



Anemia and Outcomes in Cardiovascular Disease

Shivak Sharma, MD

Chief Resident, Shatz-Strauss Firm A
Department of Internal Medicine

Disclosures - None

Outline

- Anemia – Definition?
- Impact of Anemia on Coronary Artery Disease (CAD)
- Impact of Anemia on Heart Failure (HF)
- *Impact of Anemia on Atrial Fibrillation (AF)*
- Anemia and outcomes of interventions
- Mediator or Marker?
- Clinical Implications
- The Future...

Anemia

- **Prevalence** : 26% among people over the age of 85 and 12% among people in the age group of 75 to 84 (WHO-defined anemia)¹.
- Significant limitations in the current approaches of defining anemia:
 - 2.5-5% of “normal” population classified as anemic (2 standard deviations below the mean)
 - Special populations –African Americans, elderly, smokers, high altitude dwellers, athletes, ACE-Is, etc.
- One study has suggested that the lower limits of an **optimal** hemoglobin (Hgb) level, as assessed by all-cause mortality data, are 13.0 and 14.0 g/dL for elderly women and men, respectively.²

1. Steensma et al. *Mayo Clin Proc* 2007;82:958 - 66.

2. Culleton et al. *Blood*. 2006;107(10):3841-6

Anemia and CAD

- *Acute Coronary Syndrome*: Anemia independently predicts mortality and morbidity.
 - In an observational study, the risk of cardiovascular mortality, nonfatal MI, or recurrent ischemia at 30 days was significantly increased in patients with a Hgb concentration below **11 g/dL** [An adjusted OR of 1.45 (95% CI 1.33 - 1.58, $P < 0.001$) for each 1 g/dL decrement in hemoglobin]³. *Also observed a reverse J-shaped relationship.*
 - Worsening anemia was associated with decreased 2-year survival in patients after ACS [AHR of 2.46 (95% CI 1.25 to 4.85)].⁴

3. Sabatine et al. *Circulation* 2005;111(16):2042-9

4. Vaglio et al. *Am J Cardiol* 2005;96:496 - 9.

Anemia and CAD

- *Chronic Angina: Anemia independently predicts mortality and morbidity.*
 - In an observational study of elderly patients with stable symptomatic CAD, a decrease in 1 g/dL Hgb increased the risk of all-cause death by 34% (adjusted risk ratio 1.34, $P < .01$), of cardiac death by 28% (adjusted risk ratio 1.28, $P = .02$).⁵
- *Percutaneous Coronary Intervention: Anemia independently predicts mortality and morbidity.*
 - After adjustment for comorbidities, anemia was associated with a higher risk of mortality after percutaneous coronary intervention (RR 2.22, 95% CI 1.02-4.43; $P = 0.024$).⁶

5. Muzzarelli et al. *Am Heart J.* 2006;152(5):991-6

6. Liu et al. *Zhonghua Nei Ke Za Zhi.* 2008;47:114-6

Anemia and Heart Failure

- A large number of retrospective studies have concluded that anemia independently predicts adverse clinical outcomes in HF.
 - In a large cohort of community-dwelling patients with HF, hazard ratio of mortality, adjusting for covariates, was 1.34 (CI: 1.24 to 1.46) in anemic patients.⁷
 - In NYHA Class III and IV HF, multivariate analysis adjusting for known HF prognostic factors, low Hgb proved to be an independent predictor of mortality (relative risk 1.13, CI: 1.05 to 1.22 for each decrease of 1 g/dl).⁸
 - In severe HF, lowest quintile of Hct had a 52% higher risk of death (AHR 1.52, 95% CI: 1.11 to 2.10), compared with the highest quintile.⁹

