Managing CKD Anemia with 2020 vision

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Outline

- Anemia – a few thoughts
- How we got here – our Anemia Management Protocol
- Recent evidence to consider – what the PIVOTAL trial adds to Normal Hematocrit, DRIVE, DRIVE 2, CREATE, CHOIR and TREAT
- Comparing our protocol with PIVOTAL
- HIF inhibitors and SGLT2 inhibitors
- Steps moving forward for managing anemia in BC
  - Renal Community input
  - Incorporating PROMIS analytics

Anemia

A few thoughts

Co-morbidities of CKD impacting outcomes

- Anemia
- Bone disease
- Cardiovascular disease(s)
- Depression
- Infections
- Impaired cognition
- Malnutrition

Multiple medications
Multiple events
Multiple interactions

From Dr. A Levin

Anemia : The Facts

- Hgb values vary within normal populations
  - Male vs female
  - “Bell curve” distribution
  - Altitude

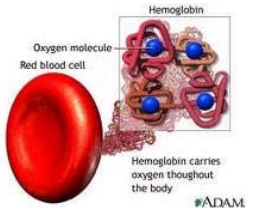
- In all populations studied, lower Hgb is associated with poor outcomes
  - General populations
  - Disease specific
    - Cancer, CHF, GI, Autoimmune diseases
    - CKD, Dialysis and Transplant

From Dr. A Levin

Chronic Kidney Disease Populations: Anemia

- Important comorbidity
  - Multi-factorial : iron, ESA resistance, ESA deficiency (relative), inflammation

- Associated with symptoms : Patient reported outcomes…
  - Fatigue, cognitive dysfunction
  - Exercise intolerance

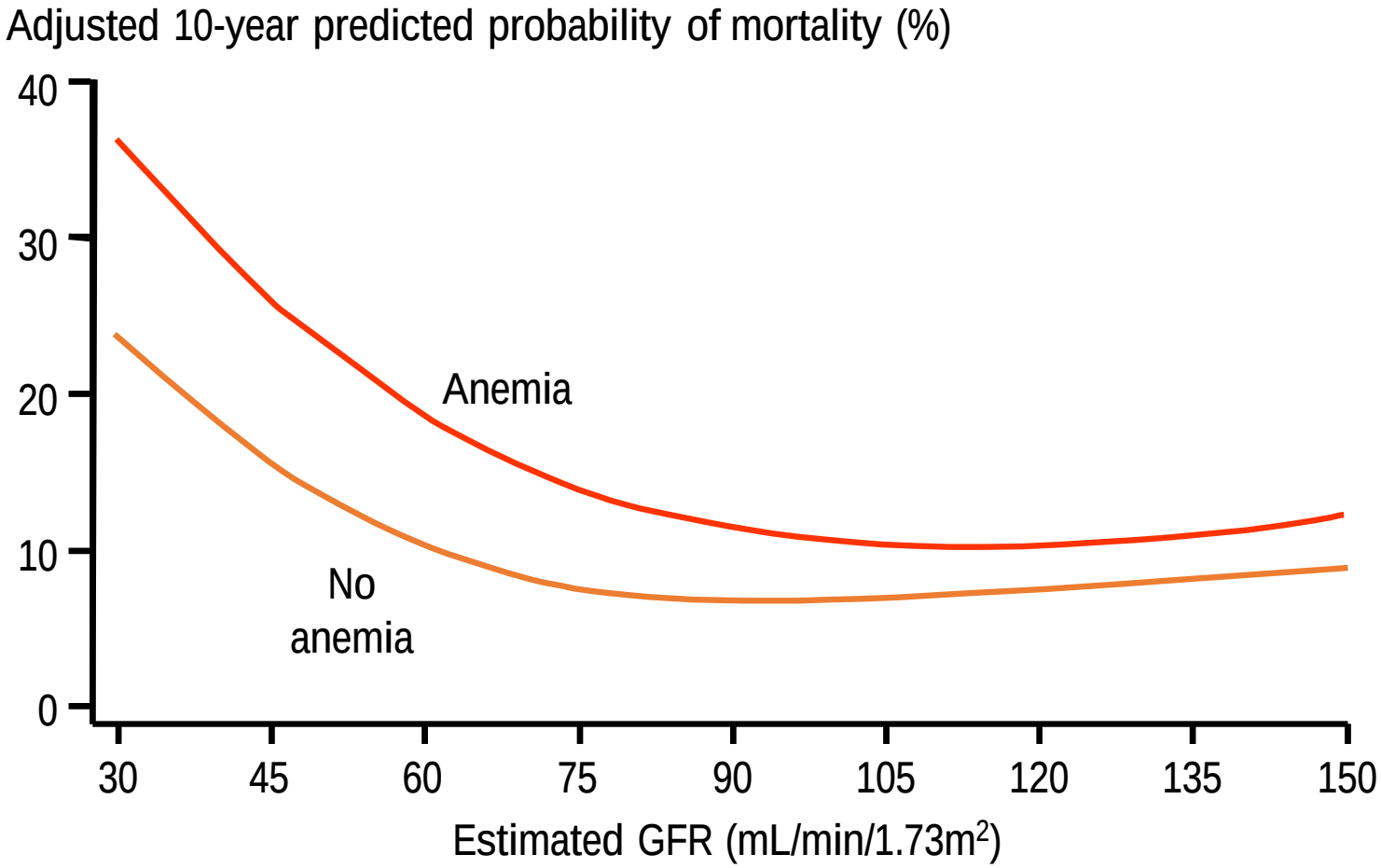


- Associate with adverse outcomes:
  - LVH, CHF and worsening angina symptoms
  - Transfusions: interfering with transplantability
  - CVE, hospitalizations
  - Death

From Dr. A Levin

Consistent Association : All-Cause Mortality in CKD

By GFR and anemia – 10-year ARIC



Anemia defined as Hb <13.5 g/dL in men, <12 g/dL in women

Astor et al 2004

From Dr. A Levin

Association of Anemia in CKD : consistent and persistent

	Dialysis	CKD
• Ischemic Heart Disease	x	x
• LVH	x	x
• Impaired Quality of Life	x	x
• Reduced Exercise Capacity	x	x
• Impaired Cognition	x	
• Hospital Stay	x	x
• Mortality	x	x

From Dr. A Levin

What has the “AMP” accomplished?

- Reduction in costs
- Greater % of patients in target (Hemoglobin, TSAT, Ferritin)
- Achieving target sooner
- Avoiding harm (MI, hypertension, stroke, hospitalizations)?
- Standardization based on evidence?
- Fewer blood transfusions?
- Lower death rate?
- More vascular access thrombosis & infections??

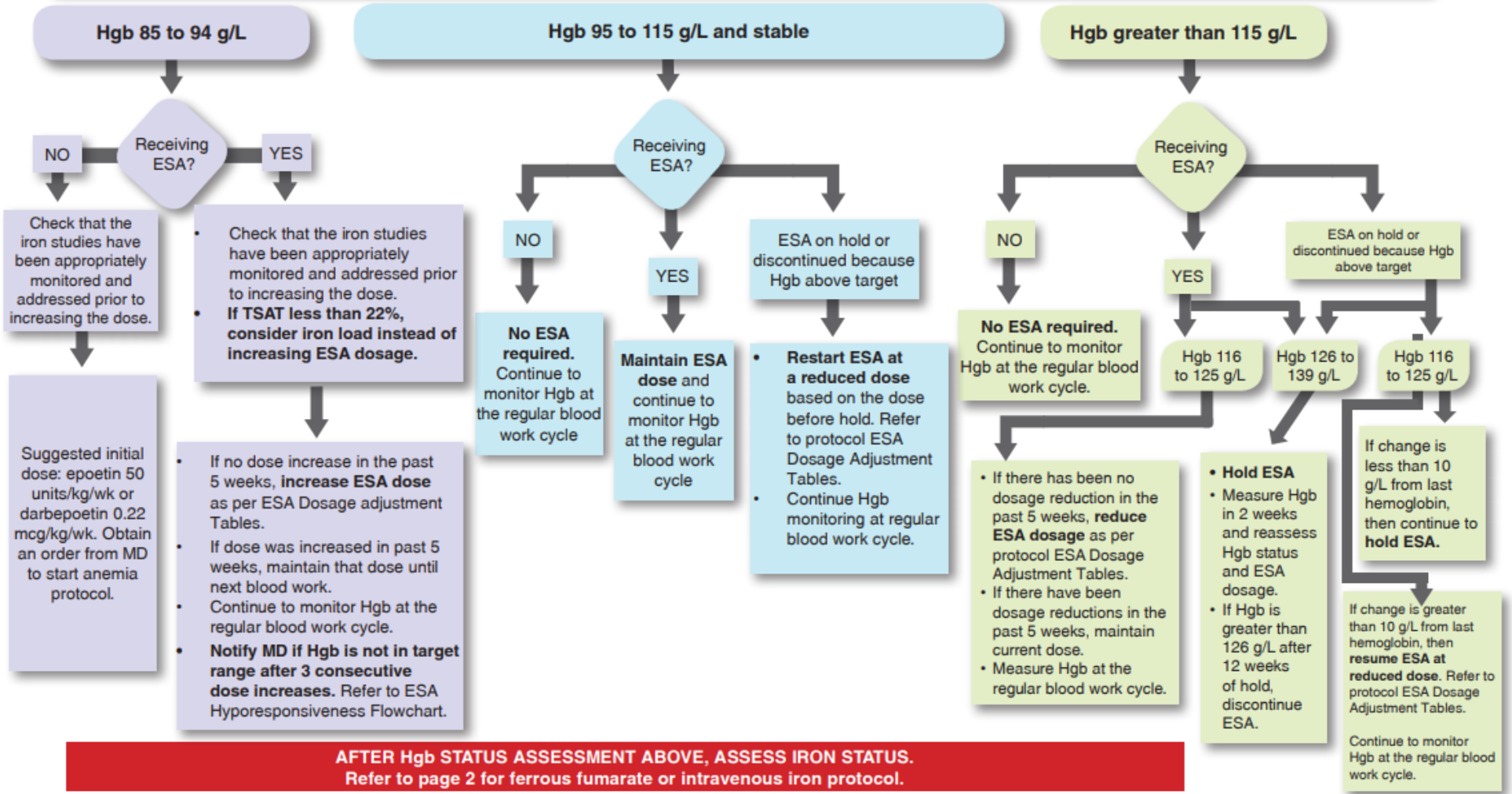
BC Anemia Protocol

CKD non-dialysis, dialysis, peritoneal dialysis

BCPRA CKD Non-Dialysis Anemia Management Protocol

The following protocol, on order of physician, transfers anemia management of CKD non-dialysis patients to non-physician staff (i.e. RNs and renal pharmacists). **The following protocol is intended to serve as a guide and cannot replace clinical judgement.** The recommendations included may be inappropriate for specific clinical situations (e.g. patients with hemochromatosis, thalassemia, PRCA, allergy to IV iron or an erythropoiesis stimulating agent (ESA), hx of stroke, active malignancy, hx of malignancy, etc.). The lowest ESA dosage to achieve acceptable Hgb range should be used. This algorithm is based on the assumption that the patient is compliant to medication and blood work.
Note: ESA refers to both epoetin alfa (Eprex®) and darbepoetin alfa (Aranesp®).

Any change in Hgb greater than or equal to 15 g/L, OR if Hgb is less than 85 g/L OR if Hgb is greater than 139 g/L AND on ESA (or ESA on hold) → Notify MD



AFTER Hgb STATUS ASSESSMENT ABOVE, ASSESS IRON STATUS.
Refer to page 2 for ferrous fumarate or intravenous iron protocol.

BCPRA CKD Non-Dialysis Anemia Management Protocol

BCRenal an agency of the Provincial Health Services Authority

PAGE 2: ASSESS IRON STATUS (Standard Iron Parameters — TSAT & Ferritin)

If at anytime the serum ferritin is above 1000 mcg/L, or the patient is on IV antibiotics or has signs and symptoms of sepsis (e.g. temperature greater than 38°, chills, rigors, unexplained hypotension), notify the MD to assess ongoing iron.

Notify MD if ferritin less than 20 mcg/L

TSAT less than 22%
REPLETE IRON STORES

If patient is currently not receiving iron therapy:
- **Contact MD to start ferrous fumarate (e.g. 300 mg po HS)**
- If TSAT less than 10%, order ferrous fumarate 300 mg po HS x 1 week, then 600 mg po HS

If patient is currently receiving oral iron therapy:
- Assess iron compliance and proper administration (empty stomach)
- Increase ferrous fumarate by 300 mg/day as tolerated (max.

If patient's Hgb gr
ferrous fumarate d

Notify MD if iron p
consecutive blood

If oral iron ineffect
consider giving IV

Measure TSAT and f
cycle and reas

TSAT 22% to 49%
MAINTAIN IRON STORES

If receiving PO iron:
Continue current maintenance dose

If PO iron is currently on hold due to iron overload:
Consider restarting ferrous fumarate 300 mg po HS (this becomes new maintenance dose)

TSAT greater than or equal to 50%
POSSIBLE IRON OVERLOAD

HOLD IRON

Measure TSAT and ferritin at next routine blood work cycle and reassess iron dosage regimen.

tify MD if iron indices igh for 3 consecutive od work cycles.

