

# Evidence-based Synthesis Program (ESP)

## Treatment of Anemia in Patients with Heart Disease

A Systematic Review of the Evidence

**Devan Kansagara MD, MCR**

**David Kagen MD**

**Edward Dyer MD**

**Cyberseminar 4/16/12**

# Evidence-based Synthesis Program (ESP)

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### **Co-Authors/Collaborators**

- Honora Englander MD
- Michele Freeman MPH
- Rose Relevo MLIS, MS

### **Expert Panel/Reviewers**

- Sunil Rao MD
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- Nick Fitterman MD
- Barry Massie MD
- Inderjit Anand MD
- Jack McAnulty MD

# Evidence-based Synthesis Program (ESP)

## Disclosure

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# Evidence-based Synthesis Program (ESP)

## VA Evidence-based Synthesis (ESP) Program Overview

- Sponsored by VA Office of Research & Development, Quality Enhancement Research Initiative (QUERI).
- Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers and policy-makers, as they work to improve the health and healthcare of Veterans.
- Builds on staff and expertise already in place at the Evidence-based Practice Centers (EPC) designated by AHRQ. Four of these EPCs are also ESP Centers:
  - Durham VA Medical Center; VA Greater Los Angeles Health Care System; Portland VA Medical Center; and Minneapolis VA Medical Center.

# Evidence-based Synthesis Program (ESP)

- Provides evidence syntheses on important clinical practice topics relevant to Veterans, and these reports help:
  - develop clinical policies informed by evidence,
  - the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
  - guide the direction for future research to address gaps in clinical knowledge.
- Broad topic nomination process – e.g. VACO, VISNs, field – facilitated by ESP Coordinating Center (Portland) through online process:

<http://www.hsrd.research.va.gov/publications/esp/TopicNomination.cfm>

# Evidence-based Synthesis Program (ESP)

- Steering Committee representing research and operations (PCS, OQP, ONS, and VISN) provides oversight and guides program direction.
- Technical Expert Panel (TEP)
  - Recruited for each topic to provide content expertise.
  - Guides topic development; refines the key questions.
  - Reviews data/draft report.
- External Peer Reviewers & Policy Partners
  - Reviews and comments on draft report
- Final reports posted on VA HSR&D website and disseminated widely through the VA.

<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>

# Outline

- Poll
- Anemia in heart disease
- Summarize systematic review of anemia treatment efficacy
  - Methods
  - Results: ESAs, iron, transfusions
- Implications
- Questions

# Poll Question 1

- How would you describe your primary responsibility?
  - 1) Researcher
  - 2) Clinician, mainly outpatient
  - 3) Clinician, mainly inpatient
  - 4) Clinician, subspecialty
  - 5) Administration

# Poll question 2

- Do you believe erythropoiesis stimulating agents (eg EPO) should be used to treat anemia in patients with congestive heart failure?
  - 1) Yes
  - 2) No
  - 3) Unsure

# Poll question 3

- Have you used iron supplementation to treat symptomatic patients with heart failure?
  - 1) yes
  - 2) no, but I have seen it used at my institution
  - 3) no
  - 4) unsure

# Poll question 4

- A 68 yo male is hospitalized after sustaining a hip fracture and is awaiting surgery. He has hip pain but is otherwise asymptomatic. He has a history of MI 1 year ago. I would transfuse him if hemoglobin were less than:
  - 1) 10 g/dL
  - 2) 9 g/dL
  - 3) 8 g/dL
  - 4) 7 g/dL

# Poll question 5

- A 60 yo male was admitted with unstable angina and underwent successful stent placement today. He is not bleeding, but his Hgb is slightly lower at 9 g/dL today. Would you transfuse him?
  - 1) Yes
  - 2) Only if he had symptoms
  - 3) No
  - 4) Unsure

# Prevalence of anemia in heart disease

- 10-20% of coronary heart disease patients
- One-third of congestive heart failure patients
- Iron deficiency with or without anemia also very common

# Anemia is associated with poor outcomes in CHF

- 2% increase in 1 yr mortality for each 1% lower hematocrit

Kosiborod M, Am J Med, 2003

- In stable CHF patients, development of new anemia is frequent and associated with increasing risk of death and hospitalization

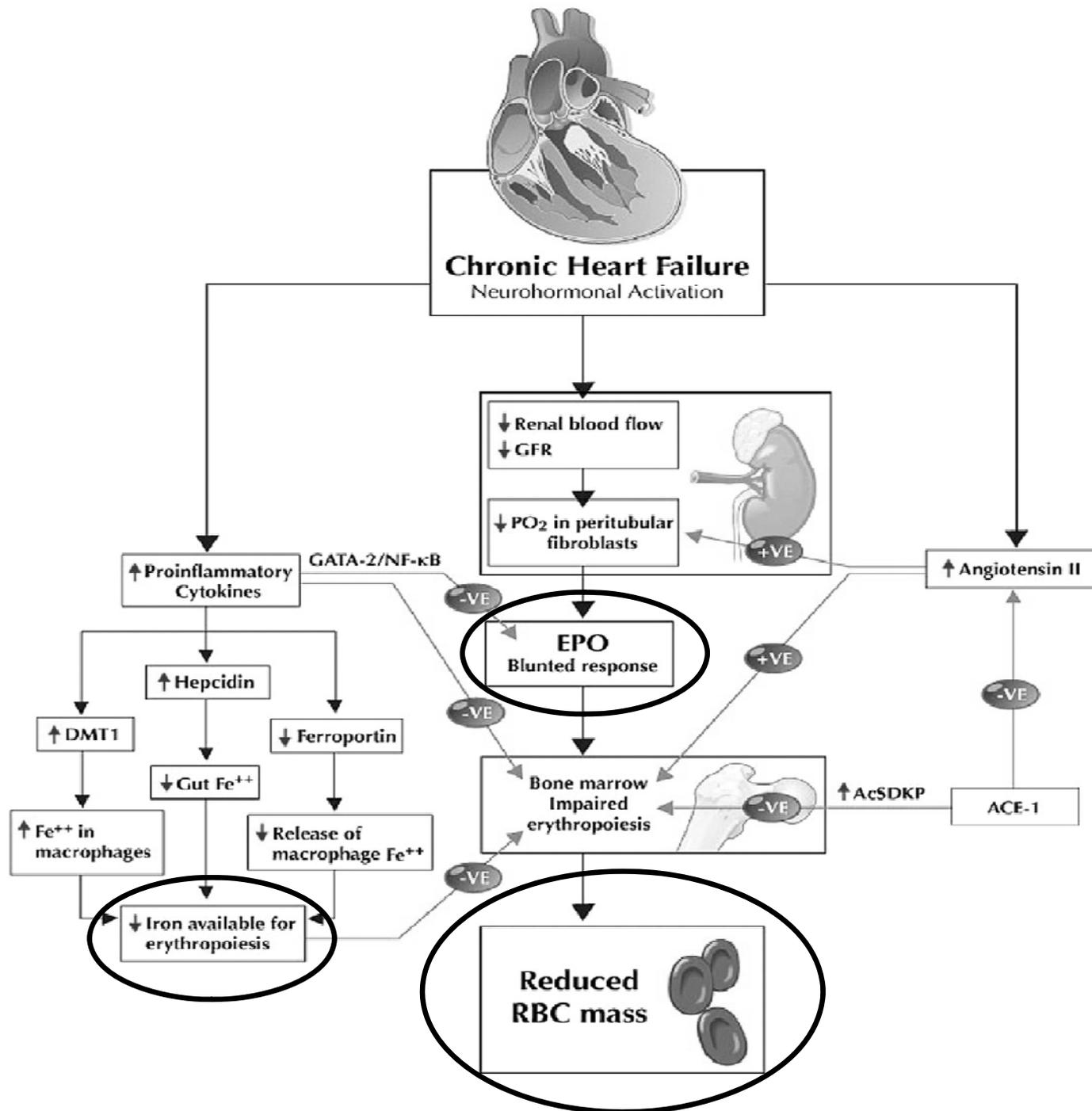
Komajda M, Eur Heart J, 2006

- The mechanism for poor outcomes may be unrelated to underlying CHD and myocardial ischemia