7. Ezekowitz et al. *Circulation* 2003;107(2):223-5

8. Horwich et al. *J Am Coll Cardiol* 2002;39(11):1780-6

9. Mozaffarian et al. *J Am Coll Cardiol* 2003;41(11):1933-9

Anemia and Heart Failure

- However, in one of the largest studies that controlled for several confounding variables in a multivariate analysis:
 - Anemia was not an independent predictor of mortality (Hct $\leq 24\%$ vs $> 40\%$ - 44% : RR, 1.02; 95% CI, 0.86-1.19; P = .85).¹⁰
 - The association between lower Hct values and HF-related readmission was significant (Hct $\leq 24\%$ vs $> 40\%$ - 44% : RR, 1.21; 95% CI, 1.04-1.38; P = .01).¹⁰
- *In retrospective studies, there remains some uncertainty whether anemia is an independent predictor of increased mortality, however majority of the data supports this correlation.*

Anemia and Atrial Fibrillation

- *Hypothesis:*
 - Anemia is associated with decreased survival and increased hospitalizations among patients with AF after adjusting for demographic information, comorbid conditions, and other relevant covariates.
- *Design*¹¹: Retrospective Cohort Study
- *Patient Population:* 23,657 Medicare beneficiaries included in the National Registry of Atrial Fibrillation (NRAF) II dataset.
- *Study Setting:* Medicare beneficiaries who were hospitalized with atrial fibrillation between 04/01/98-03/31/99 in all 50 states.

Anemia and Atrial Fibrillation

■ *Data Collection:*

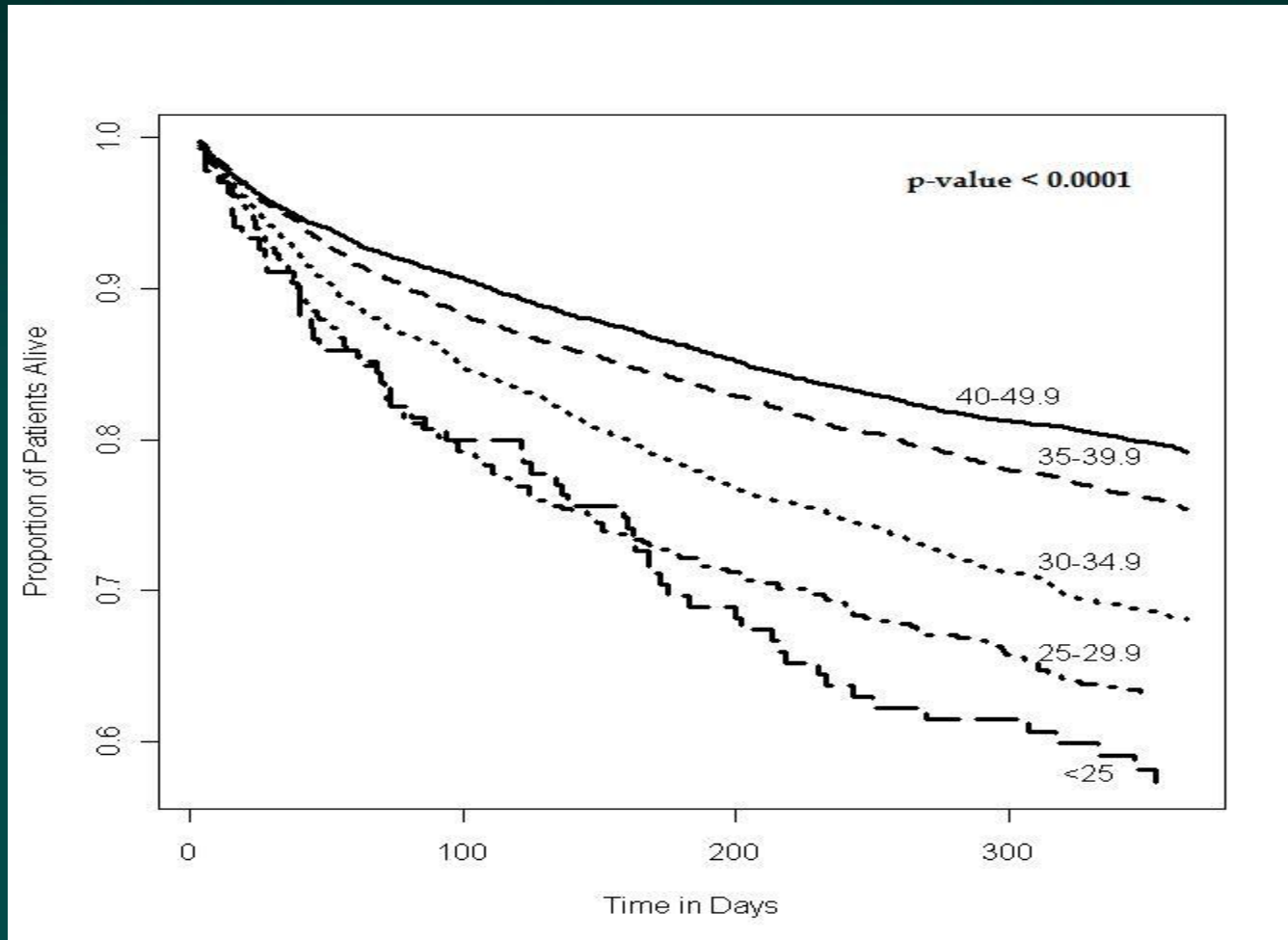
- Information on demographics, comorbid conditions, death and other relevant covariates was obtained from Medicare records.
- Index hospitalization admission Hct was classified into 7 categories, including $< 25\%$, $\geq 50\%$, and increments of 5% in between.