<u>If patient is unable to tolerate or adhere to oral iron regimen:</u>

Schedule IV iron regularly as per nephrologist's prescription. Measure TSAT and ferritin every 3 months (and at least 1 week after last IV iron dose).

<u>Usual maximum single doses tolerated of common agents:</u>

Iron sucrose (Venofer®) 300 mg IV over 3 hours
Iron dextran (DexIron®) 500 mg IV over 3 to 4 hours
Sodium ferric gluconate (Ferrlecit®) 125mg IV over 1 hour

on blood work appears
al compared to previous
(e.g. replacement of
ores, TSAT goes from
an 25% to greater than
repeat the blood work
initiating next action.

CKD NON-DIALYSIS ANEMIA MANAGEMENT PROTOCOL: ESA DOSING ADJUSTMENT TABLES

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The following tables provide guidance for most dosage adjustments. If a patient's Hgb cannot be maintained within the desired range with 3 consecutive dose modifications using the dosage schedule below, contact a nephrologist or renal pharmacist for advice. If a patient's erythropoiesis stimulating agent (ESA) dosage is not available in the tables below, please contact a nephrologist for ESA dosage modification. The lowest ESA dosage to maintain Hgb within acceptable range should be used.

Darbepoetin Alfa (Aranesp®) Dosage Adjustment Table

Pre-filled syringes available in CKD patients include: 10 mcg, 20 mcg, 30 mcg, 40 mcg, 50 mcg, 60 mcg, 80 mcg, 100 mcg, 130 mcg and 150 mcg.

Current Dose	Increase Dose*	Decrease Dose*
10 mcg subcut every 2 weeks	20 mcg subcut every 2 weeks	D/C, check Hgb in 2 weeks
20 mcg subcut every 2 weeks	30 mcg subcut every 2 weeks	10 mcg subcut every 2 weeks
30 mcg subcut every 2 weeks	40 mcg subcut every 2 weeks	20 mcg subcut every 2 weeks
40 mcg subcut every 2 weeks	50 mcg subcut every 2 weeks	30 mcg subcut every 2 weeks
50 mcg subcut every 2 weeks	60 mcg subcut every 2 weeks	40 mcg subcut every 2 weeks
60 mcg subcut every 2 weeks	80 mcg subcut every 2 weeks	50 mcg subcut every 2 weeks
80 mcg subcut every 2 weeks	100 mcg subcut every 2 weeks	60 mcg subcut every 2 weeks
100 mcg subcut every 2 weeks	130 mcg subcut every 2 weeks	80 mcg subcut every 2 weeks
130 mcg subcut every 2 weeks	150 mcg subcut every 2 weeks	100 mcg subcut every 2 weeks
150 mcg subcut every 2 weeks	100 mcg subcut every 1 week	130 mcg subcut every 2 weeks
100 mcg subcut every 1 week	130 mcg subcut every 1 week	150 mcg subcut every 2 weeks
130 mcg subcut every 1 week	150 mcg subcut every 1 week	100 mcg subcut every 1 week
150 mcg subcut every 1 week	No further increase, check with nephrologist	130 mcg subcut every 1 week

*For dosage increase or decrease, change interval to use up current syringes before starting new dosage. Refer to ESA Dosing Interval Adjustment Table.

Epoetin Alfa (Eprex®) Dosage Adjustment Table

Prefilled syringes available in CKD patients include: 1000 units, 2000 units, 3000 units, 4000 units, 5000 units, 6000 units, 8000 units and 10,000 units.

Current Dose	Increase Dose*	Decrease Dose*
1000 units subcut every 1 week	2000 units subcut every 1 week	D/C, check Hgb in 2 weeks
2000 units subcut every 1 week	3000 units subcut every 1 week	1000 unit subcut every 1 week
3000 units subcut every 1 week	4000 units subcut every 1 week	2000 units subcut every 1 week
4000 units subcut every 1 week	5000 units subcut every 1 week	3000 units subcut every 1 week
5000 units subcut every 1 week	6000 units subcut every 1 week	4000 units subcut every 1 week
6000 units subcut every 1 week	8000 units subcut every 1 week	5000 units subcut every 1 week
8000 units subcut every 1 week	10,000 units subcut every 1 week	6000 units subcut every 1 week
10,000 units subcut every 1 week	6000 units subcut twice per week	8000 units subcut every 1 week
6000 units subcut twice per week	8000 units subcut twice per week	10,000 units subcut every 1 week
8000 units subcut twice per week	10,000 units subcut twice per week	6000 units subcut twice per week
10,000 units subcut twice per week	8000 units subcut 3 times per week	8000 units subcut twice per week
8000 units subcut 3 times per week	10,000 units subcut 3 times per week	10,000 units subcut twice per week
10,000 units subcut 3 times per week	No further increase, check with nephrologist	8000 units subcut 3 times per week

For dosage increase or decrease, change interval to use up current syringes before starting new dosage. Refer to ESA Dosing Interval Adjustment Table.

NON-DIALYSIS CKD ANEMIA MANAGEMENT PROTOCOL: ESA DOSING ADJUSTMENT TABLES

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DARBEPOETIN ALFA(ARANESP®) DOSING INTERVAL ADJUSTMENT TABLE (to use up current supplies at home)

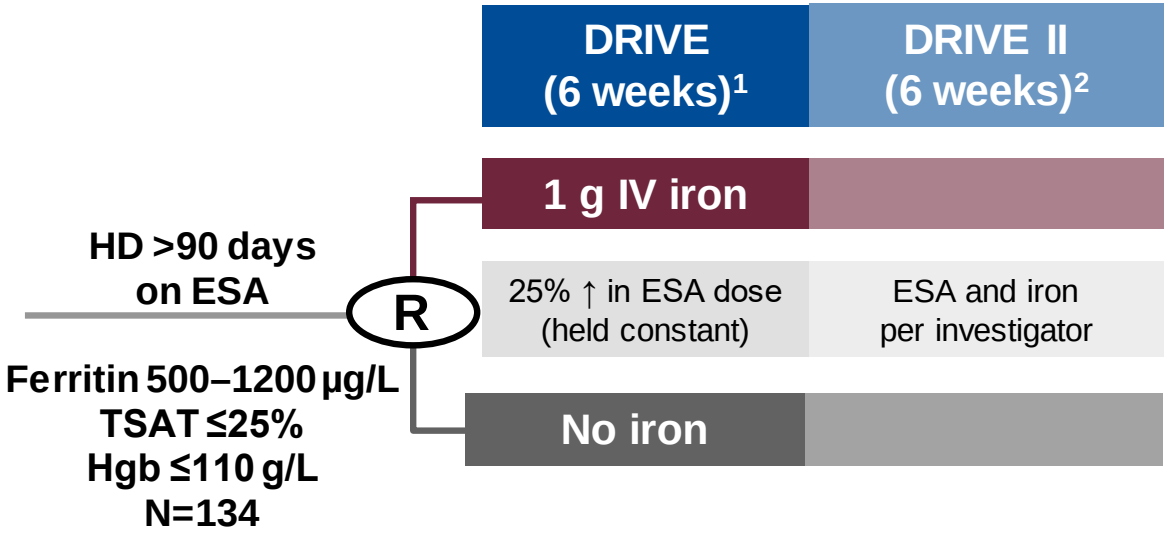
CURRENT DOSE	INCREASED DOSE CHANGE INTERVAL TO	DECREASED DOSE CHANGE INTERVAL TO
10 mcg every 2 weeks	Every 10 days	HOLD
20 mcg every 2 weeks		Every 21 days
30 mcg every 2 weeks		
40 mcg every 2 weeks		
50 mcg every 2 weeks		
60 mcg every 2 weeks		
80 mcg every 2 weeks		
100 mcg every 2 weeks		
130 mcg every 2 weeks		
150 mcg every 2 weeks		
100 mcg every 1 week	Every 5 days	Every 10 days
130 mcg every 1 week		
150 mcg every 1 week	Check with MD	

EPOETIN ALFA (EPREX®) DOSING INTERVAL ADJUSTMENT TABLE (to use up current supplies at home)

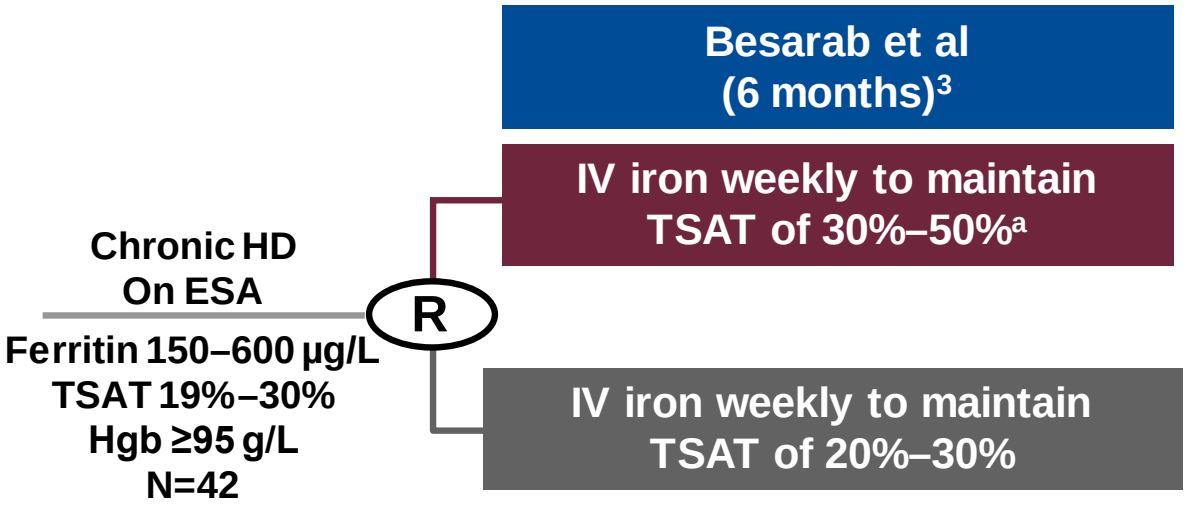
CURRENT DOSE	INCREASED DOSE CHANGE INTERVAL TO	DECREASED DOSE CHANGE INTERVAL TO
1,000 units every 1 week	Every 5 days	HOLD
2,000 units every 1 week		Every 10 days
3,000 units every 1 week		
4,000 units every 1 week		
5,000 units every 1 week		
6,000 units every 1 week		
8,000 units every 1 week		
10,000 units every 1 week		
6,000 units twice per week	Every 3 days	Every 5 days
8,000 units twice per week		
10,000 units twice per week		
8,000 units three times per week	Every 2 days	Every 3 days
10,000 units three times per week	Check with MD	

Updated September 2014

More iron reduces ESA dose safely



- Among anemic patients with 'high' ferritin, IV iron ↑ Hgb and allowed for ↓ ESA use
- No safety signals emerged over 12 weeks

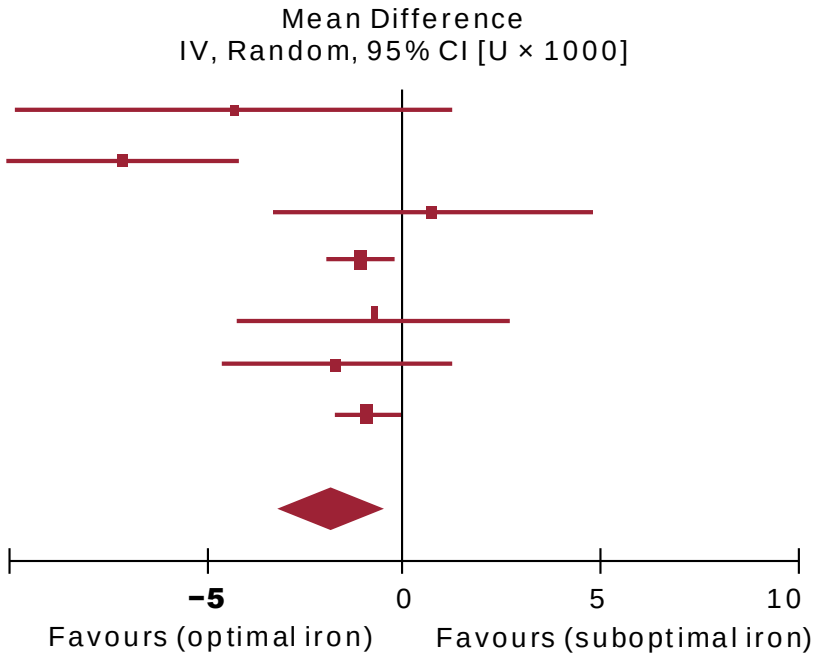


- Increasing TSAT to 30%–50% among 'iron-replete' patients allowed for ↓ ESA use
- No differences in hospitalization or infection rates

DRIVE=Dialysis Patients' Response to IV Iron with Elevated Ferritin.
[a]IV iron administered initially as 4–6 doses of 100 mg to increase TSAT to >30% and thereafter as weekly maintenance doses of 25–150 mg/wk to maintain TSAT of 30%–50%.
1. Coyne DW et al. *J Am Soc Nephrol*. 2007;18(3):975-984; 2. Kapoian T et al. *J Am Soc Nephrol*. 2008;19(2):372-379; 3. Besarab A et al. *J Am Soc Nephrol*. 2000;11(3):530-538.