Felker G, Eur J Heart Fail, 2006

# Anemia and CHD

- Lower hemoglobin associated with higher mortality risk after STEMI and NSTEMI
- Anemia can decrease myocardial oxygen delivery distal to a stenosis, and increase myocardial oxygen demand



Anand, I. S. J Am Coll Cardiol 2008;52:501-511

# Potential treatments

- Erythropoiesis-stimulating agents (ESAs)
- Iron
- Red Blood Cell Transfusions

# Cochrane review ESAs in CHF

“This review shows that ESAs improves anaemia, exercise tolerance, quality of life and reduces symptoms in heart failure patients with a mild anaemia. ESAs may also reduce hospital admission and improve survival. There was no increase in major side effects in those receiving ESA therapy compared to control over the 2-12 month study period...”

# Variation in transfusion practice

- “10/30” rule – dogma originating in 1942
- RBC transfusions have remained at peak levels throughout last decade
- Survey studies suggest higher thresholds used in CHD patients
- Cohort studies suggest triggers range 8-10 g/dL

# Key Questions

In patients with CHF or CHD,

- Key Question 1. What are the health outcome benefits and harms of treating anemia with erythropoiesis-stimulating agents (ESAs)?
- Key Question #2. What are the health outcome benefits and harms of using iron to treat iron deficiency with or without anemia?
- Key Question #3. What are the health outcome benefits and harms of treating anemia with red blood cell transfusions?

# Study selection

- **Patients:** Adult patients with
  - CHF (with or without reduced systolic function) or,
  - CHD (acute coronary syndrome, post-acute coronary syndrome, history of MI or angina), and anemia or iron deficiency
- **Interventions:**
  - ESAs with or without iron: These include erythropoietin and darbepoetin
  - Iron: Intravenous or oral
  - Red blood cell transfusion
- **Comparator:** Usual care, placebo

# Study Selection

- **Outcomes:**
  - Mortality (all-cause and disease specific),
  - hospitalization (all-cause and disease-specific),
  - exercise tolerance or duration (any metric, most commonly NYHA class, 6-minute walk test),
  - quality of life,
  - cardiovascular events (myocardial infarction, heart failure exacerbation, need for revascularization)
  - Harms (HTN, VTE, cerebrovascular events)