■ *Outcomes:*

- *Primary outcome* - All cause mortality during a median follow-up period of 1 year.
- *Secondary outcome* – Hospitalization for any reason during the same follow-up period.

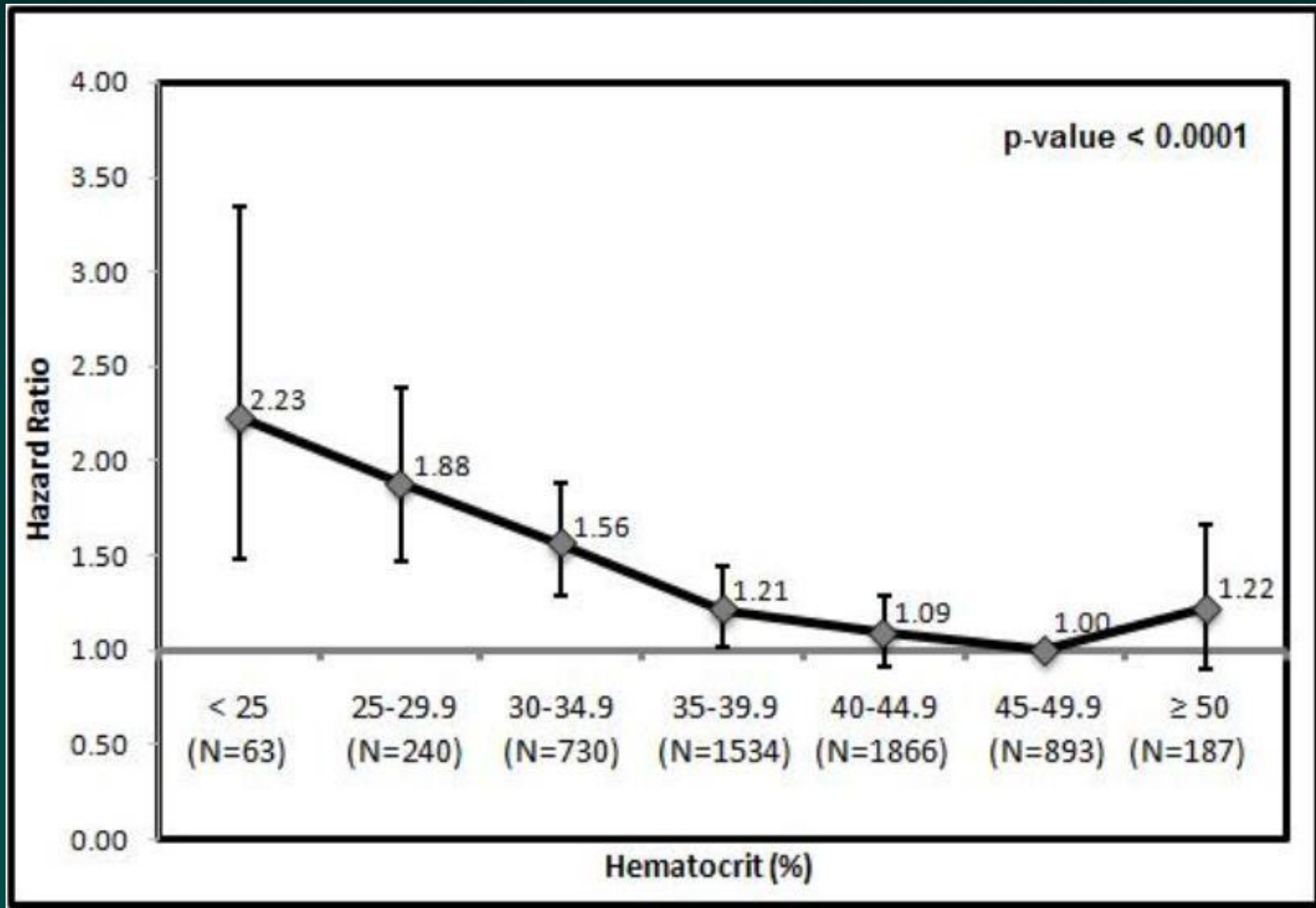
Anemia and Atrial Fibrillation

Fig 1: Kaplan-Meier survival according to Hct categories; $p < 0.0001$



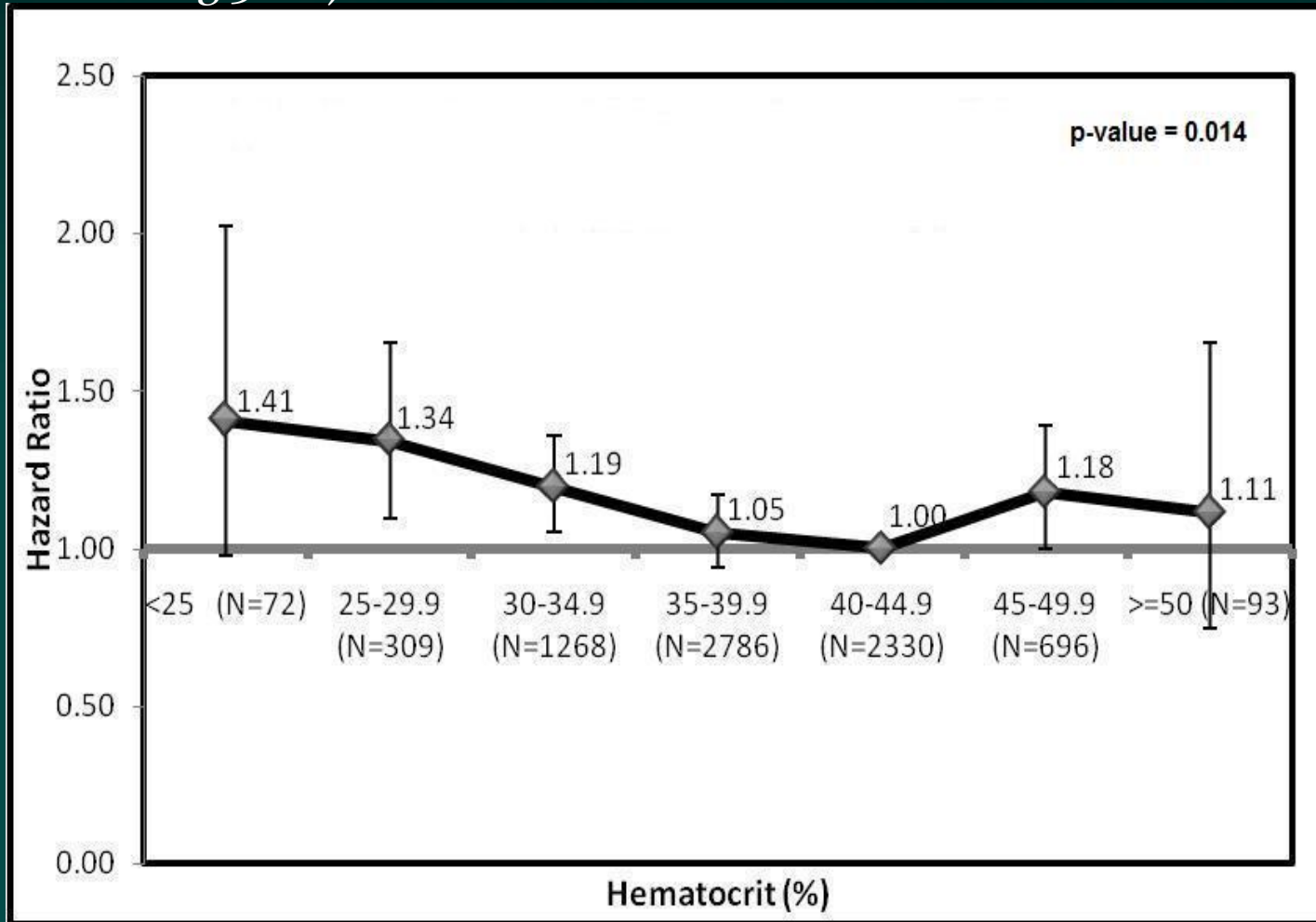
Anemia and Atrial Fibrillation

Fig 2: Adjusted Hazard Ratio of Death for Men



Anemia and Atrial Fibrillation

Fig 3: Adjusted Hazard Ratio of Death for Women



Anemia and Atrial Fibrillation

■ *Conclusions:*

- Striking and significant trend of increasing mortality with declining Hct.
- ***The nadir of mortality for the entire population was in the Hct range of 40-44.9%.***
- Significant Gender Interaction ($p = 0.006$); association between anemia and mortality is significant in women but stronger in men.
- In women, Hct of 40-44.9% had the most favorable survival.