Overall results demonstrate IV iron spares ESA dose

	Optimal Iron			Suboptimal Iron				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
DeVita, 2003	11,074	8,141	19	15,267	8,890	17	4,8%	−4193.00 [−9783.93, 1397.93]
Fishbane, 1995	8,100	5,670.7	20	15,126	4,276.6	32	12.3%	−7026.00 [−9919.43, −4132.57
Fishbane, 2001	11,772	11,780	74	10,949	12,154	64	8.1%	823.00 [−3185.77, 4831.77]
Kaneko, 2003	2,629	2,640	97	3,606	3,347	100	26.0%	−977.00 [−1817.45, −136.55]
Kotaki, 1997	9,400	4,405.5	15	10,062.5	5,420	16	9.9%	−662.50 [−4129.99, 2804.99]
Li, 2008	4,500	8,776.6	70	6,140	8,237.8	66	12.5%	−1640.00 [−4499.53, 1219.53]
Macdougall, 1996	5,259	1,002	12	6,041.4	1,367.5	25	26.4%	-782.40 [−1562.63, −2.17]
Total (95% CI)			307			320	100.0%	−1732.50 [−3072.78, −392.23]



‘Optimal iron’ allowed for a 23% ↓ in ESA dose (compared to “suboptimal iron”)

The AMP is based on EVIDENCE

- DRIVE & DRIVE 2 – ESA resistant anemia – give more & regular iron
- Normal Hematocrit, CHOIR & CREATE – Hgb <130 g/L, ESA dose is key
- TREAT – CKD not on dialysis use ESA sparingly, Hgb not above 120 (in fact, no advantage going above 115g/L

1998

Normal Hematocrit Study

hematocrit (42%) associated with ~30% ↑ in the risk of death or nonfatal MI in HD (stopped prematurely)[1]

2006

CHOIR

34% ↑ in death + MI + HF + stroke with hemoglobin target of 135 g/L in ND-CKD vs 113 g/L[2]

(2013): Independent of Hgb, higher ESA doses ↑ risk for CV events[3]

2006

CREATE

No benefit with normalizing Hgb in ND-CKD[4]

2009

TREAT

No CV or mortality benefit of darbepoetin alfa in patients with DM and ND-CKD; 92% ↑ in stroke[5]

(2011): Risk of stroke not related to Hgb[6]

1. Besarab A et al. *N Engl J Med*. 1998;339(9):584-590; 2. Singh AK et al. *N Engl J Med*. 2006;355(20):2085-2098; 3. McCullough PA et al. *Am J Nephrol*. 2013;37(6):549-558; 4. Drüeke TB et al. *N Engl J Med*. 2006;355(20):2071-2084; 5. Pfeffer MA et al. *N Engl J Med*. 2009;361(21):2019-2032; 6. Skali H et al. *Circulation*. 2011;124(25):2903-2908.

By implementing our protocol, “these studies suggest” since 2009…*

- We avoided:
  - 560 strokes
  - 162 cancer related deaths
  - 1813 events of death, MI, CHF hospitalization, stroke (a combined endpoint)
  - 1029 deaths
  - 1670 CHF hospitalizations
  - 1573 dialysis starts.

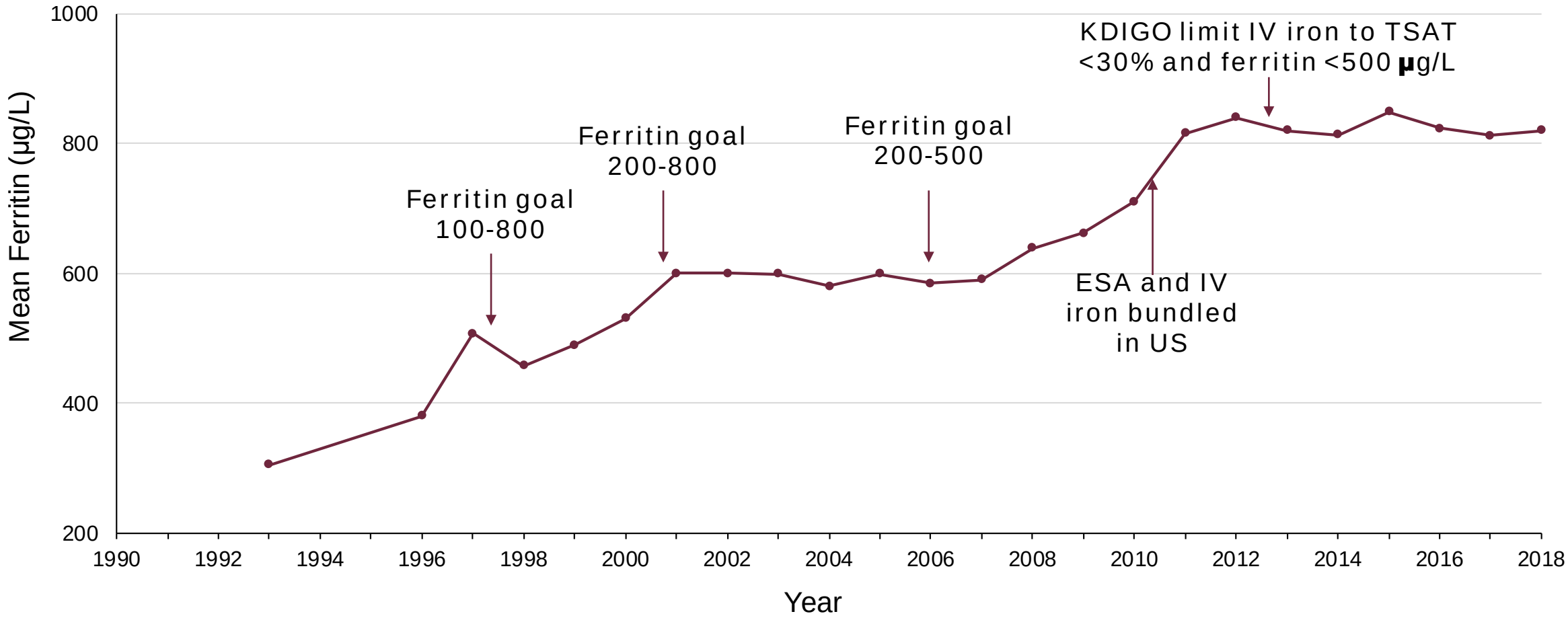
*(but we don’t really know)

(event # reduced by 50% to be conservative)

1. Besarab A et al. *N Engl J Med*. 1998;339(9):584-590; 2. Singh AK et al. *N Engl J Med*. 2006;355(20):2085-2098; 3. McCullough PA et al. *Am J Nephrol*. 2013;37(6):549-558; 4. Drüeke TB et al. *N Engl J Med*. 2006;355(20):2071-2084; 5. Pfeffer MA et al. *N Engl J Med*. 2009;361(21):2019-2032; 6. Skali H et al. *Circulation*. 2011;124(25):2903-2908.

INCREASED RELIANCE ON IV IRON INCREASED SERUM FERRITIN OVER TIME

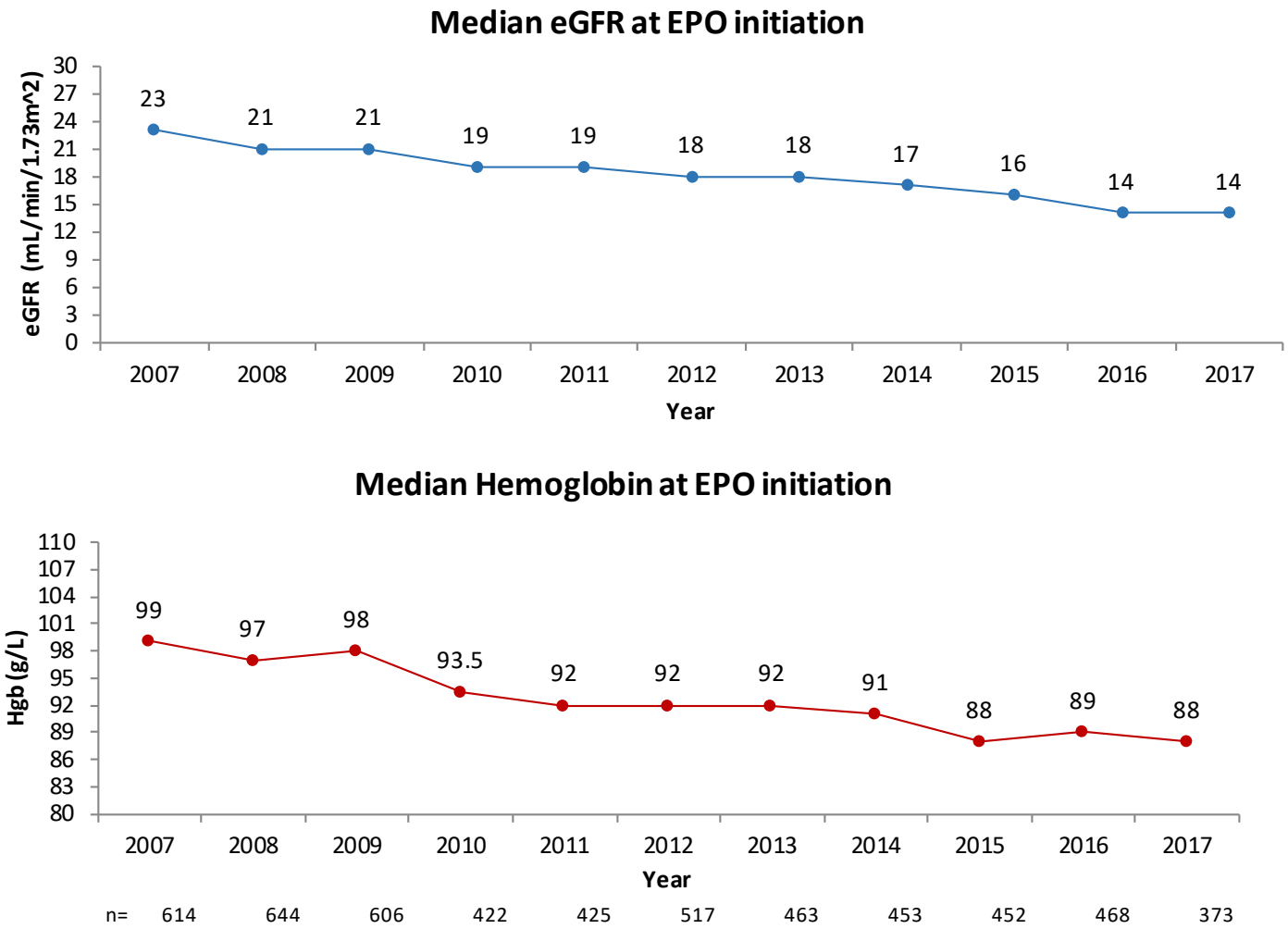
Trends in Serum Ferritin Concentrations in the US[1,2]



KDIGO=Kidney Disease: Improving Global Outcomes; TSAT=transferrin saturation.

Adapted from 1. Charytan DM et al. *J Am Soc Nephrol*. 2015;26(6):1238-1247; 2. US-DOPPS (Dialysis Outcomes and Practice Patterns Study) Practice Monitor. https://www.dopps.org/DPM/Files/meanferritinngml1_overallTAB.htm. Accessed September 10, 2018.

Changes in Practice
British Columbia
CKD patients Changes over time in EPO initiation practices: 2007- 2017



From Dr. A Levin

…but questions remained about IV iron

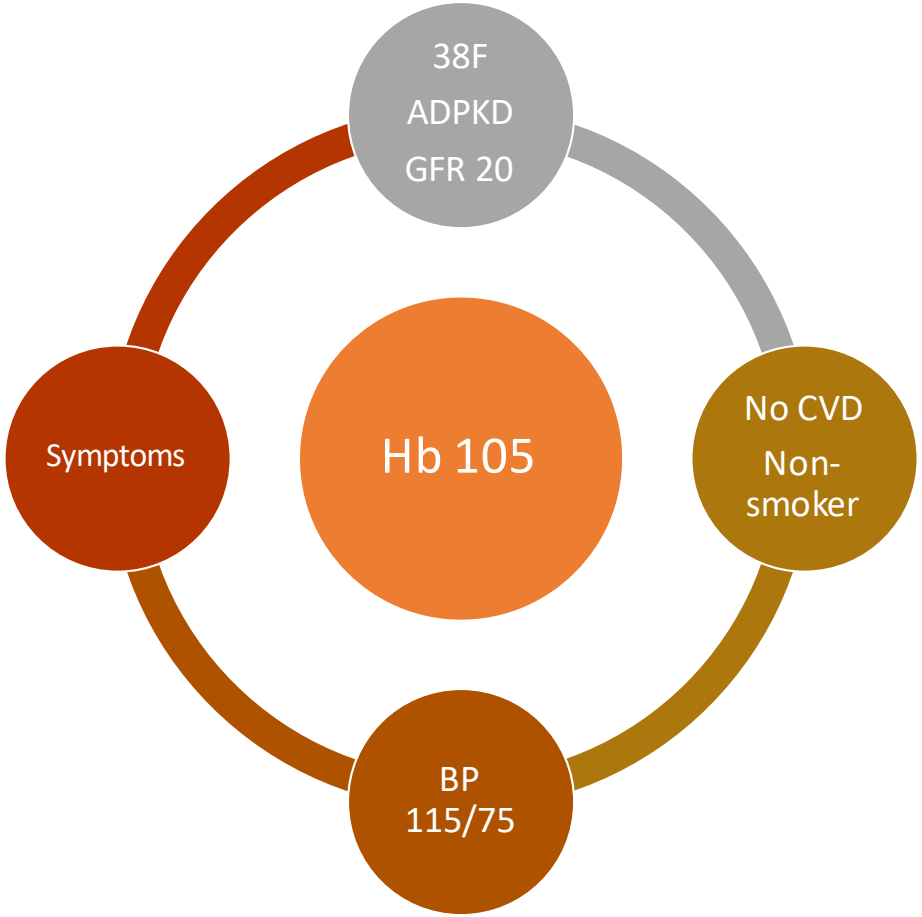
High vs low ferritin threshold?