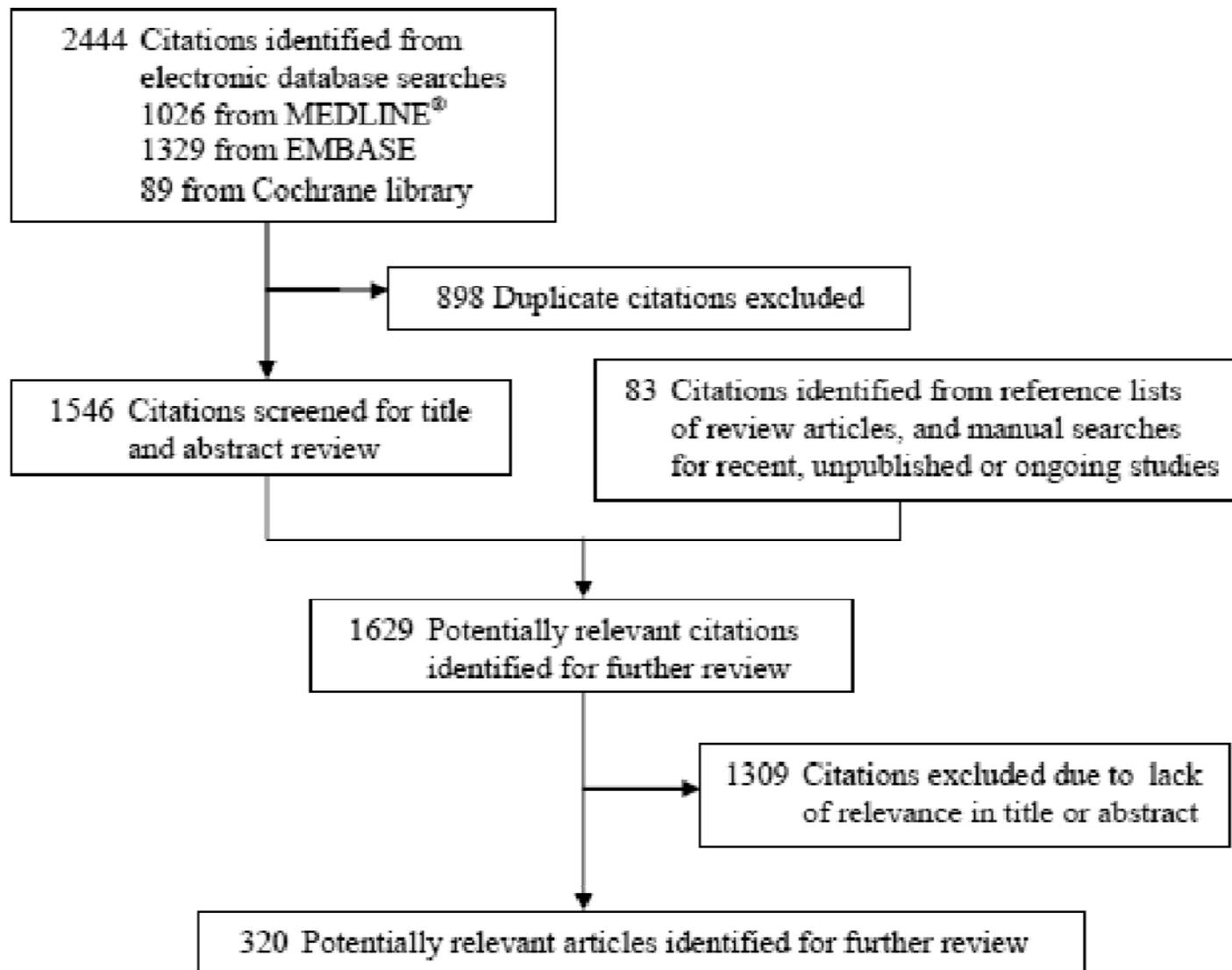
# Study selection

- Transfusions – included observational studies
  - Except cardiac surgery

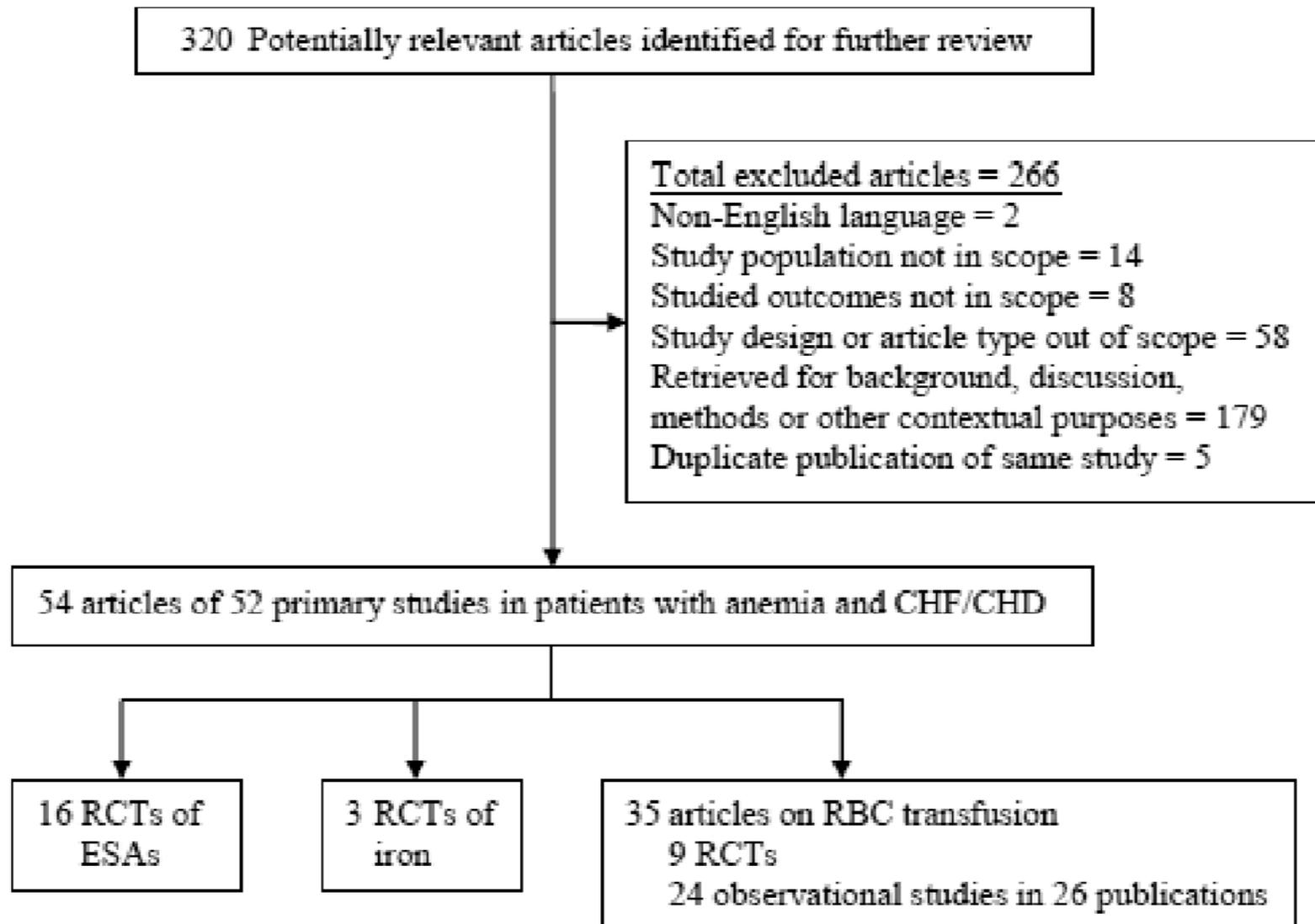
# Search

- MEDLINE and Cochrane
- 1947-Nov 2010
- ClinicalTrials.gov
- Directly contacted drug companies