- In men, Hct of 45-49.9% had the most favorable survival.
- In both women and men, $\text{Hct} \geq 50\%$ tended to have increased mortality – **Reverse J-shaped relationship.**

Anemia and Outcomes

- Anemia is an independent and powerful predictor of adverse outcomes in a broad range of cardiovascular conditions.
- Correlation is not causation and confounding is difficult to eliminate completely.
- Can interventions aimed at treating anemia improve outcomes in patients with cardiovascular disease?

Anemia and Interventions

■ *Coronary Artery Disease*

- **Blood Transfusion:** No Consensus with variable outcomes.
 - Blood transfusion in patients presenting with ACS and with Hct < 33% is associated with a reduction in 30-day mortality (adjusted odds ratio, 0.69; 95% CI, 0.53 - 0.89)¹²
 - Post hoc analysis of clinical trials data (the GUSTO IIb, PURSUIT, and PARAGON B trials) revealed that transfusion was associated with an increased hazard for 30-day death (AHR, 3.94; 95% CI, 3.26-4.75). The predicted probability of 30-day death was higher with transfusion at nadir Hct values above 25%.¹³
 - No ACC/AHA and ACCP guidelines.

12. Wu et al. *N Engl J Med.* 2001;345(17):1230-6

13. Rao et al. *JAMA.* 2004;292(13):1555-62

Anemia and Interventions

■ *Heart Failure*

- **Erythropoiesis stimulation agents:** Encouraging data but concern for potential harm.
 - Prospective RCT (STAMINA-HeFT) showed that darbopoeitin alfa was well tolerated with no significant clinical benefits but a trend towards a lower risk of HF hospitalization and mortality (HR 0.68; 95% CI, 0.43 - 1.08; P=0.10).¹⁴
 - Other small studies have shown that combination therapy of EPO with Iron resulted in improved clinical outcomes.^{15,16}
 - In the Normal Hct Trial of EPO therapy in patients with ESRD and HF/IHD, a “normal” Hct (42%) was associated with a trend of increasing morbidity and mortality (RR 1.3; 95% CI, 0.9 to 1.9)¹⁷