Iron vs ESA?

Ferritin vs TSAT?

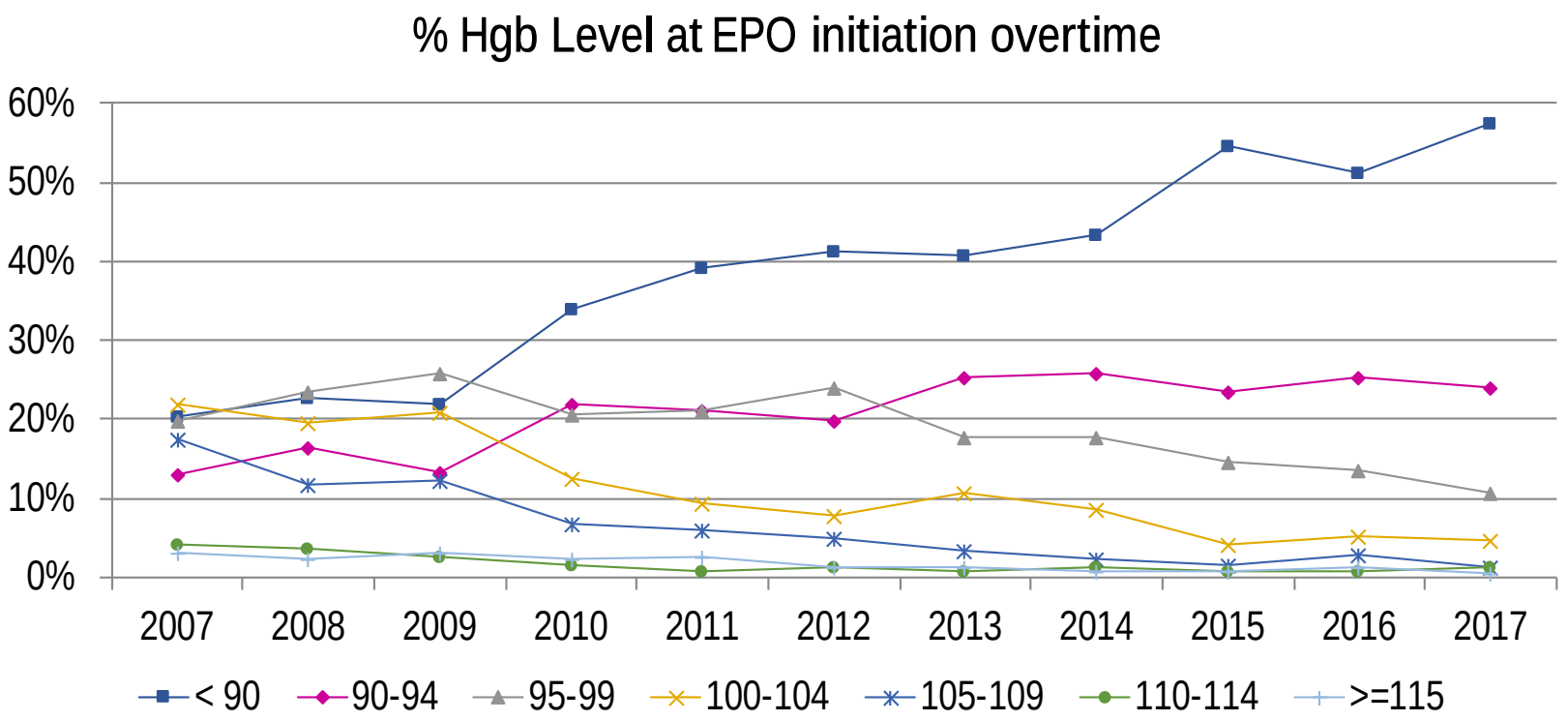
Conservative vs liberal dosing strategies?

Patients come in all shapes and sizes



From Dr. A Levin

British Columbia
CKD patients Changes over time in EPO initiation practices: 2007- 2017



n=	614	644	606	422	425	517	463	453	452	468	373

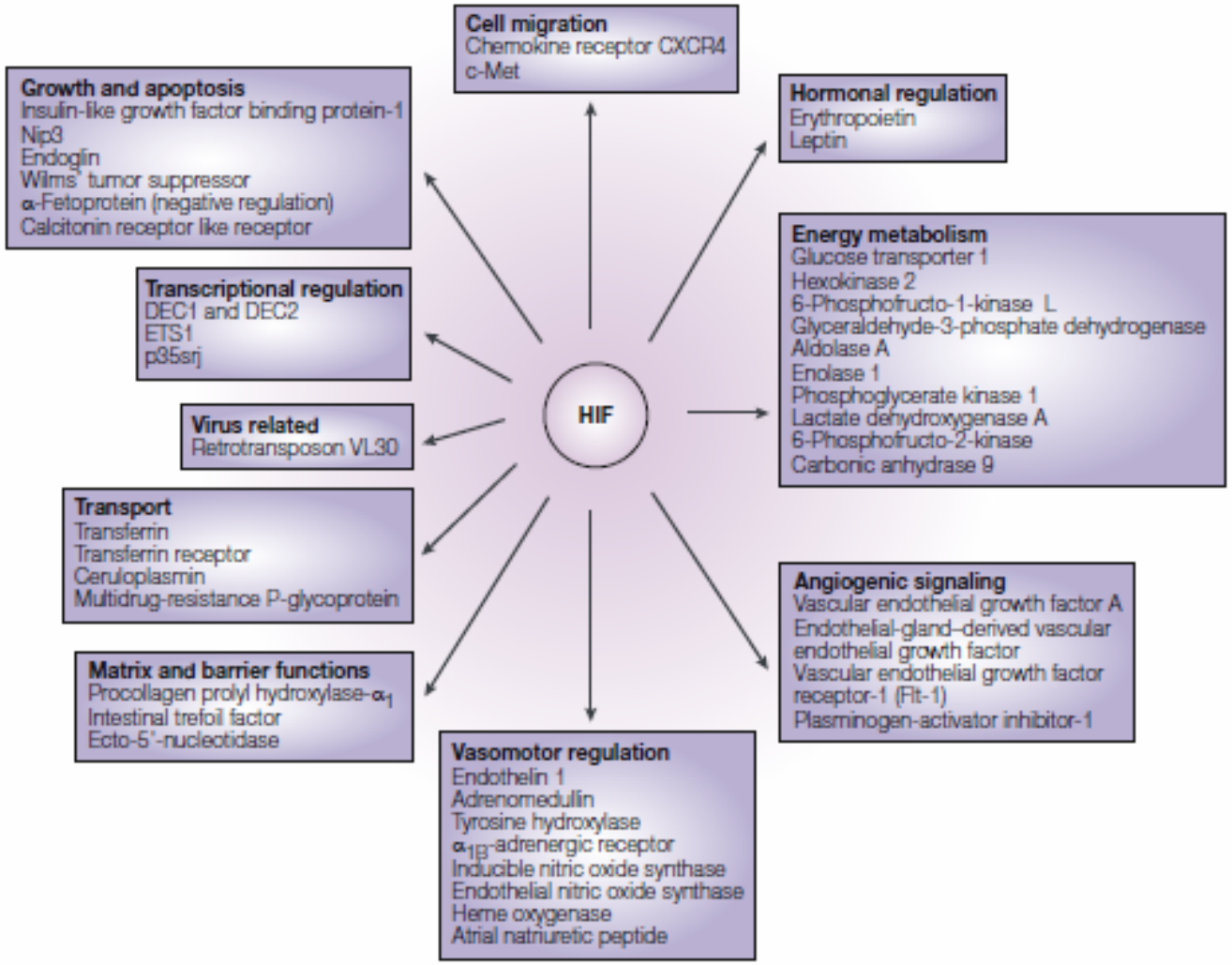
From Dr. A Levin

HIF inhibitors

An oral agent coming soon for anemia…

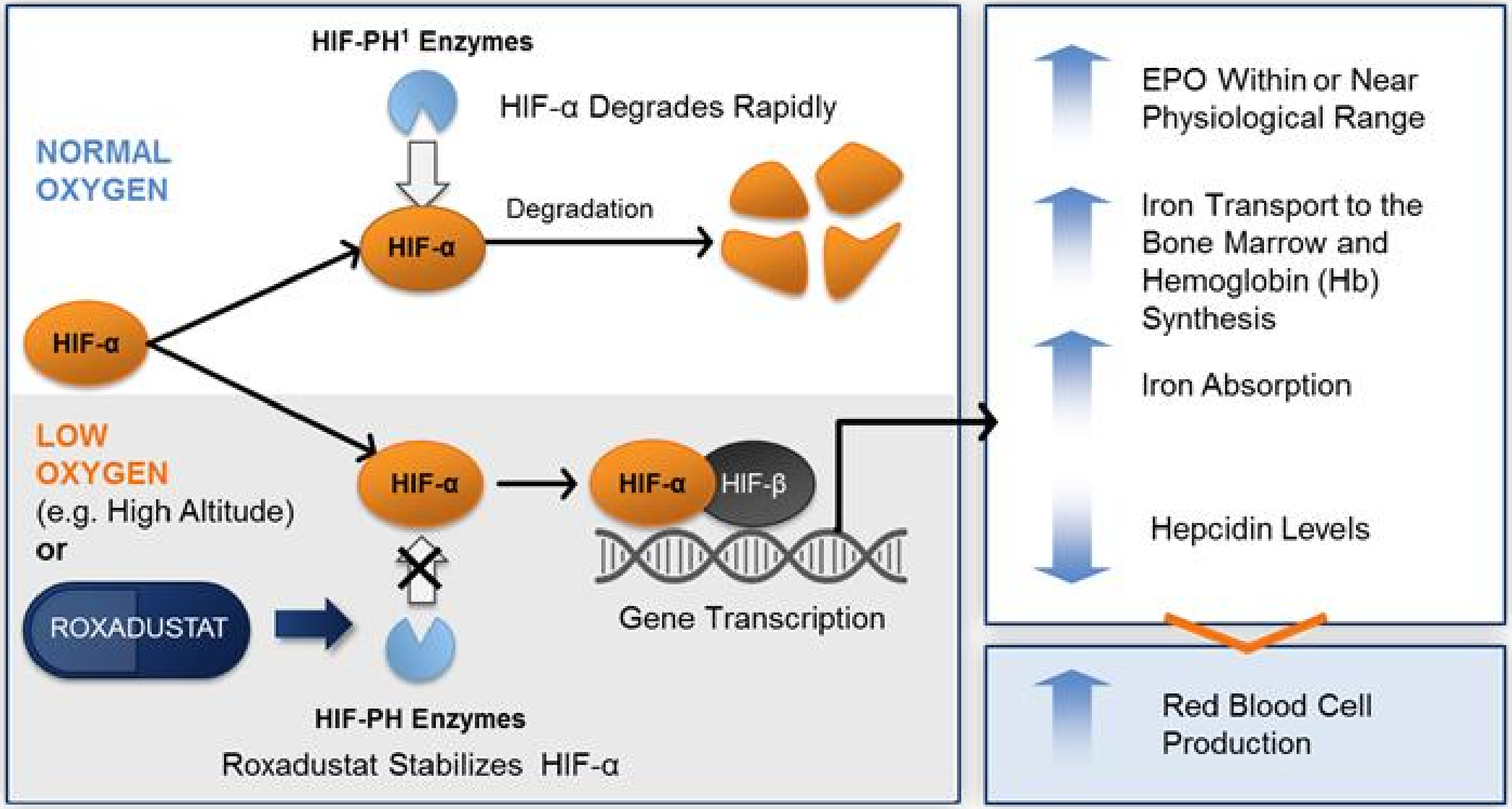
Anemia, CKD and HIF therapies

- *Hypoxia-inducible factor (HIF) Prolyl Hydroxylase Inhibitors or HIF stabilizers*
  - *Oral medication*
  - *Stimulate iron absorption, endogenous EPO production*
  - *Inhibit proinflammatory cytokines*
  - *Act on multiple genes*
  - *? Additional beneficial effects*



From Dr. A Cunningham

Mechanism of Action



Conclusions

Non-inferior to ESA in maintaining Hb level for stable patients who are relatively EPO responsive and iron replete

Potential Benefits:

- Oral medication

- Avoid ESAs
- Iron mobilization in the absence of IV iron
- Suppression of inflammation

- Ischemic protection

Potential Concerns:

- Higher rates of discontinuation
- Adverse events, including hyperkalemia

- Tumour progression
- Pulmonary hypertension
- Metabolism
- Angiogenesis, DM retinopathy
- Progression of CKD
- Thromboembolic events