# Literature Flow – Anemia and CHF



# Literature flow, continued

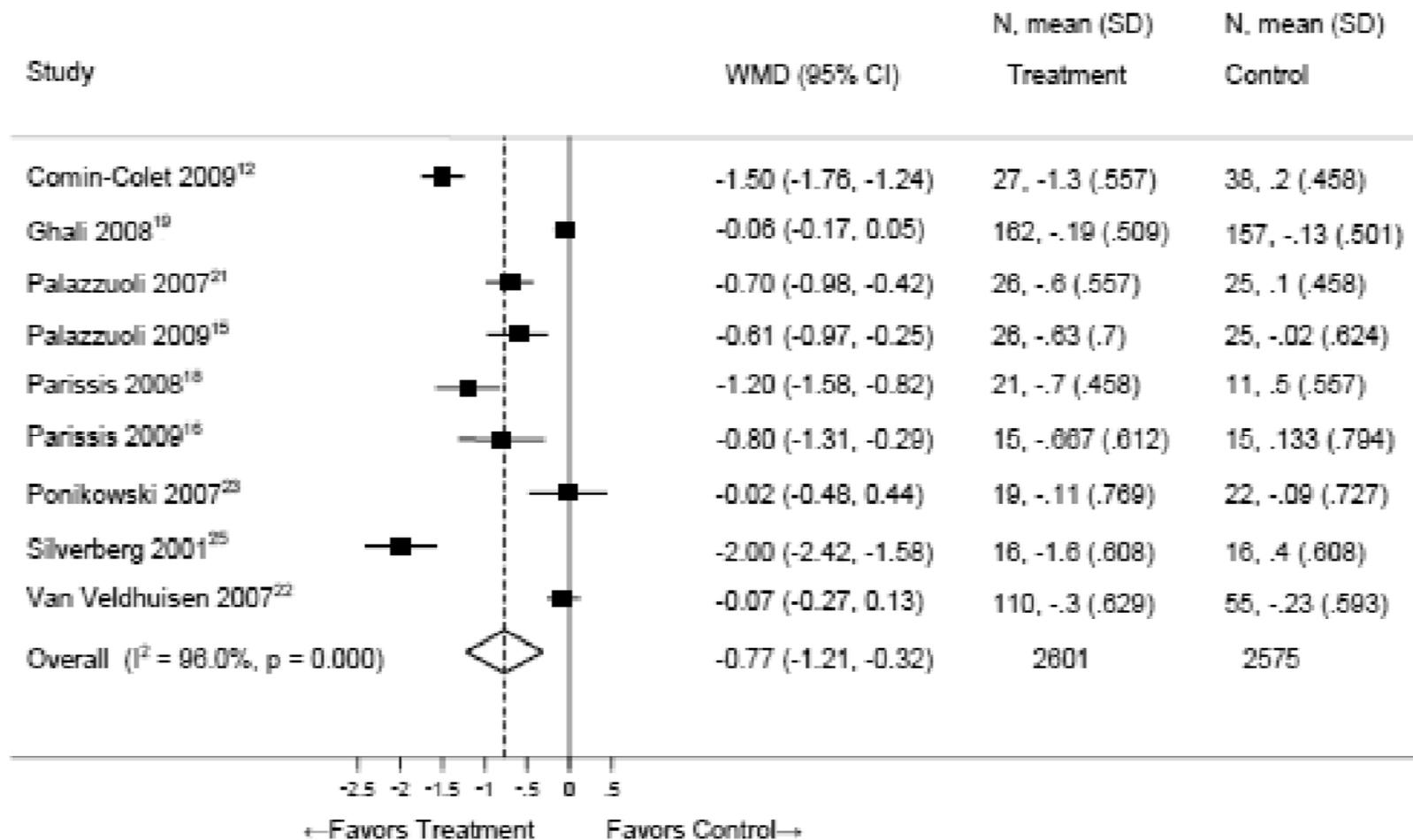


# Erythropoiesis stimulating agents

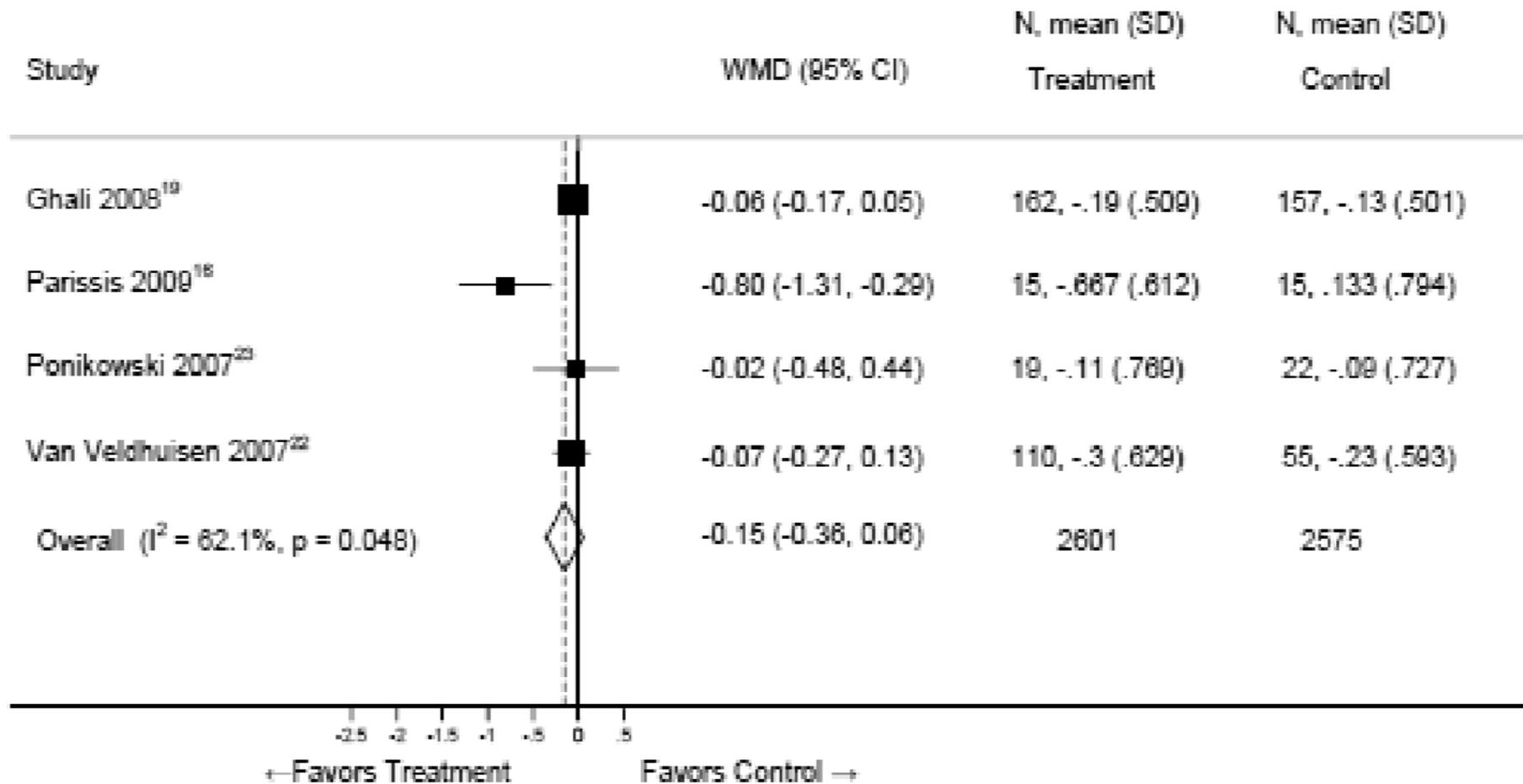
# Erythropoiesis stimulating agents

- 16 RCTs
  - 11 trials enrolled patients with CHF
    - Mean LVEF < 35%
    - Most patients had comorbid CHD
    - Mean GFR of CKD 3 or worse in most studies
  - 2 trials enrolled equal numbers CHD and CHF
  - 1 trial focused on CHD only
  - 2 trials analyzed a CHF or CHD subgroup from larger trial of CKD patients

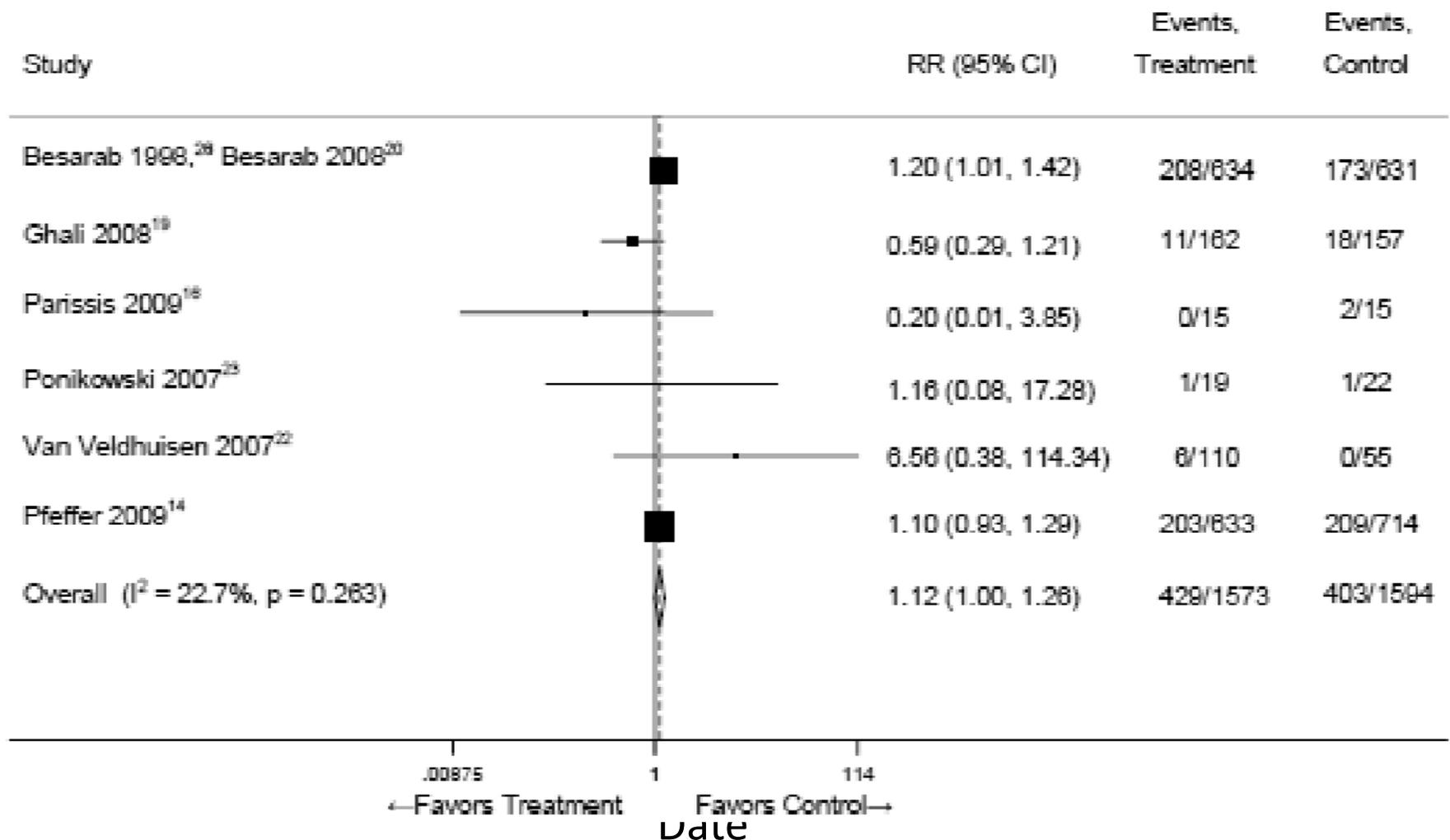
# Change in NYHA scores in CHF patients: mean difference comparing ESA to control group