14. Ghali et al. *Circulation*. 2008;117(4):526-35

15. Silverberg et al. *J Am Coll Cardiology* 2001;37:1775 – 80

16. Palazzuoli et al. *Am Heart J* 2006;152:1096.e9 – 15

17. Besarab et al. *N Engl J Med* 1998;339(9):584-90

Anemia and Interventions

■ *Heart Failure*

- *Iron*: Promising results from small trials.
 - Two small studies (one randomized) suggest that treatment with IV Iron improves exercise capacity, decreases symptoms and has a favorable effect on other surrogate markers of HF.^{18,19}
 - Large trials are needed before recommendations for routine iron administration can be made.

18. Bolger et al. *J Am Coll Cardiol*. 2006 Sep 19;48(6):1225-7

19. Toblli et al. *J Am Coll Cardiol*. 2007 Oct 23;50(17):1657-65

Anemia and Interventions

■ *Other Diseases:*

- No therapeutic trials or post-hoc trial analysis in anemic patients with atrial fibrillation.
- Among patients with CKD, the use of EPO to achieve a target hemoglobin of 13.5 g/dl was associated with an increased composite risk of death, MI, stroke and hospitalization for HF.²⁰
- In a recent meta-analysis, use of erythropoiesis-stimulating agents for cancer-related anemia was associated with improved quality of life but elevated mortality.²¹
- Randomized trial of transfusion therapy in critically ill patients showed no overall mortality benefit, although favorable trends were noted in patients with acute myocardial infarction or unstable angina.²²

20. Singh et al. *N Engl J Med* 2006;355:2085 – 2098

21. Tonelli et al. *CMAJ* 2009; 180:E62

22. Hebert et al. *N Engl J Med* 1999;340:409-17

Mediator or Marker?

- Is Anemia a mediator or marker of mortality in patients with cardiovascular disease? – No consensus!
- Inconsistent results of intervention trials targeting anemia in patients with cardiovascular disease.
- No clear evidence that anemia represents an appropriate therapeutic target in these patients.
- Black-box warning to prescribing erythropoiesis stimulating agents presents challenges for recruiting patients to future RCTs.²³
 - Increased mortality and serious CV events in patients with CKD
 - Increased mortality and/or tumor progression in cancer patients
 - Increased risk of thromboembolic events in surgery patients

Clinical Implications

- Expert Opinion²⁵: It is unlikely that transfusion is beneficial for patients with an ACS who have a Hct > 30%, but the benefits probably exceed the risks for patients with a Hct < 21%
- British Blood Transfusion Task Force recommendations:²⁶
 - Transfusion not indicated when estimates of actual and anticipated Hgb concentrations are > 10 g/dl.
 - Transfusion is indicated when the Hgb concentration is < 7 g/dl.
 - Indication is unclear when Hgb concentrations between 7 and 10 g/dl.
 - *Patients over the age of 65 years and patients with cardiovascular or respiratory disease, consider adopting a higher concentration at which transfusions are indicated, e.g. when the Hgb concentration becomes < 8 g/dl.*

25. Hebert et al. JAMA 2004; 292:1610

26. Murphy et al. Br J Haematol 2001; 113:24

The Future...

- **IRON-HF Study** - Effects of iron supplementation alone (IV or PO) on parameters of functional capacity in HF patients with anemia with decreased availability of iron.
- **RED-HF Trial** - Efficacy of treatment of anemia with darbepoetin alfa compared to placebo on the composite of time to death from any cause or first hospital admission for worsening HF in subjects with symptomatic left ventricular systolic dysfunction and anemia.
- **HFPEF Trial** – Efficacy of treating anemia in HF and preserved EF with EPO and its effect on ventricular function, exercise capacity and health status.
- Future exploration of anemia as a potential therapeutic target in patients with atrial fibrillation.



Special Thanks

- Michael W. Rich M.D.
- Brian F. Gage M.D.
- Elena Deych M.S.

- Victoria Sharma M.D.