From Dr. A Cunningham

Current Therapies in Anemia in CKD

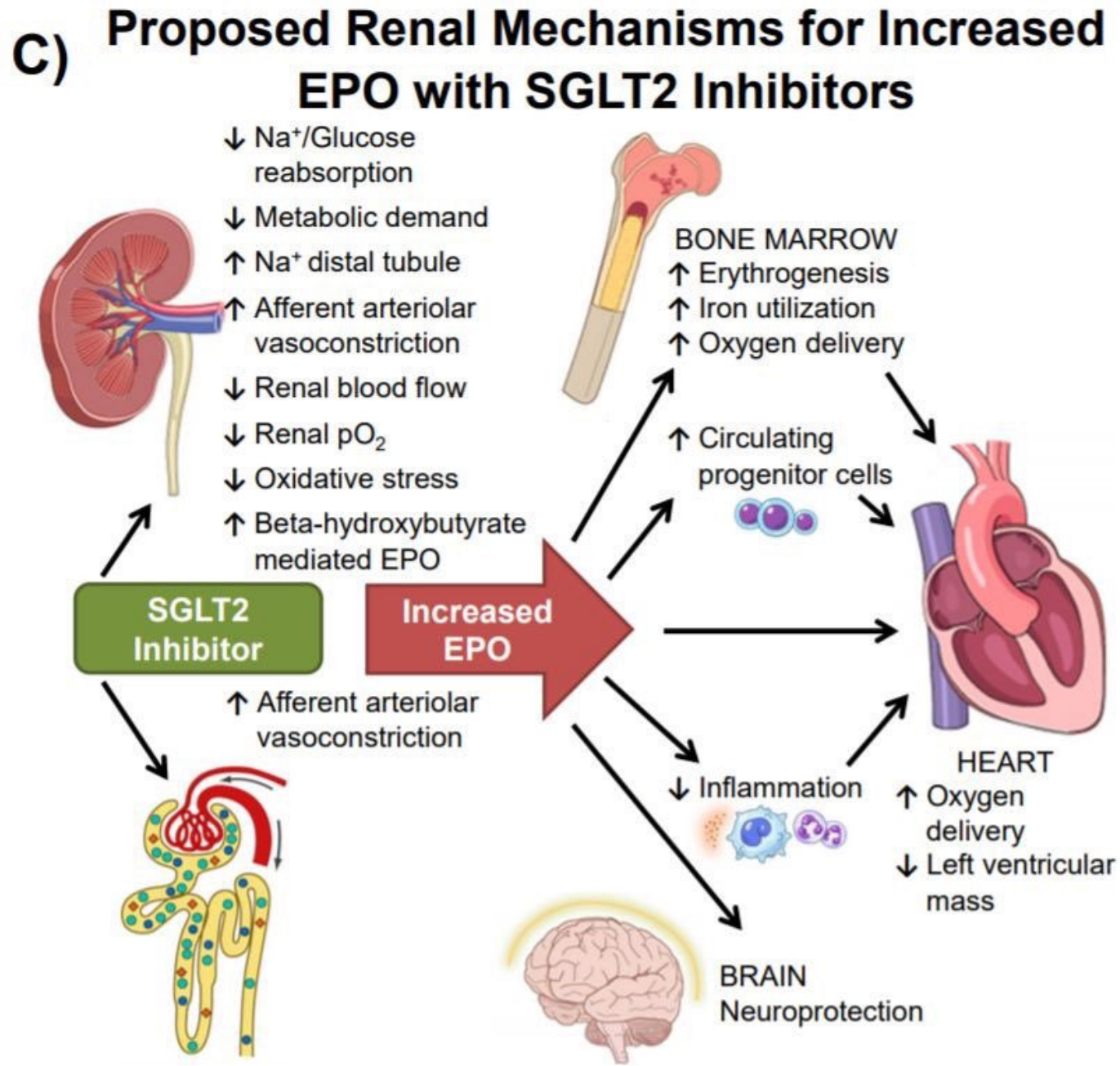
- Various treatments work to raise Hb
  - Iron, ESA and HIF stabilizers

- Issues from clinical trial data:
  - Sick populations do not benefit from attempts to raise Hb with very high doses of ESA
  - Guidelines suggest narrow range of target Hb for non dialysis and dialysis pts
  - Adverse effects of ESAs in specific populations not well defined
  - Individualization of therapy

- Ongoing questions:
  - What level of Hb is appropriate for CKD, Dialysis pts?
  - What are appropriate outcome measures?
    - QOL, survival, exercise ability
    - Other

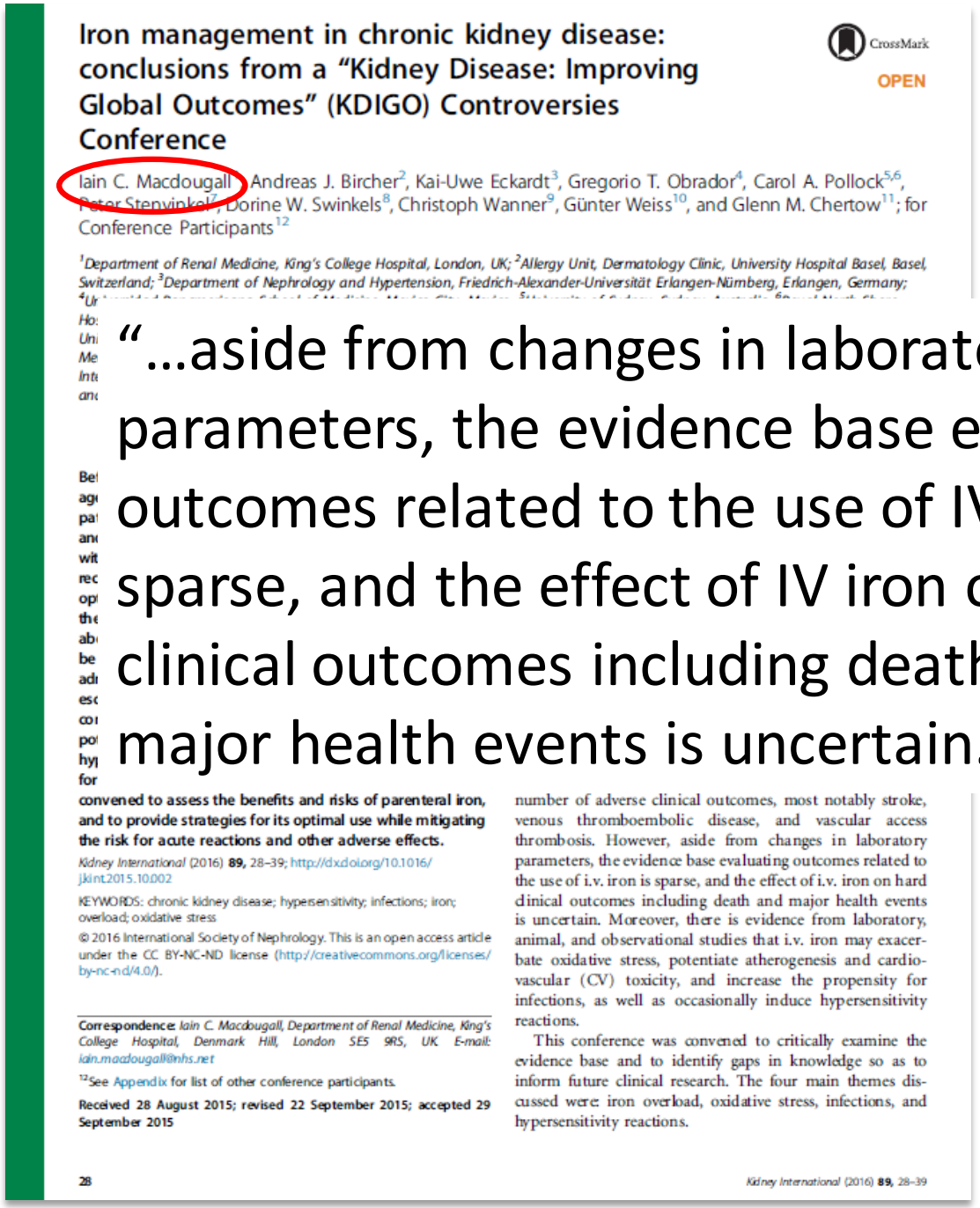
From Dr. A Cunningham

A diabetes drug for anemia??



Practical changes to AMP

CKD non-dialysis, dialysis, peritoneal dialysis



Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

OPEN

Iain C. Macdougall[1], Andreas J. Bircher[2], Kai-Uwe Eckardt[3], Gregorio T. Obrador[4], Carol A. Pollock[5,6], Peter Stenvinkel[7], Dorine W. Swinkels[8], Christoph Wanner[9], Günter Weiss[10], and Glenn M. Chertow[11]; for Conference Participants[12]

[1]Department of Renal Medicine, King's College Hospital, London, UK; [2]Allergy Unit, Dermatology Clinic, University Hospital Basel, Basel, Switzerland; [3]Department of Nephrology and Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany;

convened to assess the benefits and risks of parenteral iron, and to provide strategies for its optimal use while mitigating the risk for acute reactions and other adverse effects.

Kidney International (2016) **89,** 28–39; http://dx.doi.org/10.1016/j.kint.2015.10.002

KEYWORDS: chronic kidney disease; hypersensitivity; infections; iron; overload; oxidative stress

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[12]See Appendix for list of other conference participants.

Received 28 August 2015; revised 22 September 2015; accepted 29 September 2015

number of adverse clinical outcomes, most notably stroke, venous thromboembolic disease, and vascular access thrombosis. However, aside from changes in laboratory parameters, the evidence base evaluating outcomes related to the use of i.v. iron is sparse, and the effect of i.v. iron on hard clinical outcomes including death and major health events is uncertain. Moreover, there is evidence from laboratory, animal, and observational studies that i.v. iron may exacerbate oxidative stress, potentiate atherogenesis and cardiovascular (CV) toxicity, and increase the propensity for infections, as well as occasionally induce hypersensitivity reactions.

This conference was convened to critically examine the evidence base and to identify gaps in knowledge so as to inform future clinical research. The four main themes discussed were: iron overload, oxidative stress, infections, and hypersensitivity reactions.

"…aside from changes in laboratory parameters, the evidence base evalua outcomes related to the use of IV iror sparse, and the effect of IV iron on ha clinical outcomes including death anc major health events is uncertain."

A need to know more…

"Studies should be conducted to determine whether treatment with iron has clinically relevant

"There is an urgent need for RCTs to assess the relative safety and efficacy of IV iron in the management of CKD-related anemia, particularly in relation to hard clinical end points, as well as infection risk and other patient-related outcomes."

Proactive IV irOn Therapy in hemodiALysis

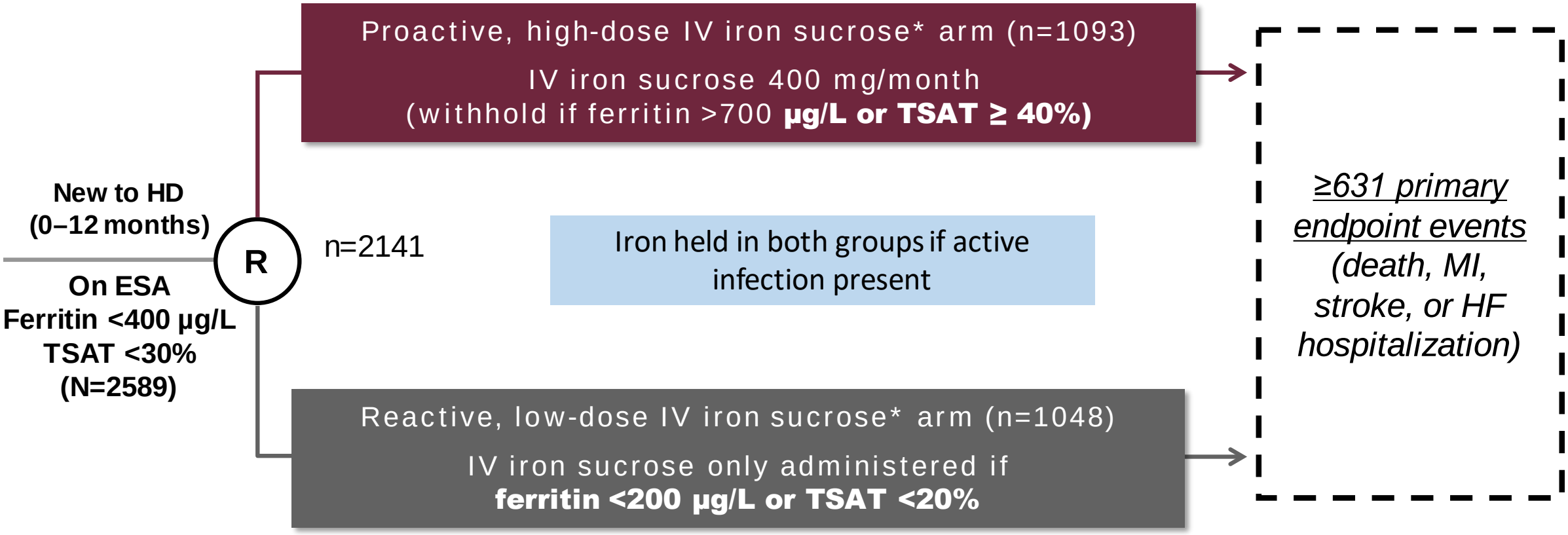
- Largest study to date : 2141 patients
- Trial was well conducted – we can believe the results
- Compared “proactive” to “reactive” iron sucrose dosing
- Population similar to our HD population

HYPOTHESIS:

Proactive, high-dose IV iron sucrose would be non-inferior to reactive, low-dose IV iron sucrose for the outcome of all-cause mortality and CV events in HD patients.