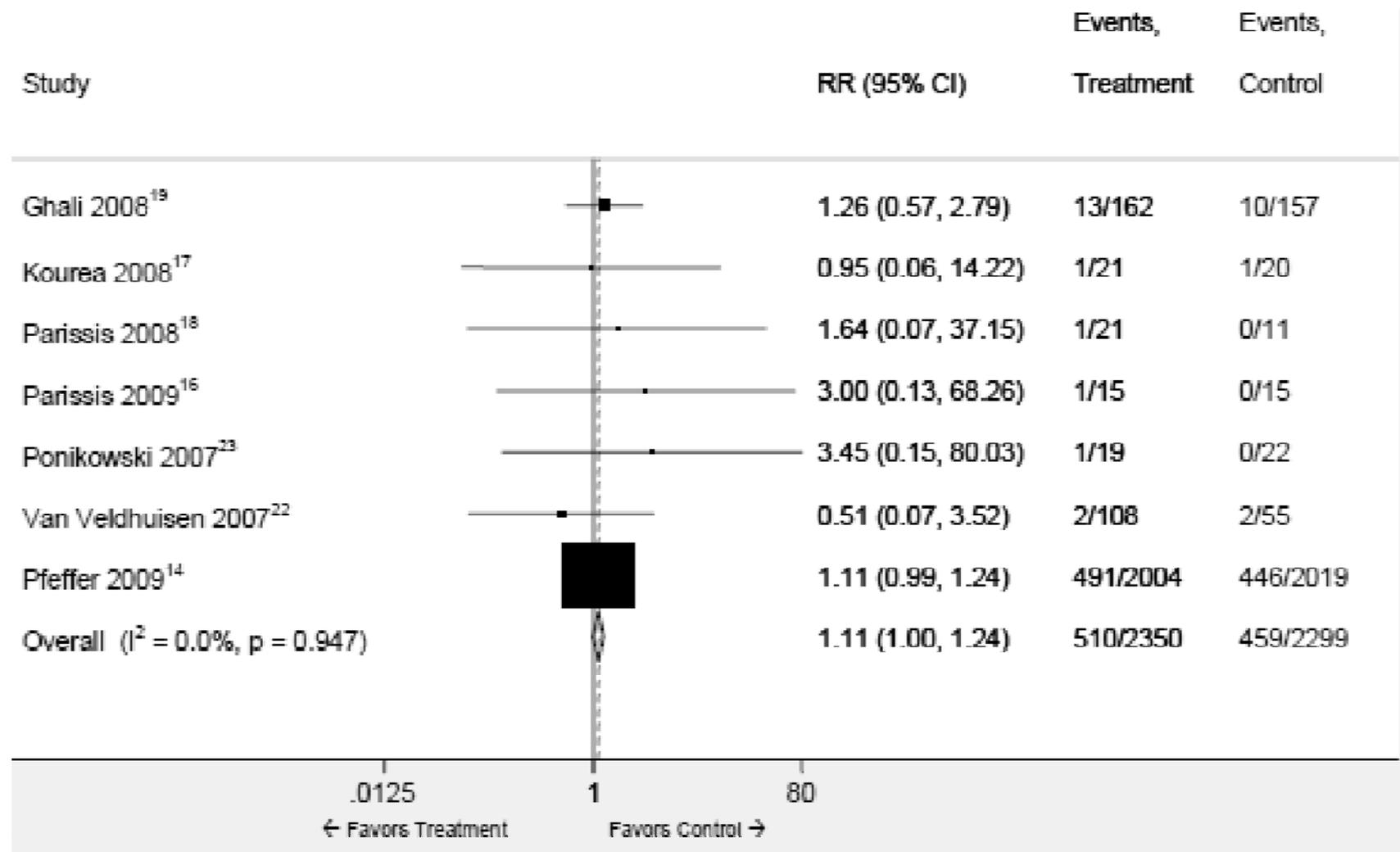
# Change in NYHA scores in CHF patients – studies with low risk of bias, excluding studies with duplicate patient populations: mean difference comparing ESA to control



# All-cause mortality in patients with CHF or CHD – studies with low risk of bias: ESA vs. control



# Hypertension events in patients with CHF or CHD: ESA vs. control



# ESAs in patients with CKD and heart disease

Harms results dominated by 2 large studies of patients with CKD and heart disease

<b>Studies by size</b>	<b>N</b>
TREAT, CHD subgroup; Pfeffer 2009	2636
Besarab 1998, 2008	1233
CHOIR, CHF subgroup; Szczech 2010	375
STAMINA-HeFT; Ghali 2008	319
Van-Veldhuisen 2007	165
Other studies	23-65

# Erythropoiesis-stimulating agents: Pfeffer 2009, subgroup of TREAT

TREAT: multicenter, international RCT

Darbepoietin vs Placebo in anemic diabetic CKD

Targeted Hgb: 13 g/dL vs >9.0 g/dL

Event driven, 29 months, n=4,044

No difference in primary endpoint of CV events

but examined a previously defined subgroup:

Cardiovascular disease, n=2,636

of which 50% had CHF

**Pfeffer MA et al, AJKD 2009;54(1):59-69.**

# Erythropoiesis-stimulating agents: Pfeffer 2009, subgroup of TREAT

TREAT: subgroup with cardiovascular disease

CHF 50%, mean GFR 34, mean Hgb 10.4

g/dL

Mortality	NS
Risk of cardiovascular event	NS
Risk of cerebrovascular event	RR 1.92*
Risk of VTE	RR 1.80*

**Pfeffer MA et al, AJKD 2009;54(1):59-69.**

# Erythropoiesis-stimulating agents: Besarab 1998, 2008

Multicenter, USA, RCT (unblinded)

Comparative dose study: Epoetin 1-3x/week

Patients on hemodialysis with either CHD or CHF

Targeted Hct: 42% (n=618) vs 30% (n=615)

Most patients also received IV iron

Primary endpoint: event-free survival

Halted early due to mortality

**Besarab A et al, NEJM 2008;358:433-434.**

# Erythropoiesis-stimulating agents: Besarab 1998, 2008

Primary endpoint: event-free survival  
Halted early (median 14 months)

Mortality	RR 1.20
Risk of cardiovascular event	NS
Risk of VTE	RR 1.37

**Besarab A et al, NEJM 2008;358:433-434.**

Iron

# Analysis of the benefits and harms of iron therapy in CHF or CHD

Only 3 RCTs.

