Debate: Are HIF Stabilizers a Viable Alternative to ESAs in the Management of Anemia in CKD? CON

Jay Wish, MD

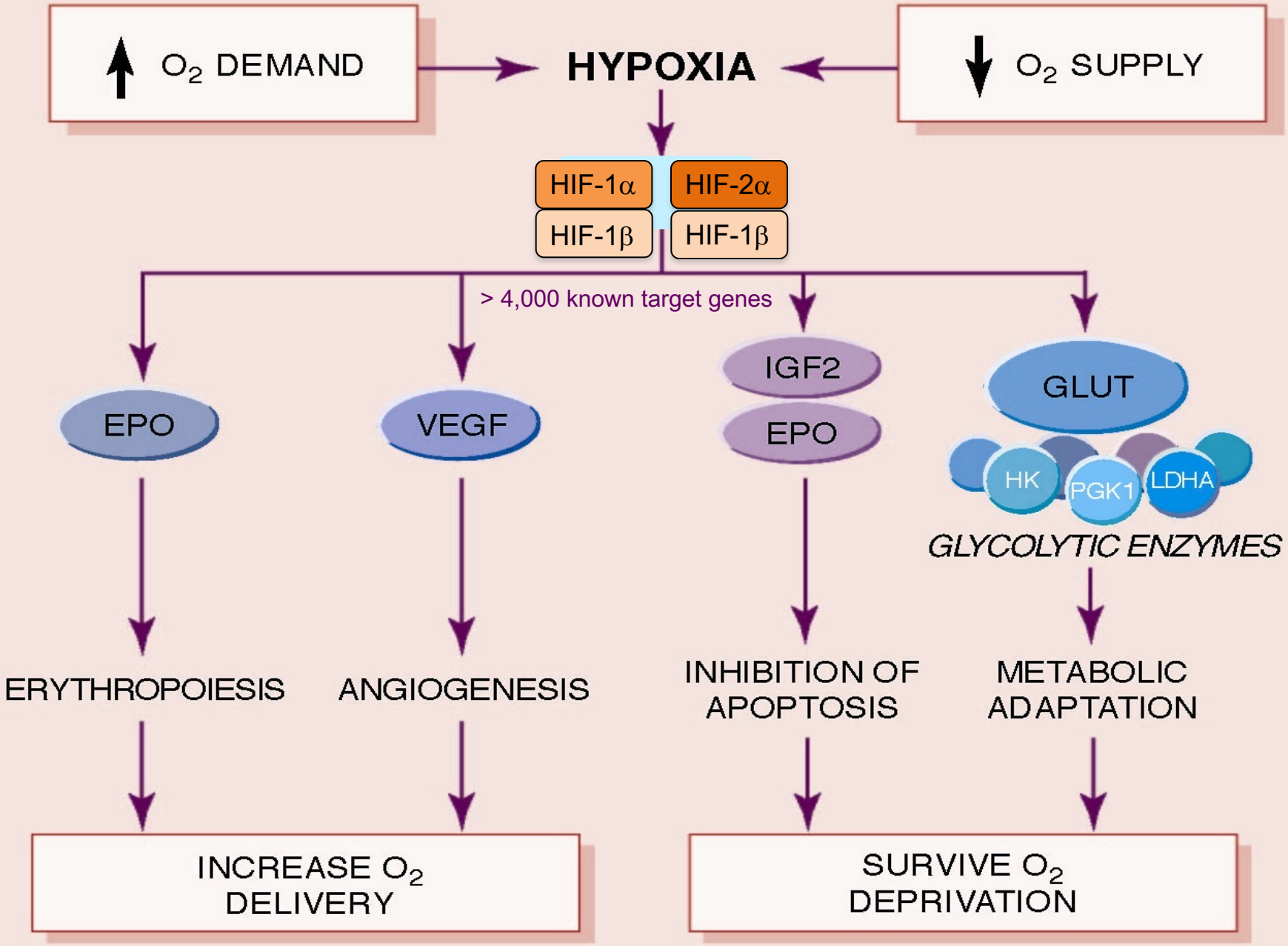
DISCLOSURES

- Consultant – Fibrogen
- Advisory Boards – AstraZeneca, Akebia/Otsuka, GSK, Vifor Pharma, Rockwell Medical, Amgen, CSL Behring
- Speakers Bureaus – AstraZeneca, Akebia

The Promise of HIF-PHIs vs ESAs (circa 2019)