Macdougall IC et al. *Am J Nephrol*. 2018;48(4):260-268.

PIVOTAL Design



Adapted from Macdougall IC et al. *Am J Nephrol*. 2018;48(4):260-268.

1. Macdougall IC et al. *Am J Nephrol*. 2018;48(4):260-268; 2. Macdougall IC et al. [published online October 26, 2018; published correction appears in *N Engl J Med*. January 14, 2019. doi:10.1056/NEJMx180044]. *N Engl J Med*. doi:10.1056/NEJMoa1810742

PIVOTAL OUTCOMES

Primary Endpoint

Composite of nonfatal MI, nonfatal stroke, hospitalization for HF, or all-cause death, analyzed as time-to-first event

Components of the Primary Endpoint (Secondary Endpoints)

- All-cause death
- Composite of CV events (MI, stroke, and hospitalization for HF [first event])
- MI (fatal or nonfatal)
- Stroke (fatal or nonfatal)
- Hospitalization for HF

Recurrent Events (Secondary Endpoint)

MI, stroke, hospitalization for HF, and deaths analyzed as first + recurrent events

Macdougall IC et al. *Am J Nephrol*. 2018;48(4):260-268.

Additional Efficacy Endpoints

- ESA dose requirements
- Transfusion requirements
- Quality-of-life measures

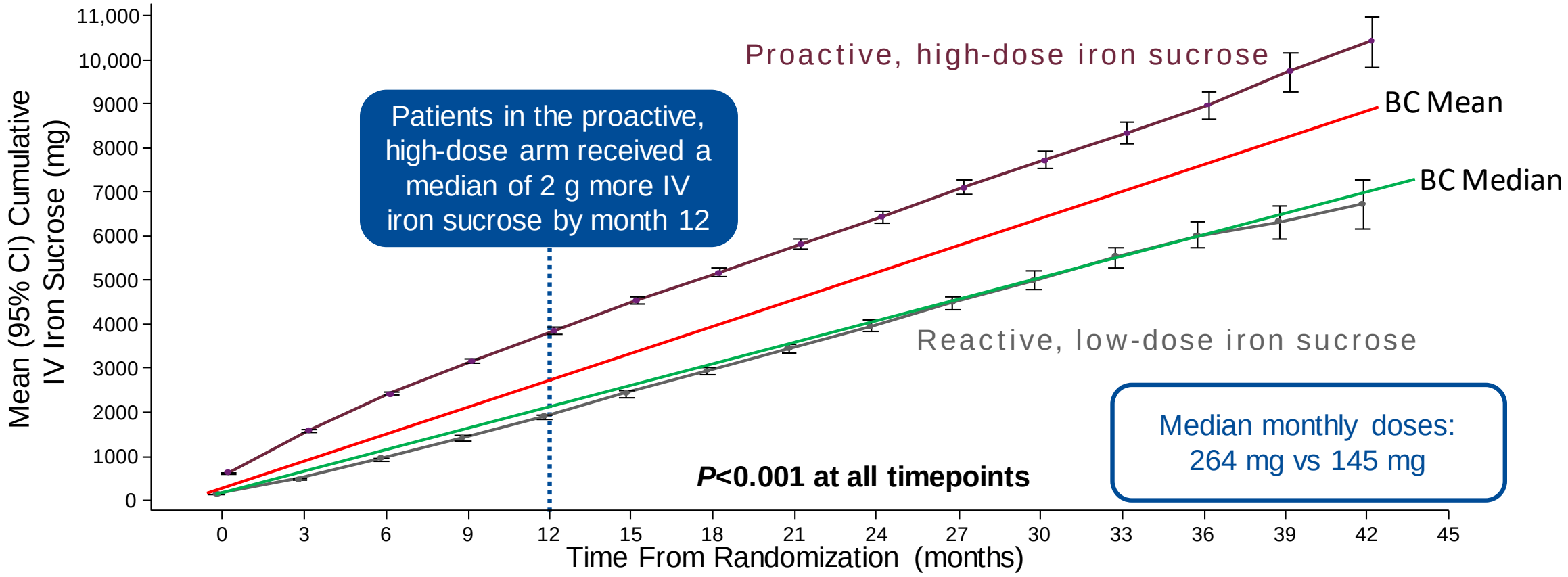
Safety Endpoints

- Vascular access thrombosis
- All-cause hospitalization
- Hospitalization for infection
- Infection episodes

Laboratory Endpoints

- Cumulative dose of iron
- Hemoglobin concentration
- Serum ferritin concentration
- Platelet count
- Serum albumin concentration
- TSAT

“Proactive” group had 119 mg more iron/month



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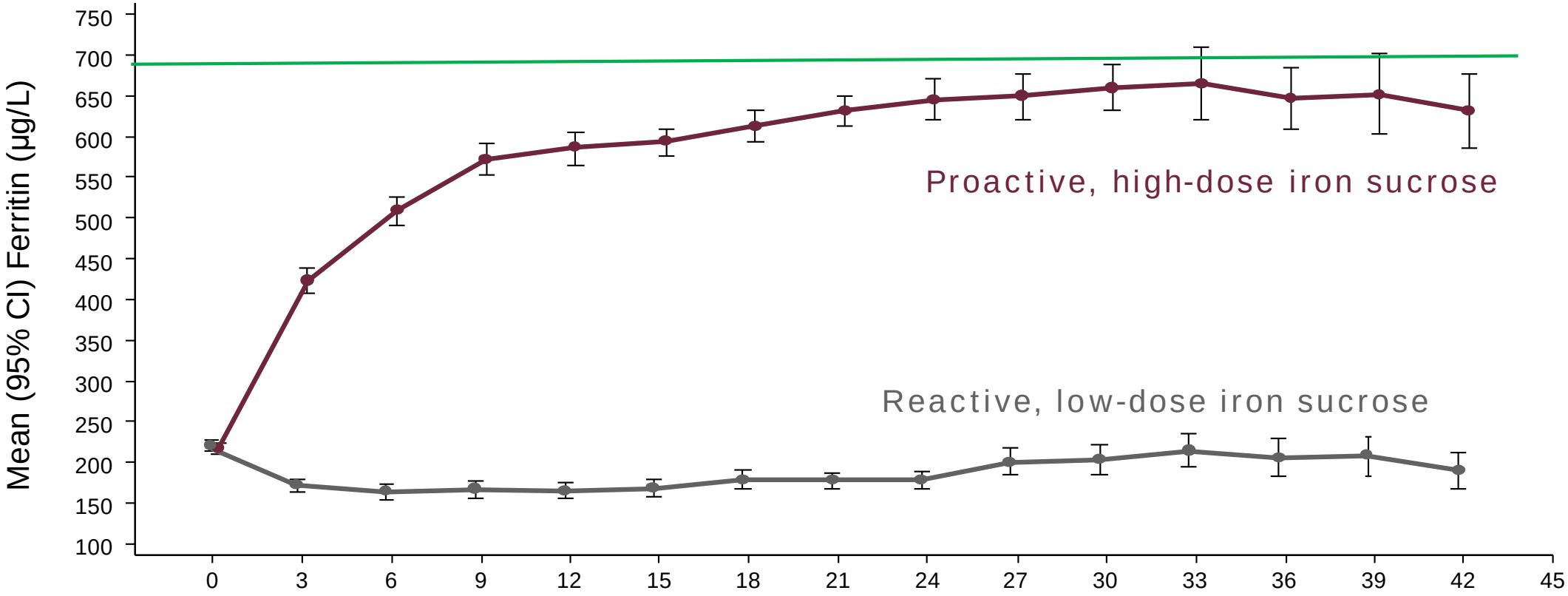
Ferritin rose rapidly in higher dose iron group



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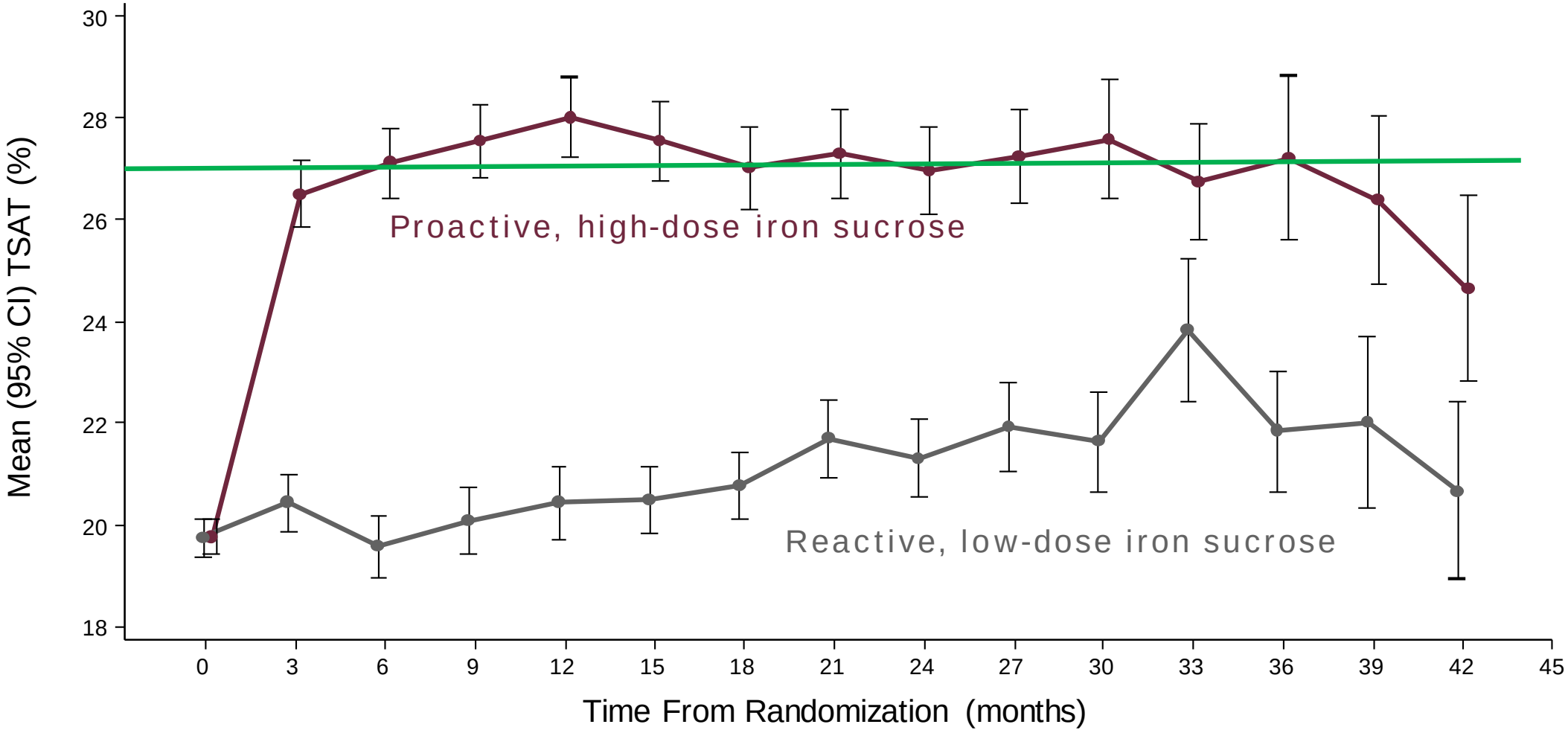
Macdougall IC et al. [published online October 26, 2018; published correction appears in *N Engl J Med*. January 14, 2019. doi:10.1056/NEJMx180044].
N Engl J Med. doi:10.1056/NEJMoa1810742