Dominated by 1 large trial.

<b>Studies of iron</b>	<b>N</b>
FAIR-HF, Anker 2009	459
FERRIC-HF, Okonko 2008	35
Tobili 2007	40

# Iron therapy in CHF: FAIR-HF, Anker 2009

FAIR-HF: multicenter, international, RCT.

24 weeks: all with CHF

IV iron weekly (n=304) vs Placebo (n=155)

1<sup>st</sup> study with ferric-carboxymaltose

Note: **Mean Hgb 11.9 g/dL!**

~50% were not anemic

Mean ferritin 55, Transferrin Sat% 17

Note: **80% NYHA class III**, remainder class II

Anker SD et al, NEJM 2009;361:2436-2448.

# Iron therapy in CHF: FAIR-HF, Anker 2009

## Results:

Similar outcomes for anemic and non-anemic patients

Improvement in NHYA by 1	OR 2.40
Improvement in PGA	OR 2.51
6-MWT (meters)	313 vs 277
QOL: KCCQ score	66 vs 59
QOL: EQ-5D score	63 vs 57

All values significant at  $p < 0.001$

Anker SD et al, NEJM 2009;361:2436-2448.

# Transfusions

# Transfusion Literature Search

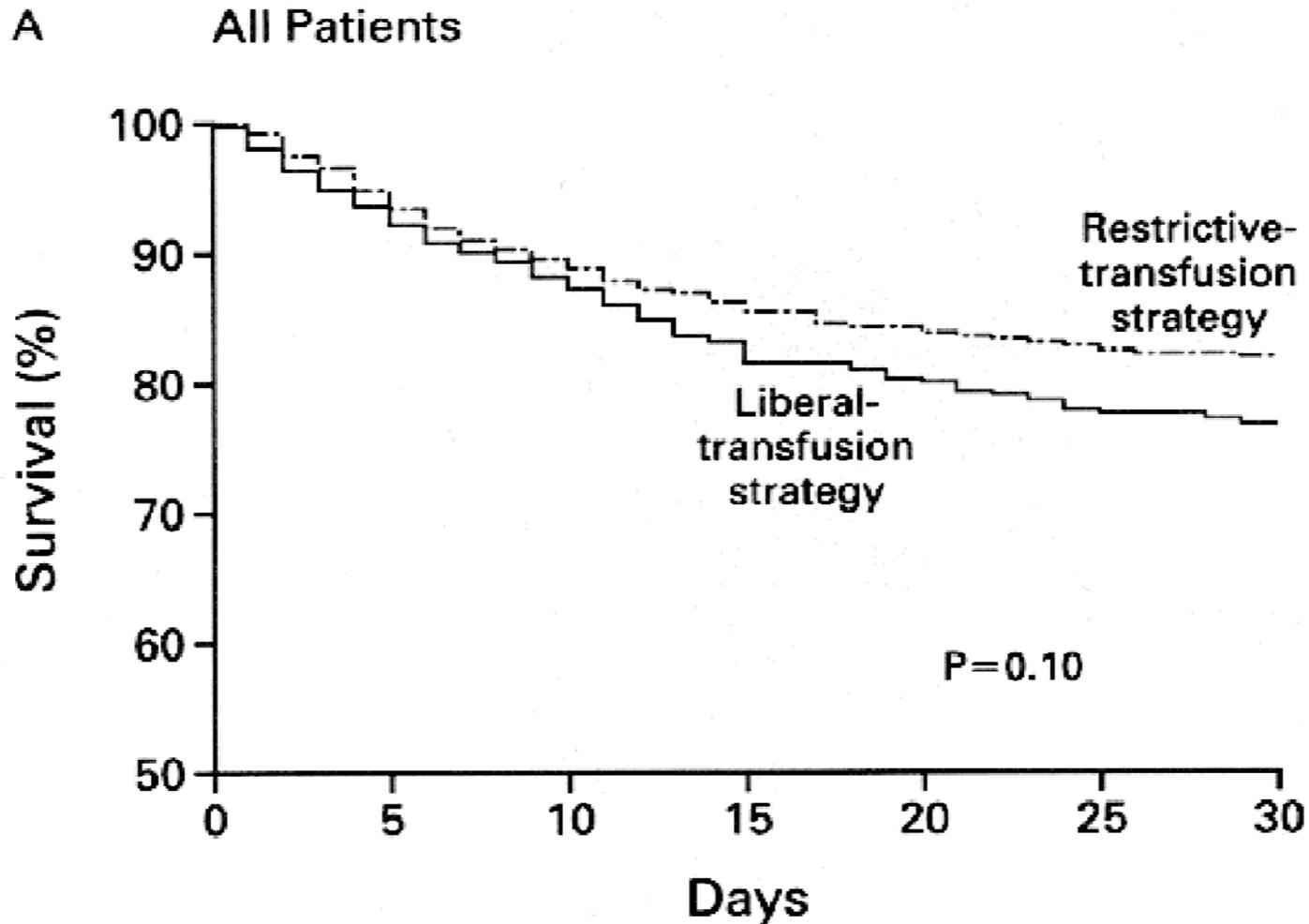
- 9 controlled trials
  - 2 in medical populations
  - 4 in cardiac surgery
  - 3 in non-cardiac surgery
- 24 observational cohort studies
  - 21 in medical populations
  - 3 in non-cardiac surgery

# TRICC Trial

- Hebert PC et al – NEJM 1999
  - Multicenter (all in Canada) RCT (unblinded), 60 day f/u
  - 838 ICU pts, all w/ hgb  $\leq 9$  g/dL within 72 hrs of admission, all considered euvolemic
  - Intervention:
    - Restrictive strategy – transfuse at hgb  $< 7$ , 1 unit at a time, w/ goal hgb 7-9 g/dL
    - Liberal strategy – transfuse at hgb  $< 10$ , 1 unit at a time, w/ goal hgb 10-12 g/dL

**Hebert PC et al, NEJM 1999; 340: 409-417.**

# TRICC Trial Outcomes



Hebert PC et al, NEJM 1999; 340: 409-417.