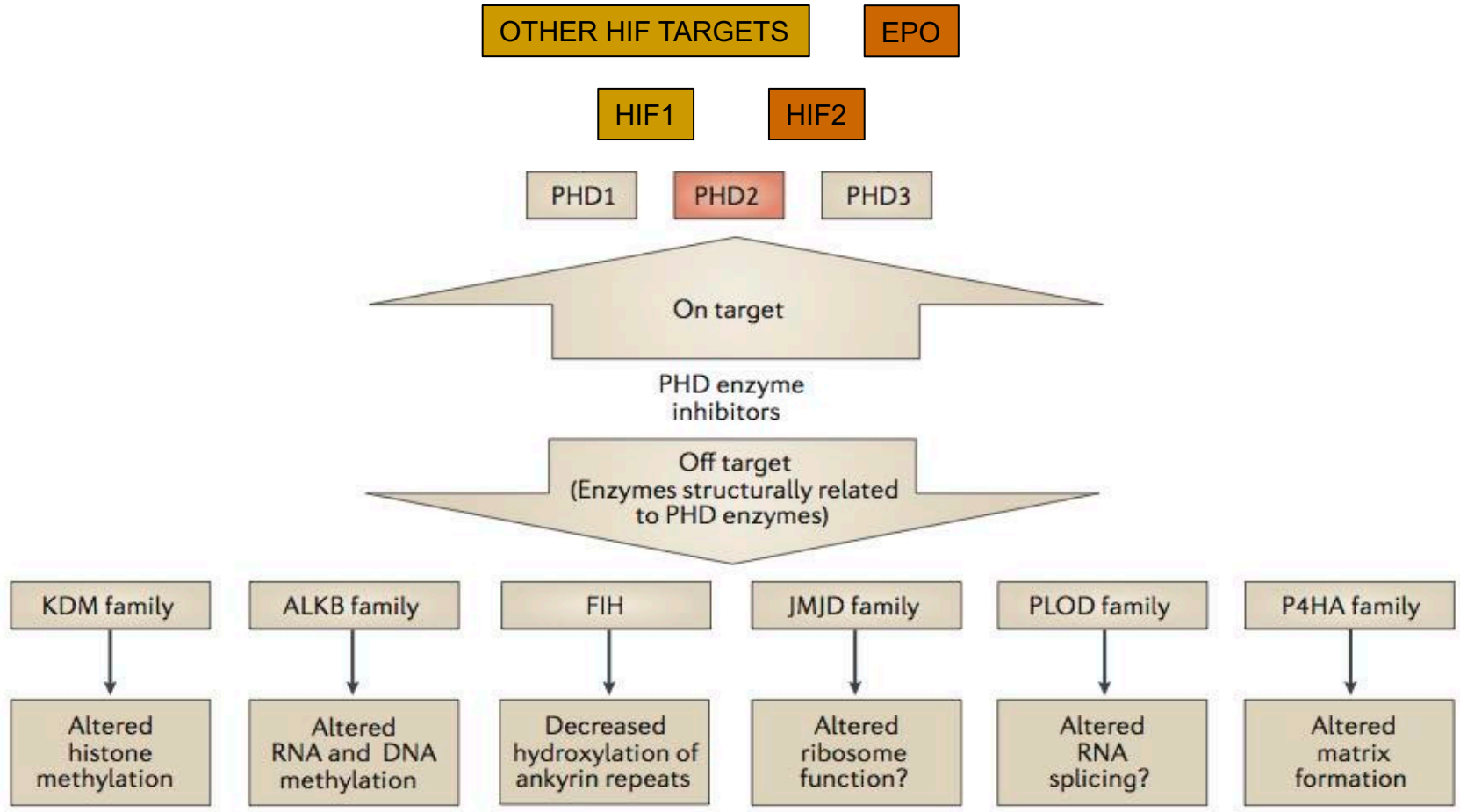
- Lower plasma EPO levels than with ESAs would decrease ESA off-target effects leading to improved MACE outcomes
- Decreased ESA off-target effects (MACE) would allow for higher Hgb targets and improved quality of life
- Improved iron mobilization would lead to decreased IV iron requirements in NDD and DD patients
- Improved iron mobilization would lead to ability to achieve target Hb level in ESA-hyporesponsive patients

Hypoxia-Inducible Factors (HIFs) Maintain Oxygen Homeostasis



Semenza, NKF HIF-PHI Workshop, 2019

PHD Inhibitors Not Only Activate HIF But May Also Activate Structurally-Related 2-OG Dependent Enzymes



