]
Poor responsiveness may be acute or chronic[b]

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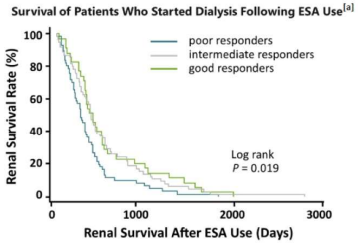
ESA Hyporesponsiveness



- High-dose ESA can overcome hyporesponse[c]
- High-dose ESA associated with increased risk of[c]:
  - Hypertension
  - Seizures
  - Thrombosis
  - Stroke
  - Heart failure
- Clinical need for alternative treatment options

Poor ESA response associated with poorer survival[a]
Poor responsiveness may be acute or chronic[b]

a. Kuwahara M, et al. *Clin Exp Nephrol*. 2015;19:598-605; b. Sibbel SP, et al. *BMC Nephrol*. 2015;16:144; c. Locatelli F, et al. *Am J Nephrol*. 2017;45:187-199.

Images are only used for educational purposes

What Is a Biosimilar?

- A biosimilar, also referred to as a "follow-on biologic," is a biological product that is marketed as an alternative to the original biologic, which shares highly similar, but not identical, safety, and efficacy profiles with the original biologic

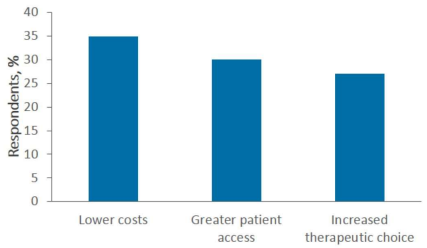
Eleryan MG, et al. *Clin Cos Investig Dermatol*. 2016;9:135-142.

Differences Between Development of Generics and Biosimilar Medications

	Classic Generics	Biosimilars
Manufacturing	Chemical synthesis Simple fermentation Standard analytics	Genetically modified cell lines Complex fermentation Complex purification process Formulation Complex analytical characterization
Preclinical (tissue/animal)	Generally none	In vitro/in vivo bioassay Toxicity studies Local tolerance studies PK/PD studies
Clinical	Generally a bioavailability study	PK/PD studies Clinical efficacy/tolerability/safety studies Postmarketing surveillance

McCamish M, et al. *mAbs*. 2011;3:209-217.

Physician Assessment of the Value of Biosimilars to the Healthcare System



Results of a panel discussion with medical representatives of 2 US-based healthcare systems (n=10)

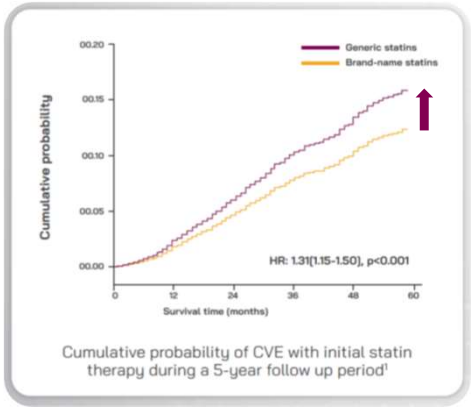
Manolis CH, et al. *J Manag Care Spec Pharm*. 2016;22:S3-S9.

Patient Attitudes Toward Biosimilars: Survey of Patients With IBD

Concern	IBD Survey Population (n=383), n (%)
Concerning biosimilars, you worry	
That the molecular basis of the biosimilar is different from that of the reference drug	126 (32.9)
About safety	178 (46.5)
About efficacy	148 (38.6)
No specific concerns about biosimilars	101 (26.4)
If a biosimilar is prescribed and explained to you by your treating physician	
You will be fully confident	123 (32.1)
You will be worried, but you will accept the treatment	146 (38.1)
You will probably not accept it	48 (12.5)
You believe biosimilars are like, or close to, generic drugs	243 (63.5)

Most patients were not familiar with biosimilars, and those who were had doubts and concerns about the biosimilars' safety and efficacy.
Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2017;11:128-133.

STATINS – Hoạt chất gốc và generic – Biến cố Tim mạch – Tây Ban Nha (n=13,244)



Cumulative probability of CVE with initial statin therapy during a 5-year follow up period[1]

Xác suất xuất hiện biến cố tim mạch: Generics so với hoạt chất gốc cao hơn

31%

 Sicras-Mainar et al. Lipids in Health and Disease (2018) 17:277

CVE: Cardio-Vascular Event

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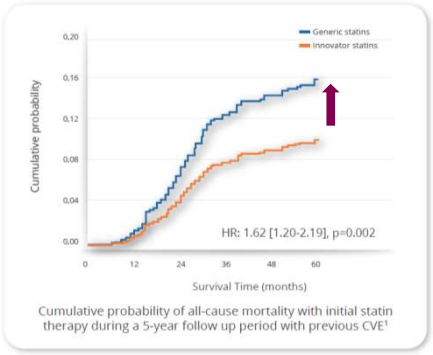
STATINS – Biệt dược gốc vs Generic – for cve – Tử vong do mọi nguyên nhân
Tây Ban Nha (n=13,244)



Cumulative probability of all-cause mortality with initial statin therapy during a 5-year follow up period with previous CVE[1]

Generic vs Original Statin,
Tử vong do mọi nguyên nhiên
cao hơn có ý nghĩa thống kê ở nhóm dùng generics

62% có biến cố TM trước đó.

 ACS: Acute Coronary Syndrome; CVE: Cardiovascular Event
Sicras-Mainar et al. Lipids in Health and Disease (2018) 17:277

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Best Medical Physicians of the Year 2019: Harry Lever **alarm on Ineffective Generics**

Sheriff" cardiologist sounds the alarm on Ineffective Generics

Harry Lever, MD, is a crusader against harmful generics drugs.

- 74yo cardiologist, directs the Cleveland Clinic's Hypertrophic Cardiomyopathy Center, wrote to FDA about his concerns that generic versions of Toprol XL were ineffective.
- For years, **his patients** who had **switched** from the brand name Toprol XR(Metoprolol) **to a generic version had complained about chest pain and other symptoms**
- **When his patient put back on the brand name TOPROL XR , the symptoms disappeared.**
- Lever is the one of the first in US to raise the alarm about **ineffective and even harmful generic drugs, largely imported from India+China.** "I wish it was more commonly known. **Everybody thinks everything is OK, but it's not…It's important this stuff works,**" said Lever

Summary and Conclusions

- Biosimilars are not generics, but then neither are they exact copies of bio-originators
  - Therefore regulatory bodies need to ensure that appropriate analytical, preclinical, and clinical studies are done to ensure comparable safety and efficacy between biosimilar and bio-originator
- Switching between a bio-originator and a biosimilar appears not to compromise efficacy and safety
  - However, more studies, and more real-world data, will be needed to ensure that safety is maintained
  - Multiple switching, between biosimilar and biosimilar, remains an unknown
- Extrapolation of clinical trial results between disease states, such as rheumatic disease and gastrointestinal diseases should proceed with caution, since safety and immunogenicity issues may arise
- Settling upon biosimilar naming conventions is critically important


Thank you for
your attention