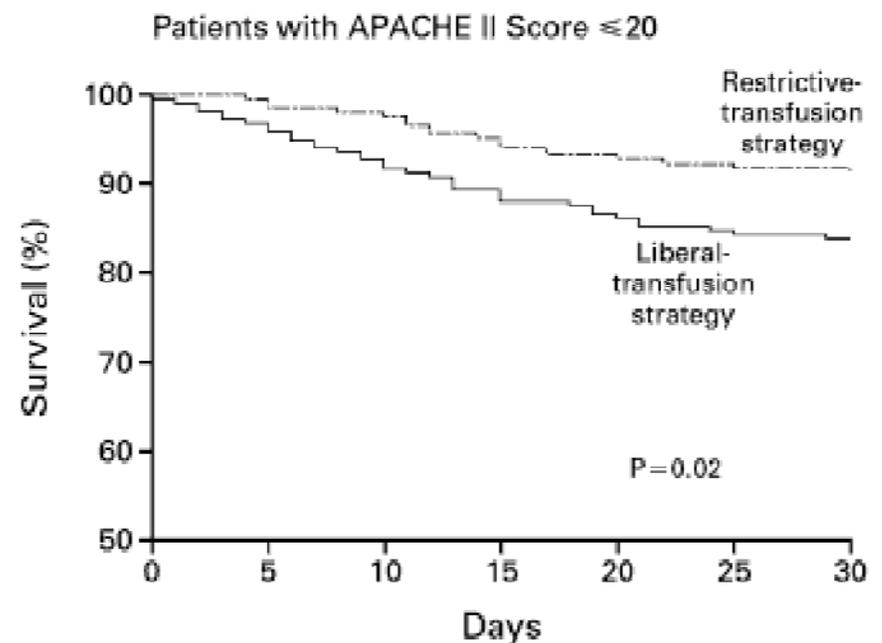
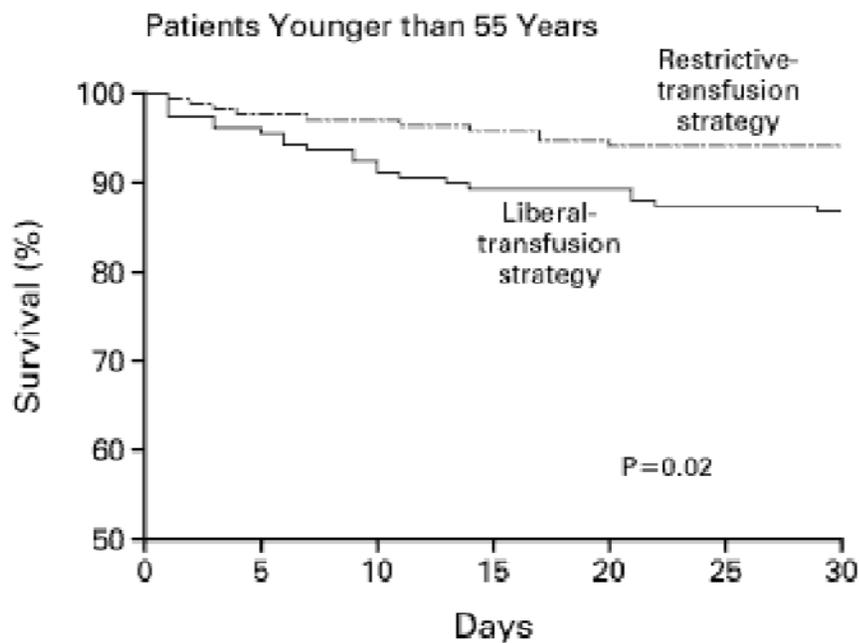
# TRICC Trial - Outcomes

<u>Outcome</u>	R	L	
30d mortality	18.7%	23.3%	RRR 20%, p=0.11
Hospital mortality	22.2%	28.1%	RRR 21%, p=0.05
MODS, adjusted	10.7	11.8	NS
Cardiac events	13.2%	21.0%	NS
Pulmonary comps	25.4%	29.0%	NS
Infectious comps	10.0%	11.9%	NS
LOS, ICU (d)	11.0	11.5	NS
LOS, hospital (d)	34.8	35.5	NS

**Hebert PC et al, NEJM 1999; 340: 409-417.**

# TRICC Trial Outcomes

- Subgroup analyses – younger and less ill



Hebert PC et al, NEJM 1999; 340: 409-417.

# Conclusions

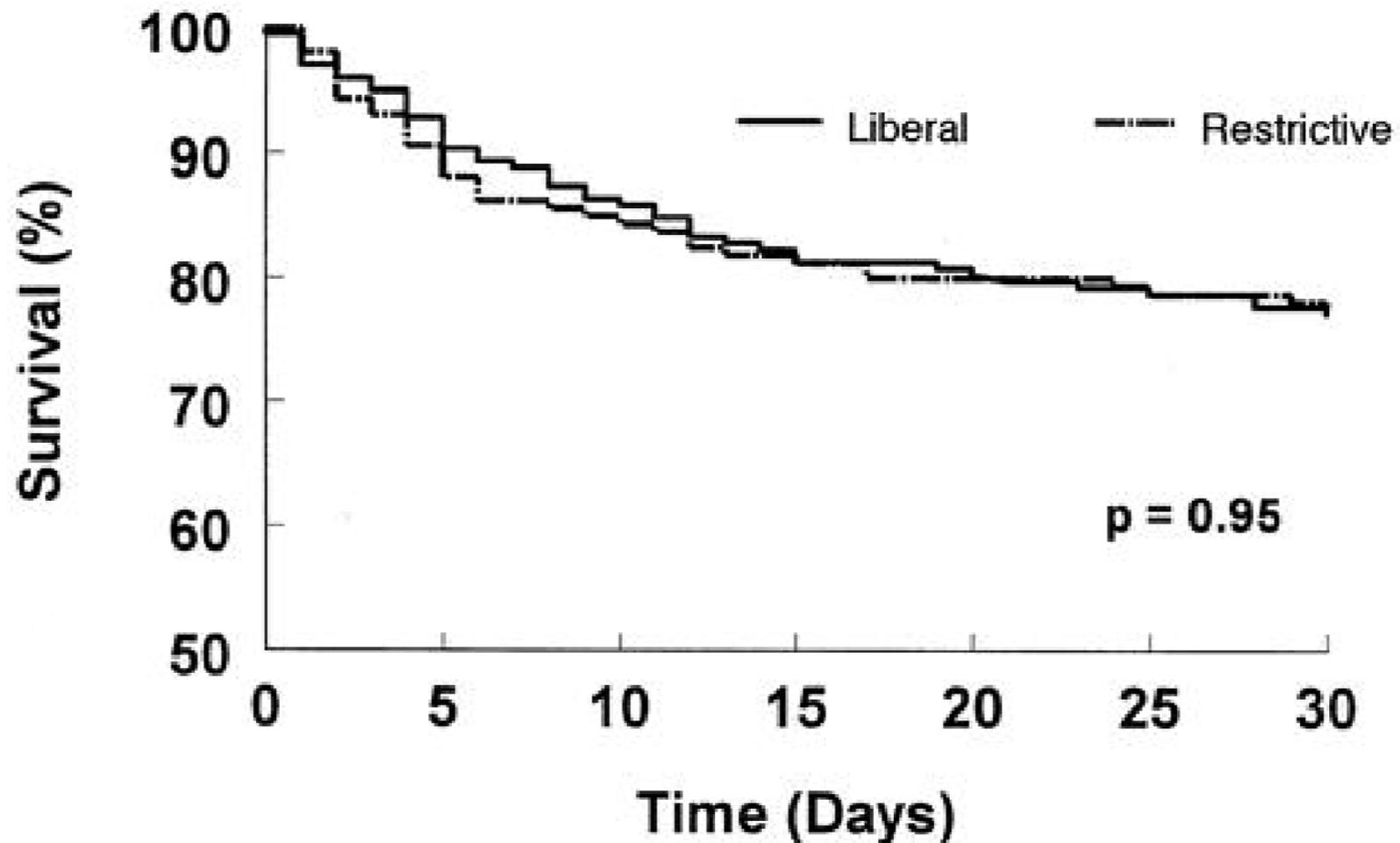
- A restrictive transfusion policy (goal hgb >7 g/dL) is safe in critically ill pts, including those being mechanically ventilated
- Withholding transfused RBCs may actually be beneficial, particularly in younger and less critically ill pts

That still leaves the question of cardiovascular disease...