Maxwell, NKF HIF-PHI Workshop, 2019

Consequences of HIF Activation in Cancer Cells

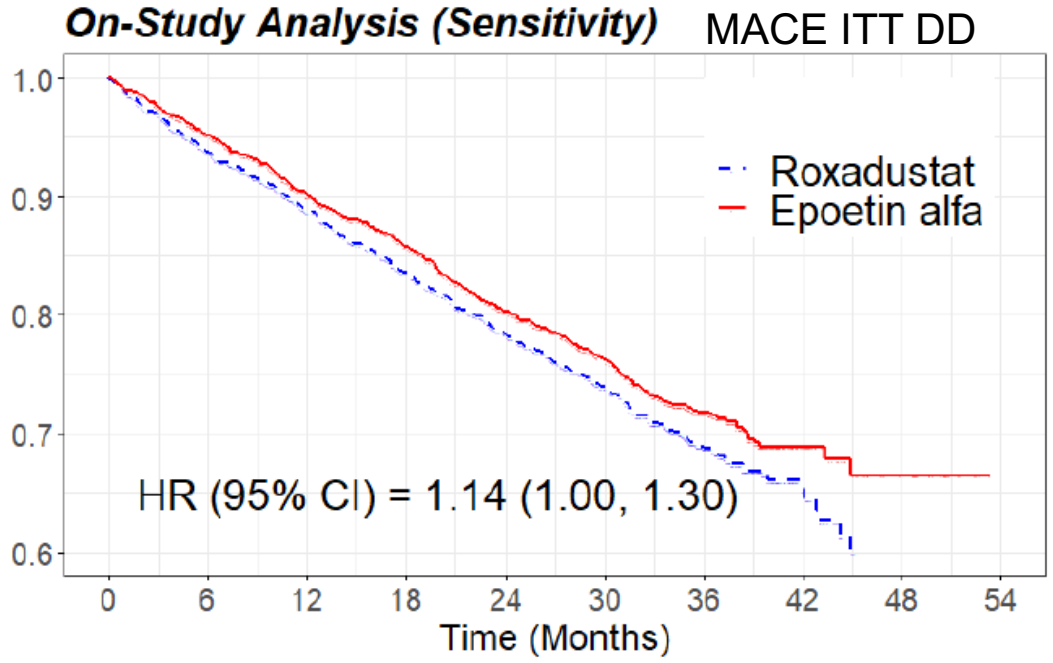
- Cell immortalization
- Maintenance of cancer stem cells
- Genetic instability
- Autocrine growth factor signaling
- Vascularization
- Glucose/Energy metabolism
- Invasion and metastasis
- Immune evasion
- Chemotherapy and radiation resistance