TSAT rose rapidly in higher dose iron group



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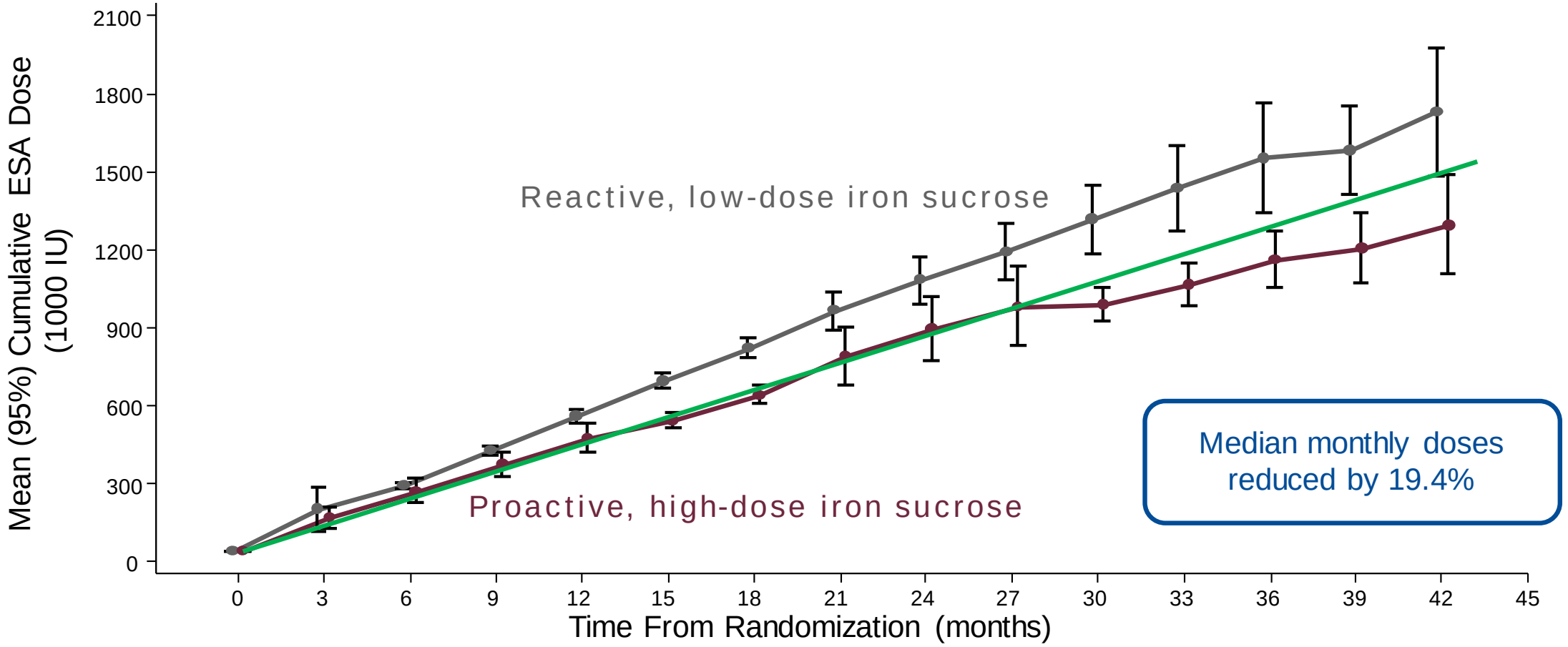
ESA dose was lower in the higher dose iron group



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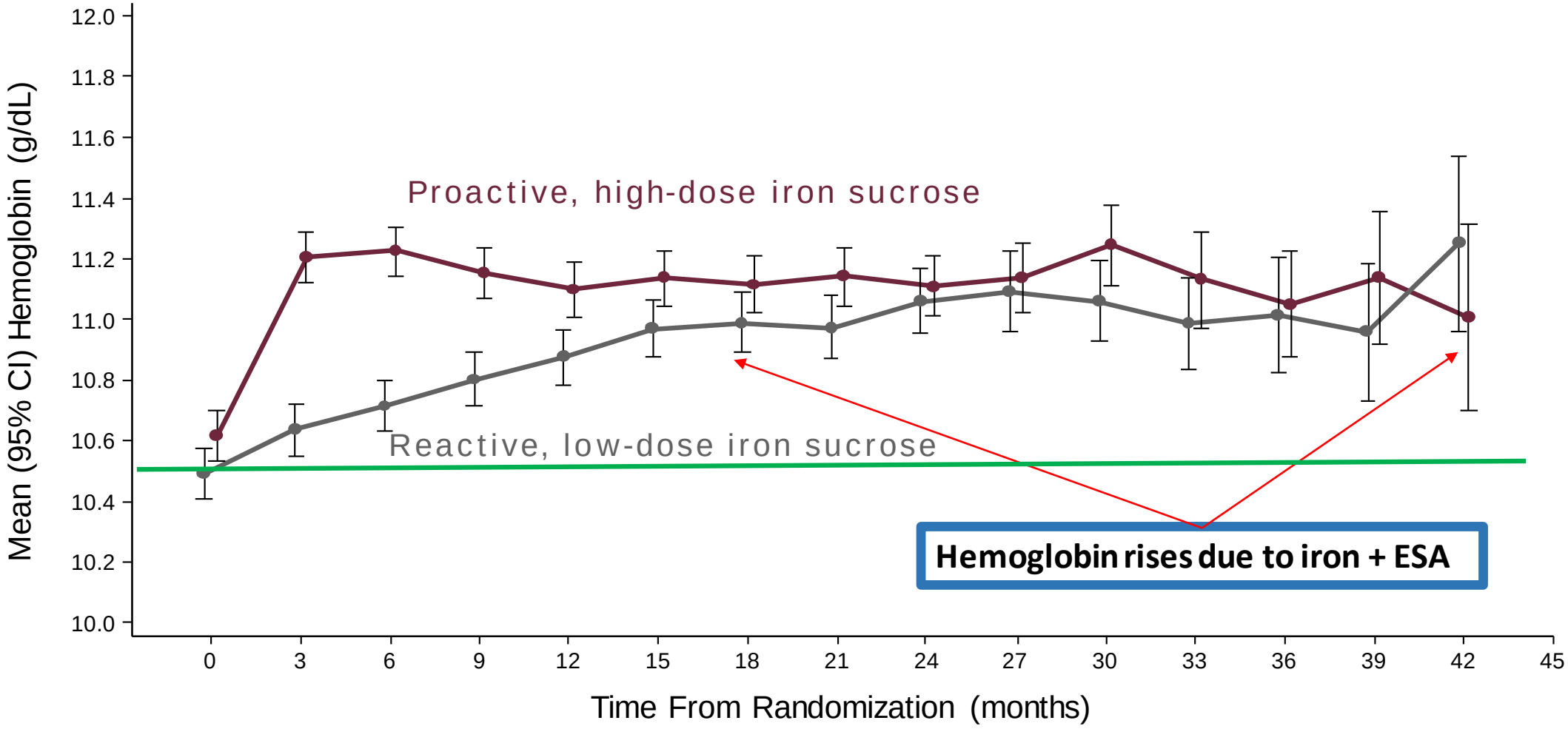
Hgb rose rapidly in higher dose iron group



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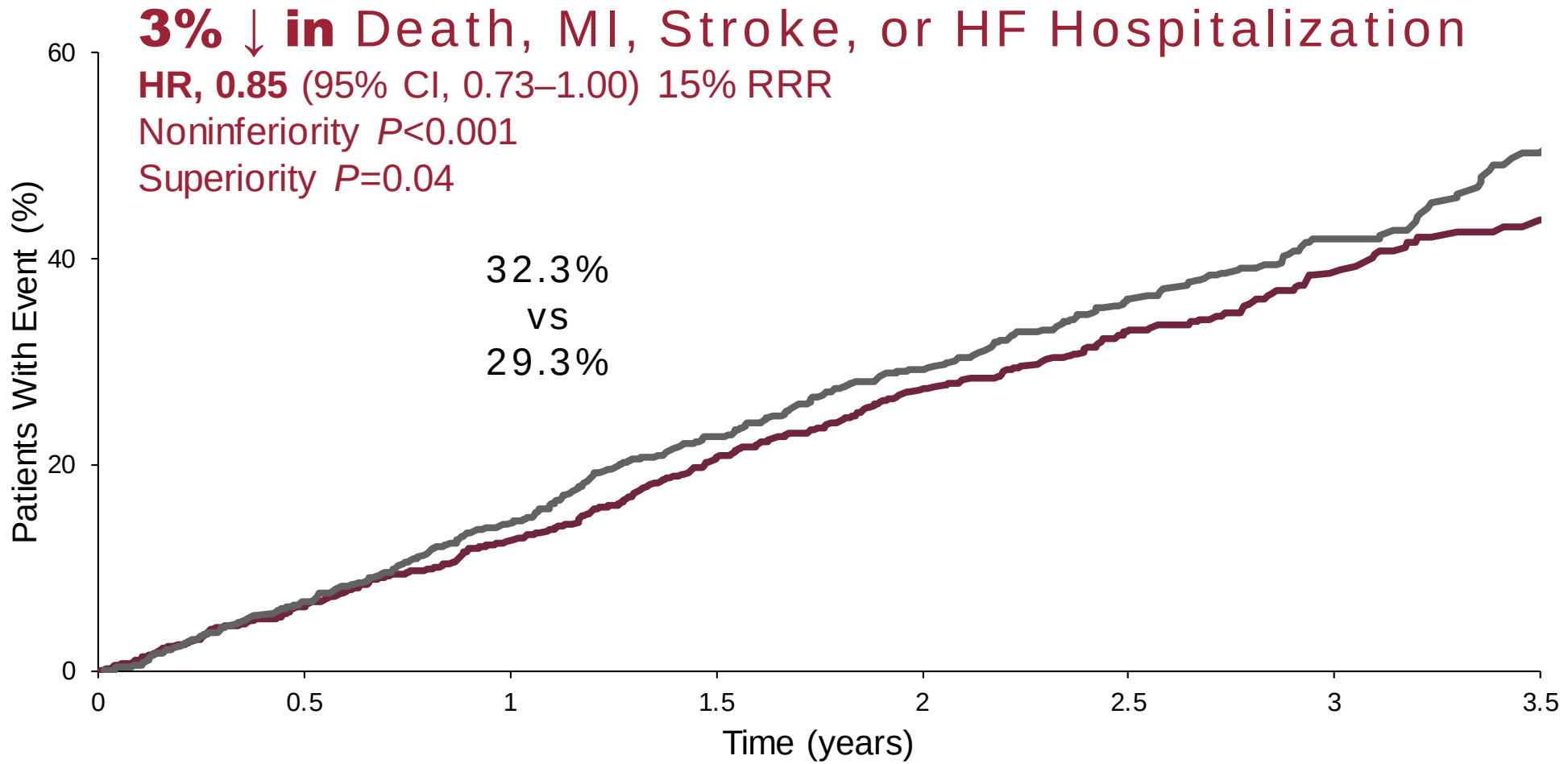
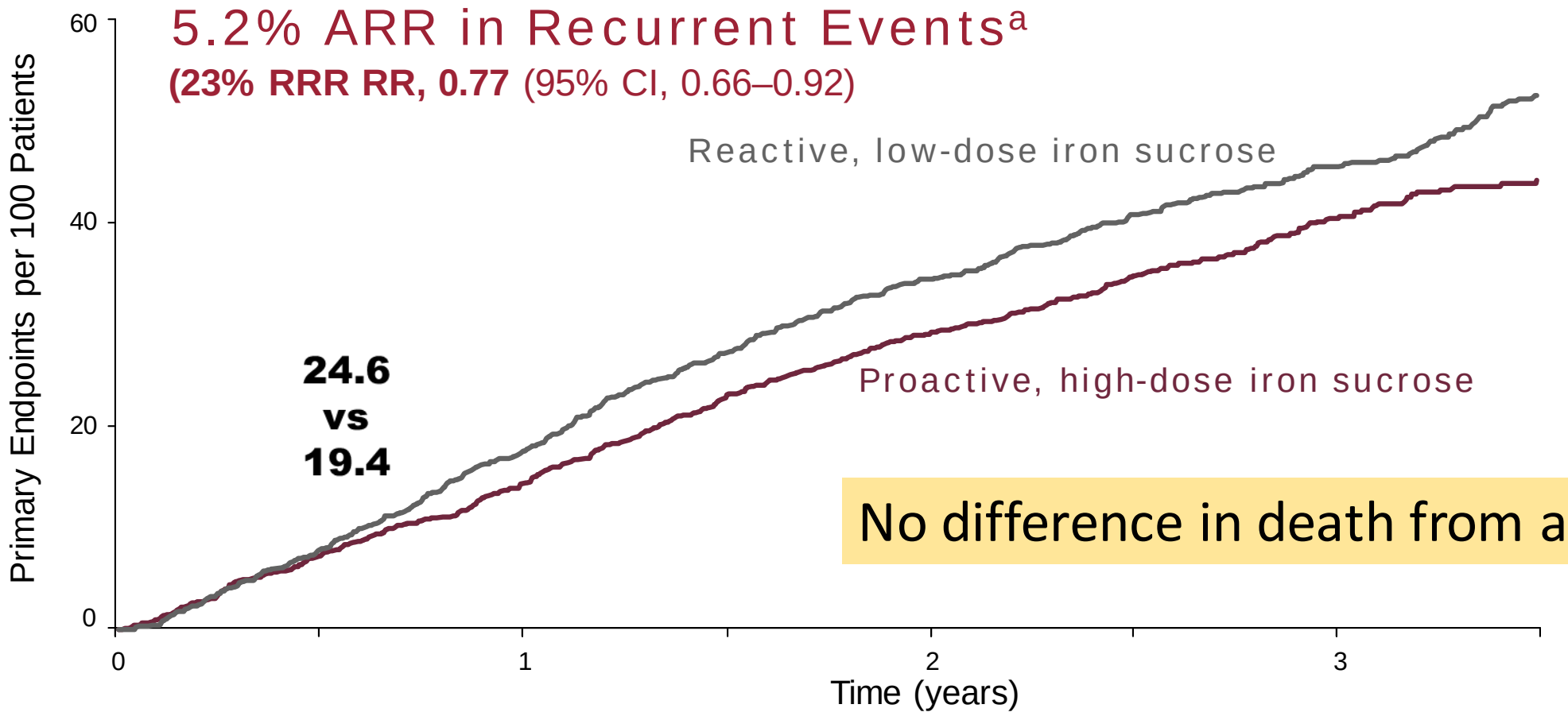
1’ Endpoint: better outcome in higher dose iron group



From the *New England Journal of Medicine*, Macdougall IC et al., Intravenous iron in patients undergoing maintenance hemodialysis, [published online October 26, 2018]. Macdougall IC et al. [published online October 26, 2018; published correction appears in *N Engl J Med*. January 14, 2019. doi:10.1056/NEJMx180044]. *N Engl J Med*. doi:10.1056/NEJMoa1810742

Less recurrent CV events in higher dose iron group



No difference in death from any cause

[a]Death from any cause, MI, stroke, and hospitalization for HF.
Recurrent events plotted in the form of mean frequency functions using the method of Ghosh and Lin (*Biometrics*. 2000;56:554-562).
From the *New England Journal of Medicine*, Macdougall IC et al., Intravenous iron in patients undergoing maintenance hemodialysis, [published online October 26, 2018].