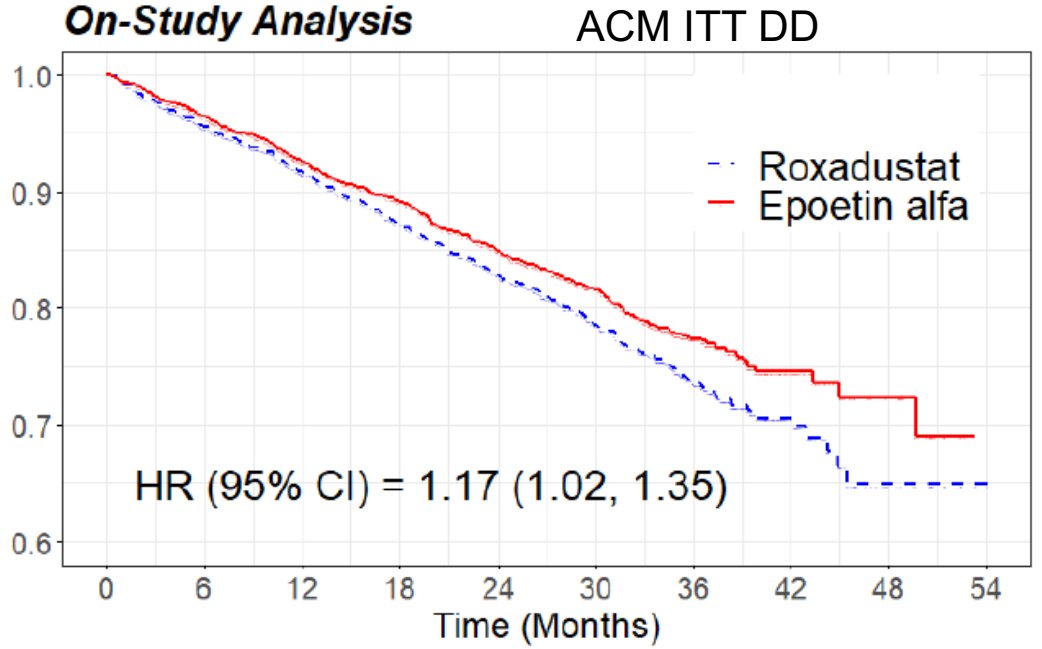
Semenza, NKF HIF-PHI Workshop, 2019

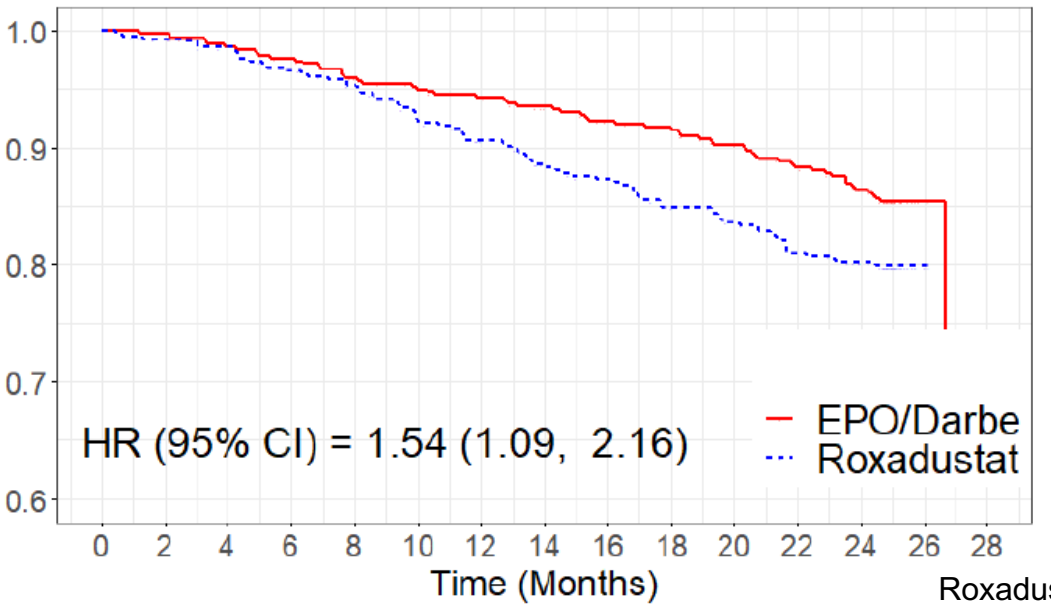
CV Events in HIF-PHI Phase 3 Clinical Trials vs ESA

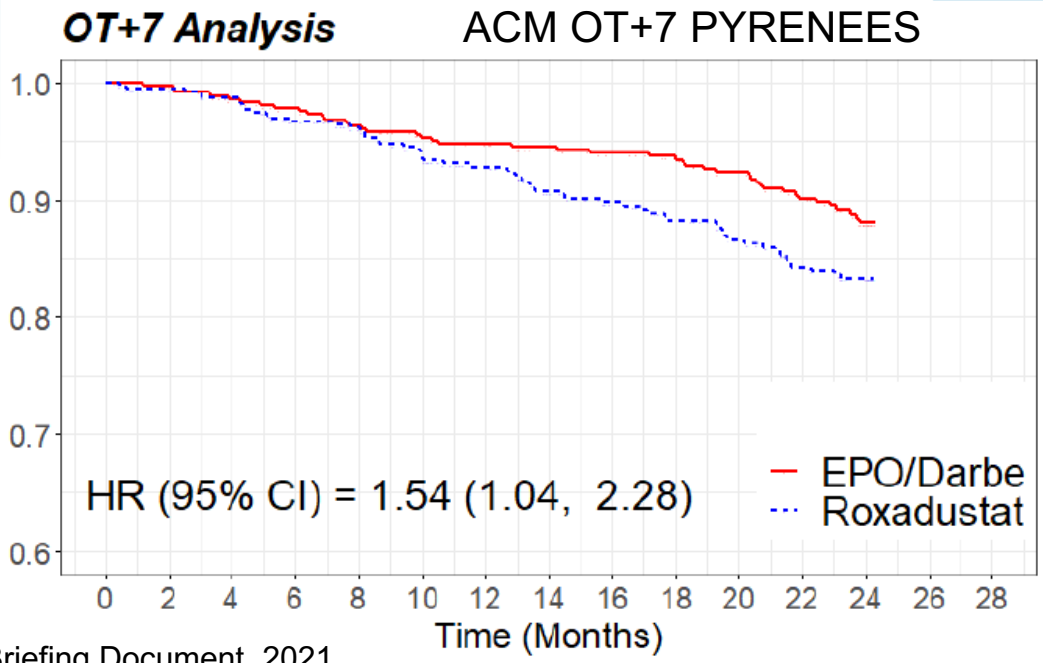
- Roxadustat
  - Increased MACE vs darbepo in DD patients in ITT analysis (HR 1.14 [1.00, 1.30])
  - Increased all cause mortality in DD patients in ITT analysis (HR 1.17 [1.02, 1.35])
  - Increased MACE vs ESA in PYRENEES study of DD patients: ITT (HR 1.54 [1.09, 2.16]), OT+7 HR 1.54 (1.04, 2.28)
  - RR for 3.9 serious DVT and 1.5 for serious vasc access thrombosis in DD patients

Roxadustat FDA Briefing Document, 2021



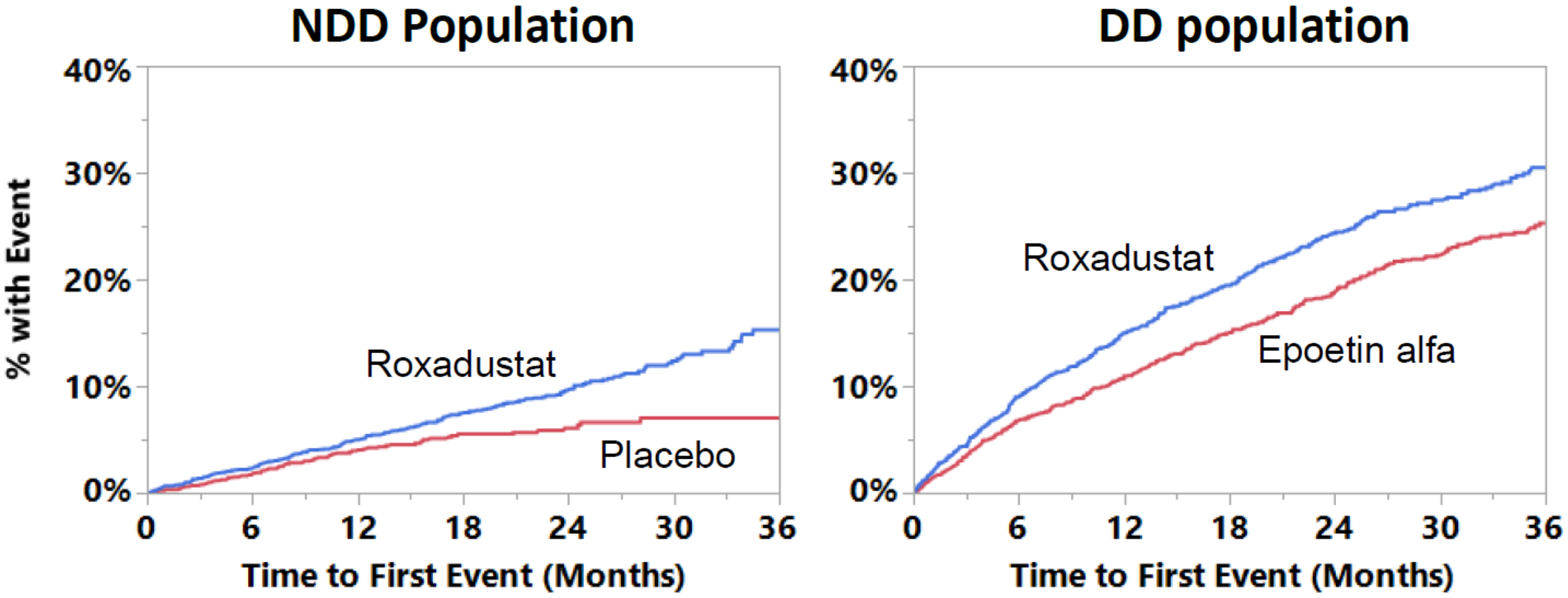






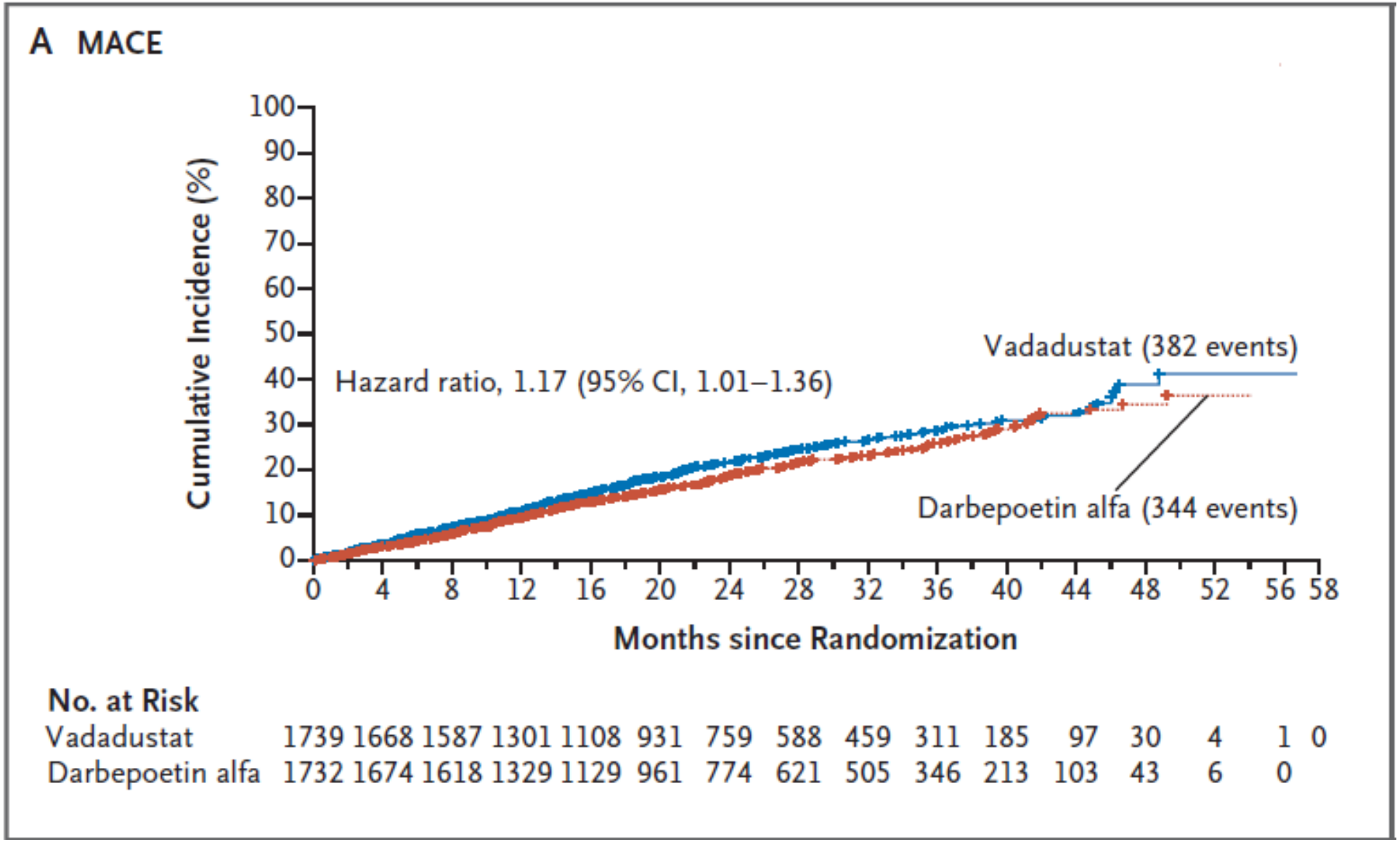
Roxadustat FDA Briefing Document, 2021

Time to First Thromboembolic Event, NDD and DD Pooled Studies; All Adverse Events (Serious and Non-serious)