Macdougall IC et al. [published online October 26, 2018; published correction appears in *N Engl J Med*. January 14, 2019. doi:10.1056/NEJMx180044]. *N Engl J Med*. doi:10.1056/NEJMoa1810742

2’ endpoints significant except for stroke and death (higher dose iron was better)

MI or Stroke or Hospitalization for HF	20% RRR HR, 0.80 (95% CI, 0.64–1.00)	2.4% ARR unadjusted (16.0% vs 13.6%)
MI	31% RRR HR, 0.69 (95% CI, 0.52–0.93)	2.6% ARR unadjusted (9.7% vs 7.1%)
Stroke	HR, 0.90 (95% CI, 0.56–1.44)	N/A (3.1% vs 3.3%)
Hospitalization for HF	34% RRR HR, 0.66 (95% CI, 0.46–0.94)	2.0% ARR unadjusted (6.7% vs 4.7%)

HR (95% CI) adjusted for stratification variables: vascular access, diabetic status, and time on dialysis.

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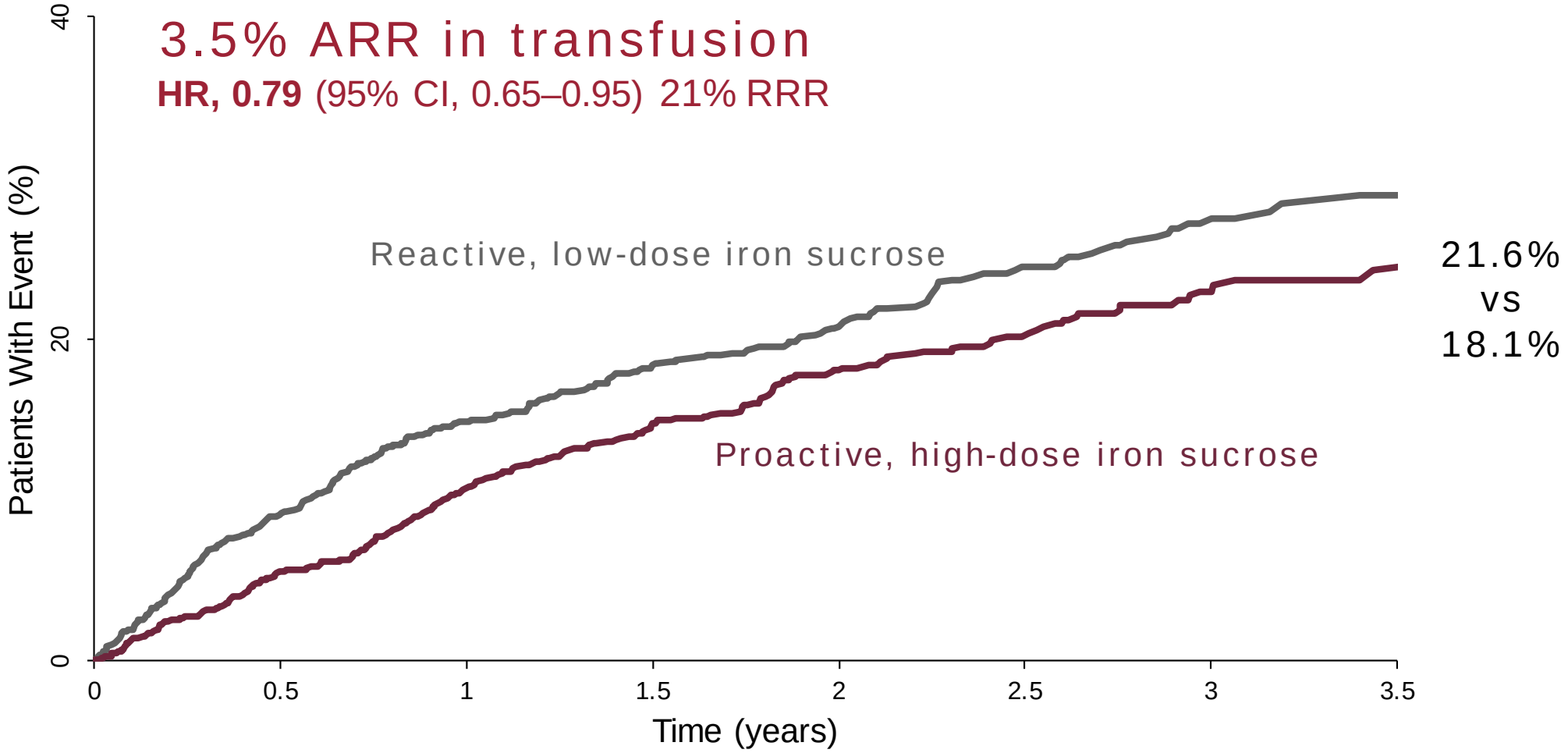
Higher dose iron group required less blood



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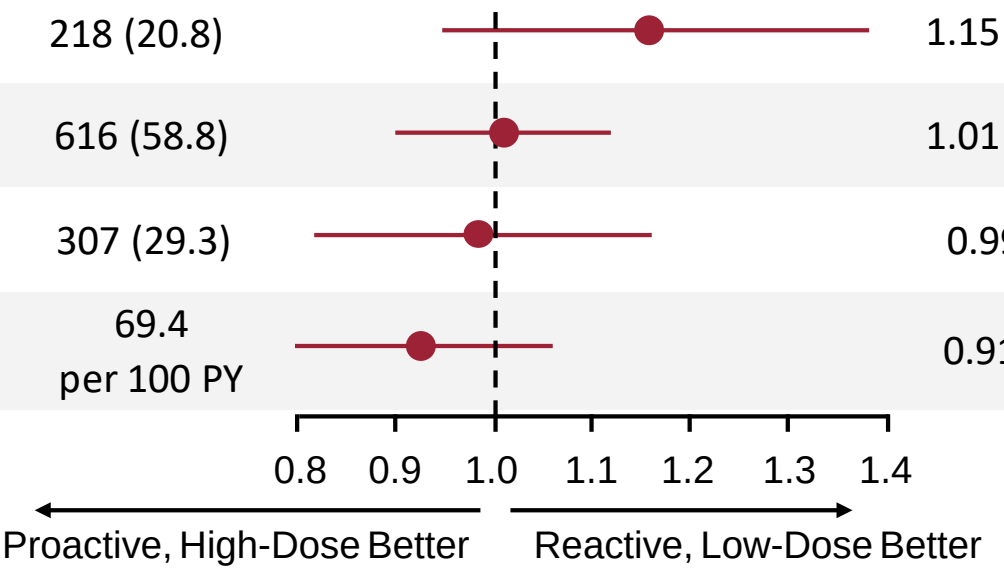
N Engl J Med. doi:10.1056/NEJMoa1810742

Higher dose iron group: equally safe

Endpoint	Proactive, High-Dose IV Iron Sucrose (N=1093) n (%)	Reactive, Low-Dose IV Iron Sucrose (N=1048) n (%)	Hazard or Rate Ratio (95% CI)	*P* Value
Vascular access thrombosis	262 (24.0)	218 (20.8)	1.15 (0.96–1.38)	0.12
All-cause hospitalization	651 (59.6)	616 (58.8)	1.01 (0.90–1.12)	0.90
Hospitalization for infection	323 (29.6)	307 (29.3)	0.99 (0.82–1.16)	0.92
Infection episodes	63.3 per 100 PY	69.4 per 100 PY	0.91 (0.79–1.05)	N/A



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BC compared to PIVOTAL, rest of Canada

	BC (2018) (iron gluc. N=1943, Iron suc N=243)	**PIVOTAL (↑iron)**	**Canada (2017 per DOPPS)**
Average TSAT (%)	27	26	24.5 ± 1.5%
Average Hemoglobin (g/L)	105.0 (% under 110 = 63 % over 130 = 2.5)	112	105.8 ± 1.4 g/L
Average Ferritin (µ/L)	686.5	~625	372 ± 54
Median monthly Iron dose (mg) (Mean)	Iron Gluconate = 156 IQR 94-229 (191) Iron Sucrose = 100 IQR 50-192 (95)	264	135
Median weekly ESA dose (units)	Median: Epoetin 6000 (IQR 4000-12,000) Darbe 20 (IQR 10-40 mg) Mean: 8416 ± 400 (InCent HD) 7786 ± 400 (Comm HD)	7,440	9913 ± 587

BCRenal
Provincial Health Services Authority

Number of Chronic Kidney Patients in BC by Type (July 1, 2009 - July 1, 2019)

	Treatment Type	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Average % Increase Per Year	10-Year Increase
CKD	Non-Dialysis CKD - Clinics	7341	7714	8644	8963	9505	10068	10473	10309	10941	11342	11632	5%	58%
CKD	Non-Dialysis CKD - MD Offices	2843	3111	2974	2962	3059	2930	3017	3714	3948	4239	4226	4%	49%
CKD	**Total CKD**	**10184**	**10825**	**11618**	**11925**	**12564**	**12998**	**13490**	**14023**	**14889**	**15581**	**15858**	**5%**	**56%**
DIALYSIS	Hospital-based Hemodialysis	1167	1238	1209	1238	1283	1203	1247	1245	1347	1377	1458	2%	25%
DIALYSIS	Community Unit Hemodialysis	751	787	804	805	813	834	785	831	839	857	918	2%	22%
DIALYSIS	Facility dependent Nocturnal Hemodialysis[1]	n/a	n/a	17	19	25	41	62	93	84	78	88	26%	n/a
DIALYSIS	**Subtotal (Hemodialysis)**	**1918**	**2025**	**2030**	**2062**	**2121**	**2078**	**2094**	**2169**	**2270**	**2312**	**2464**	**3%**	**28%**
DIALYSIS	Peritoneal Dialysis	673	691	677	718	813	791	773	811	856	852	873	3%	30%
DIALYSIS	Combination of Hemo- and Peritoneal Dialysis	n/a	n/a	19	22	25	31	27	12	12	13	18	4%	n/a
DIALYSIS	**Subtotal (Peritoneal Dialysis)**	**673**	**691**	**696**	**740**	**838**	**822**	**800**	**823**	**868**	**865**	**891**	**3%**	**32%**
DIALYSIS	Home Hemodialysis	96	91	127	134	124	137	140	133	135	145	131	4%	36%
DIALYSIS	Facility Independent Hemodialysis, including Nocturnal[2]	n/a	5	15	18	22	29	32	25	20	18	17	25%	n/a
DIALYSIS	**Subtotal (Home Hemodialysis)**	**96**	**96**	**142**	**152**	**146**	**166**	**172**	**158**	**155**	**163**	**148**	**5%**	**54%**
DIALYSIS	**Total Dialysis**	**2687**	**2812**	**2868**	**2954**	**3105**	**3066**	**3066**	**3150**	**3293**	**3340**	**3503**	**3%**	**30%**

Data source: PROMIS Database, BC Renal

[1] The facility dependent nocturnal HD program was first initiated in 2011 at St. Paul's Hospital only. Between 2013 and 2015, this program was expanded to Surrey Memorial Hospital, Royal Columbian Hospital, Royal Jubilee Hospital and Abbotsfort Reginal Hospital and Cancer Centre. The noted average % increase per year was mainly driven by the rapid gain of popularity between 2011 and 2016.

[2] The facility independent nocturnal HD program was initiated in 2010 at Vancouver General Hospital. The program continues to gain popularity to date; however, the noted average % increase per year was mainly driven by rapid growth during the first 5 years of program inception.

Pivotal outcomes applied to BC 2009-2019

- BC =2464 hemodialysis patients in 2019 (3% growth per year)
- Composite of nonfatal MI, nonfatal stroke, hospitalization for HF, or all-cause death = 3.0% ↓ = 763 fewer events
- All-cause death = NSS
- Composite of CV events (MI, stroke, and hospitalization for HF [first event]) = 2.4% ↓ = 611 fewer events
- MI (fatal or nonfatal) = 2.6% ↓ = 662 fewer events
- Stroke (fatal or nonfatal) = NSS
- Hospitalization for HF = 2.0% ↓ = 509 fewer events
- MI, stroke, hospitalization for HF, and deaths analyzed as first + recurrent events = 5.2% = 1323 fewer events
- Blood transfusions = 3.5% ↓ = 891 fewer events

So where does the BC AMP go from here??

- Our protocol is a “PROACTIVE” protocol (with a reactive “boost”)
- Can we compress iron administration to the first week or two of the month?
- Should we be less aggressive with iron? Change to 600 mg load?
- Should we copy PIVOTAL in iron dosing?
- Analyze regional differences
- Personalize the protocol (ADPKD, EPO resistant vs. not)?
- Change the protocol and monitor changes
- Trial endpoints are more difficult to analyze

Stay tuned and thank you!

Questions?