Roxadustat FDA Briefing Document, 2021

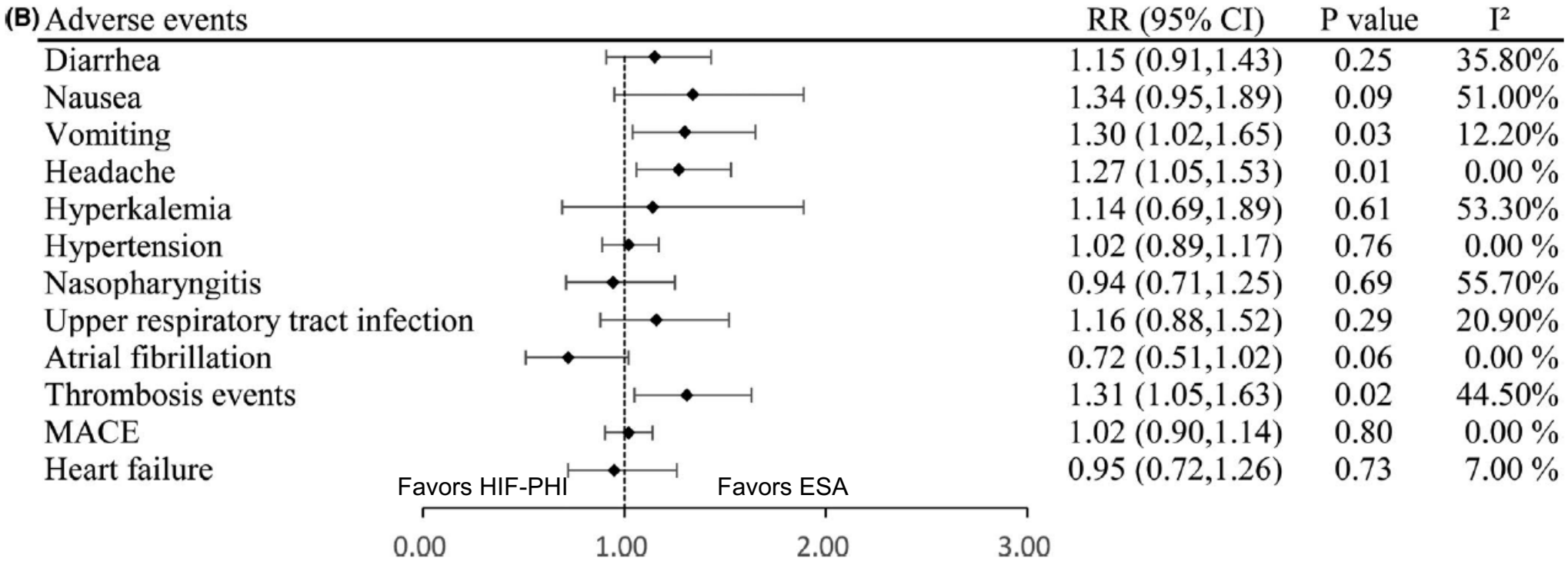
VADADUSTAT AND MACE IN GLOBAL PHASE 3 STUDIES: NDD



N Engl J Med 2021;384:1589-600.

Long-term efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in anaemia of chronic kidney disease: A meta-analysis including 13,146 patients

Huanhuan Chen MS[1,2] | Qingfeng Cheng MD[3] | Jiuxiang Wang MS[1] | Xiaofang Zhao MS[1] | Shenyin Zhu PhD[1]



J Clin Pharm Ther. 2021;00:1–11.

What About Cancer?

- In TREAT study, among 188 patients in group assigned to darbepo with pre-existing cancer there were 14 cancer deaths, as opposed to 1 cancer death among 160 patients with pre-existing cancer assigned to placebo ($p<0.002$).
- FDA has black-box warning regarding tumor progression and decreased survival with ESAs

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

- In NDD patients (ASCEND-ND), daprodustat increased cancer risk by almost 50% vs darbepo

Variable	Daprodustat (N=1937)		Darbepoetin Alfa (N=1933)		Relative Risk (95% CI)	P Value*
	Value	No. of Events	Value	No. of Events		
Cancer-related death or tumor progression or recurrence	72 (3.7)	82	49 (2.5)	67	1.47 (1.03–2.10)	0.04

DOI: 10.1056/NEJMoa2113380

CAUTION ON HIF-PHI USE ALREADY PUBLISHED

Table 2. Key policy recommendations from the institute for clinical and economic review regarding roxadustat[57]

- Clinicians should follow the principle of shared decision making to ensure that the values of patients with diverse needs and perspectives on risks and benefits of different treatments are at the heart of all treatment decisions
- Clinicians should have decision support tools and invest the time needed for shared decision making given the uncertainty and potential variability in patients' values about an oral treatment option for anemia in chronic kidney disease
- Given the level of uncertainty about the benefits vs. harms and the long-term effect of using roxadustat compared with ESAs, we strongly suggest a mandate for a registry or other rapid and comprehensive postmarketing assessment
- The manufacturer and researchers should avoid focusing primarily on hemoglobin levels and the need for transfusion. Future research should expand outcomes measured to include patient-relevant outcomes, such as quality of life, functional status, fatigue, overall cardiovascular events, and mortality, in addition to the need for transfusion
- Researchers should conduct real-world comparative studies of roxadustat vs. ESAs that evaluate a broad set of patient subgroups, including ethnic and racially diverse populations and those who are hyporesponsive to ESAs
- Given the mechanism of action for roxadustat, patients were excluded from clinical trials if they had acute coronary syndrome, acute stroke, acute seizure, or thrombotic event within the last 12 weeks. Until further data are gathered, clinicians should consider delaying treatment with roxadustat for patients with this clinical scenario
- Given that the evidence is not adequate to distinguish clinical benefit and that there are more data and years of clinical experience with ESAs, some payers may wish to consider stepping through ESAs if they are substantially lower priced than roxadustat before obtaining coverage for a more expensive option

Table 3. Key recommendations of the Asian-Pacific Society of Nephrology regarding the use of hypoxia-inducible factor prolyl hydroxylase inhibitors[84]

- Physicians can consider HIF-PH inhibitors as an alternative to ESA in correcting and maintaining hemoglobin level in NDD- and DD-CKD patients
- Iron deficiency should be corrected (ferritin $>$ 100 ng/dl and TSAT $>$ 20%) before HIF stabilizers are initiated
- HIF-PH inhibitors may be preferred to ESAs
  - If frequency of hospital/clinic visits or invasiveness of injections is a burden
  - If target hemoglobin cannot be achieved with ESA
- Administration of HIF-PH inhibitors should be undertaken with great caution, if at all, in patients with known malignancy
- Given the theoretical risk of retinopathy, prompt ophthalmologic evaluation should be ordered for patients who report visual disturbance after drug initiation
- Regular monitoring of liver function should be considered given uncommon but possible risk of liver injury from HIF-PH inhibitors
- Serum potassium should be monitored during treatment with HIF-PH inhibitors given reports of hyperkalemia in clinical trials
- Although there are no data suggesting HIF-PH inhibitors increase blood pressure, attention should be paid to blood pressure control in patients receiving these agents
- Given theoretical effects on pulmonary hypertension, attention should be paid to changes in cardiac function in patients receiving HIF-PH inhibitors
- Limited use of HIF-PH inhibitors is suggested in patients with a history of thrombotic events
- Cyst size should be monitored in patients with polycystic kidney disease receiving HIF-PH inhibitors

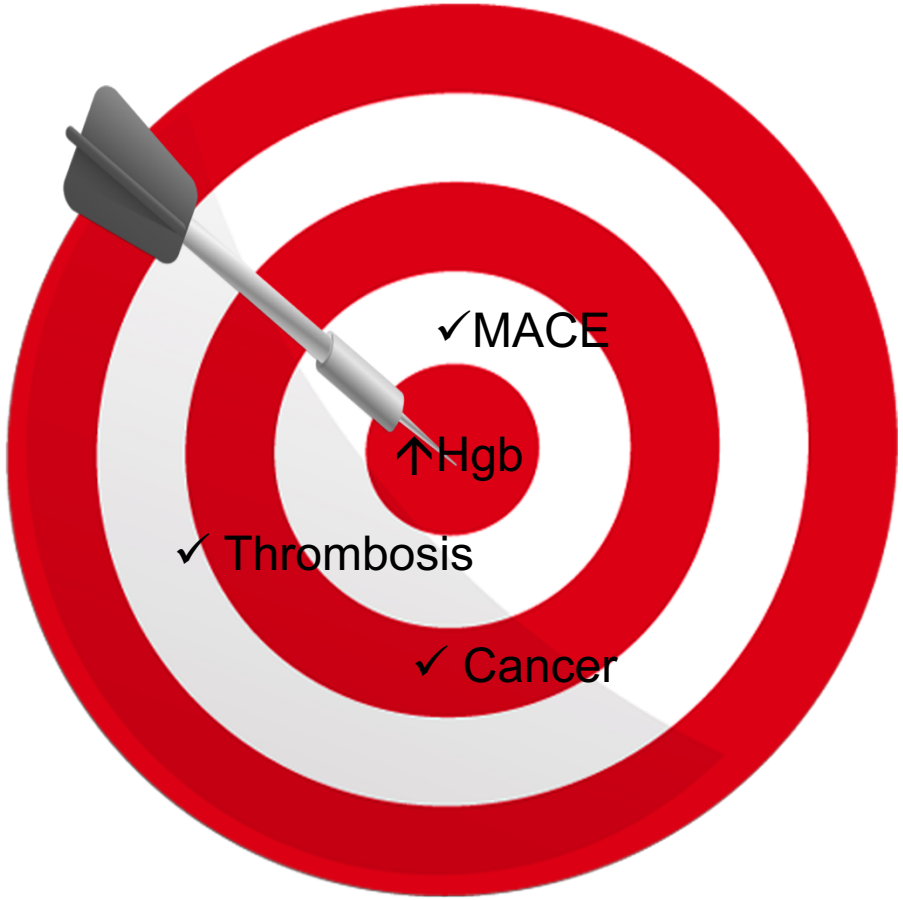
KI Reports, 6:2540–2553, 2021

THE PROMISE OF HIF-PHIS VS ESAS (CIRCA ~~2019~~ 2021)

- Lower plasma EPO levels than with ESAs would decrease ESA off-target effects leading to improved MACE outcomes Not true, MACE may actually be worse
- Decreased ESA off-target effects (MACE) would allow for higher Hgb targets and improved quality of life Not true; no improvement in QOL vs. ESAs in head-to-head studies
- Improved iron mobilization would lead to decreased IV iron requirements in NDD and DD patients May be true, but how does that translate into improved outcomes?
- Improved iron mobilization would lead to ability to achieve target Hb level in ESA-hyporesponsive patients May be true, but no studies done specifically targeting ESA-hyporesponsive patients

SUMMARY

ESAs: The devil we know



HIF-PHIs: The devil we don't know