- TRICC trial – subgroup analysis
  - 357 pts w/ 1<sup>o</sup> or 2<sup>o</sup> admitting diagnosis of CV disease
    - Over 85% mechanically ventilated, >50% w/ PA catheter
    - Average APACHE II score 23

**Hebert et al, Crit Care Med 2001; 29: 227-234.**

# TRICC Trial – CVD Subgroup Outcomes



Hebert et al, Crit Care Med 2001; 29: 227-234.

# TRICC Trial

- Cardiovascular disease patients

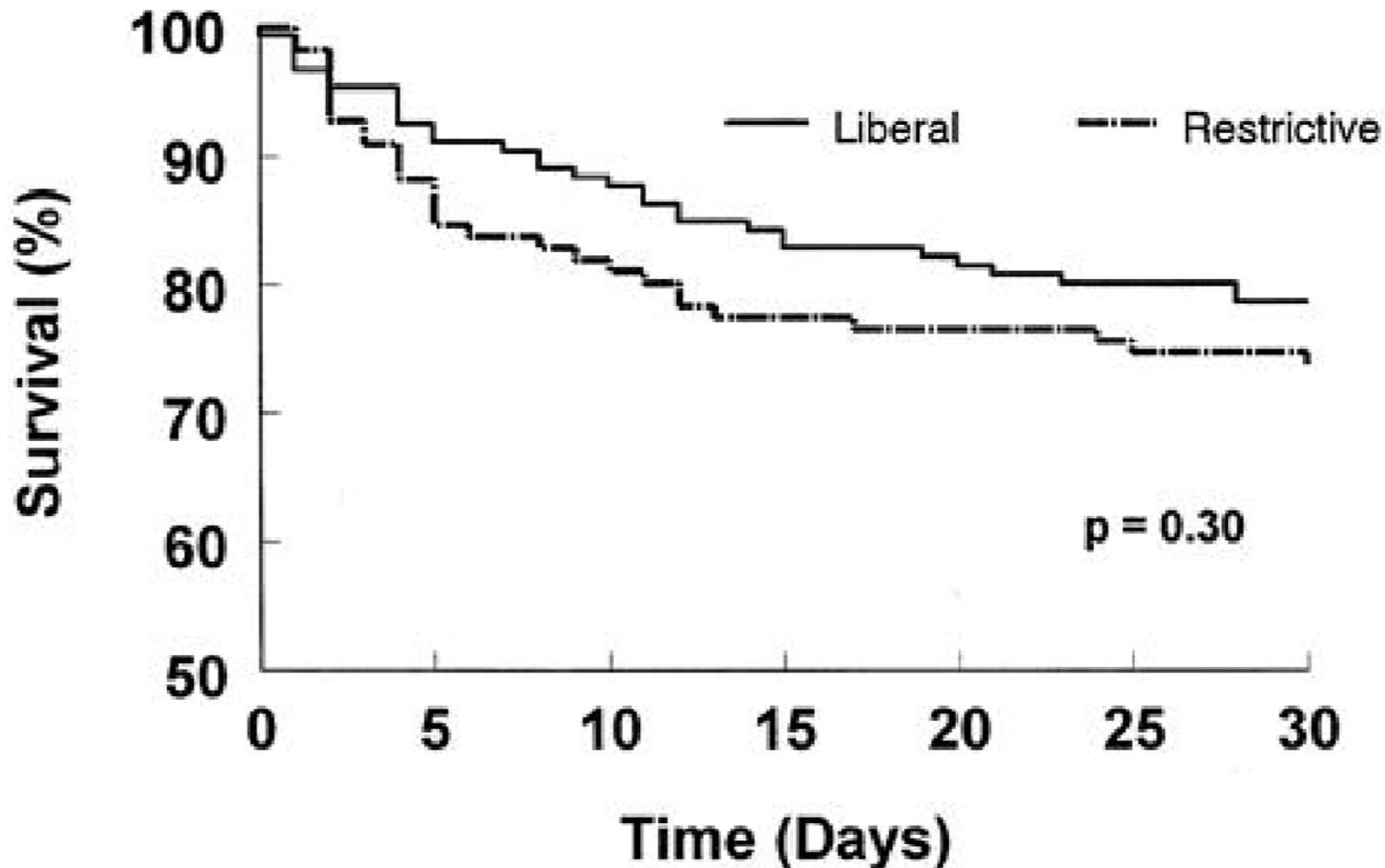
<u>Outcome</u>		R	L	
30d mortality	23%	23%	NS	
Hospital mortality	26%	27%	NS	
MODS, adjusted		11.1	11.9	NS
LOS, ICU (d)	9.2	11.3		NS
LOS, hospital (d)		33.0	35.1	NS

**Hebert et al, Crit Care Med 2001; 29: 227-234.**

# TRICC Trial

## IHD Subgroup Outcomes

Also looked at 257 pts w/ ischemic heart disease



Hebert et al, Crit Care Med 2001; 29: 227-234.

# TRICC Trial

- Ischemic heart disease patients

<u>Outcome</u>	R	L		
30d mortality	26%	21%	p=0.38	
Hospital mortality	29%	27%	NS	
MODS, adjusted	11.8	11.6		NS
LOS, ICU (d)	9.3	10.4	NS	
LOS, hospital (d)	28.8	30.6		NS

Also no significant difference in rate of new MI (data not given)

**Hebert et al, Crit Care Med 2001; 29: 227-234.**

# TRICC summary

- A restrictive strategy (goal hgb >7) appears safe in pts w/ underlying CV diseases as well
  - Caveat: more difficult to draw conclusions given smaller sample size, post-hoc subgroup analysis
- Question remains about the particular subset of pts w/ ischemic heart disease

Is there any other data available to guide decision-making in ischemic heart disease pts?

# CRIT trial – Cooper 2011

- Multicenter (US) RCT from 2003-2009
- 45 pts admitted w/ acute MI
  - 40% had STEMI, 56% received PCI
  - All w/ hct  $\leq$ 30%, no major bleeding
- Intervention:
  - Conservative strategy – transfuse at hct  $<$ 24, 1 unit at a time, w/ goal hct 24-27
  - Liberal strategy – transfuse at hct  $<$ 30, 1 unit at a time, w/ goal hgb 30-33

**Cooper HA et al, Am J Cardiol 2011; 108: 1108.**

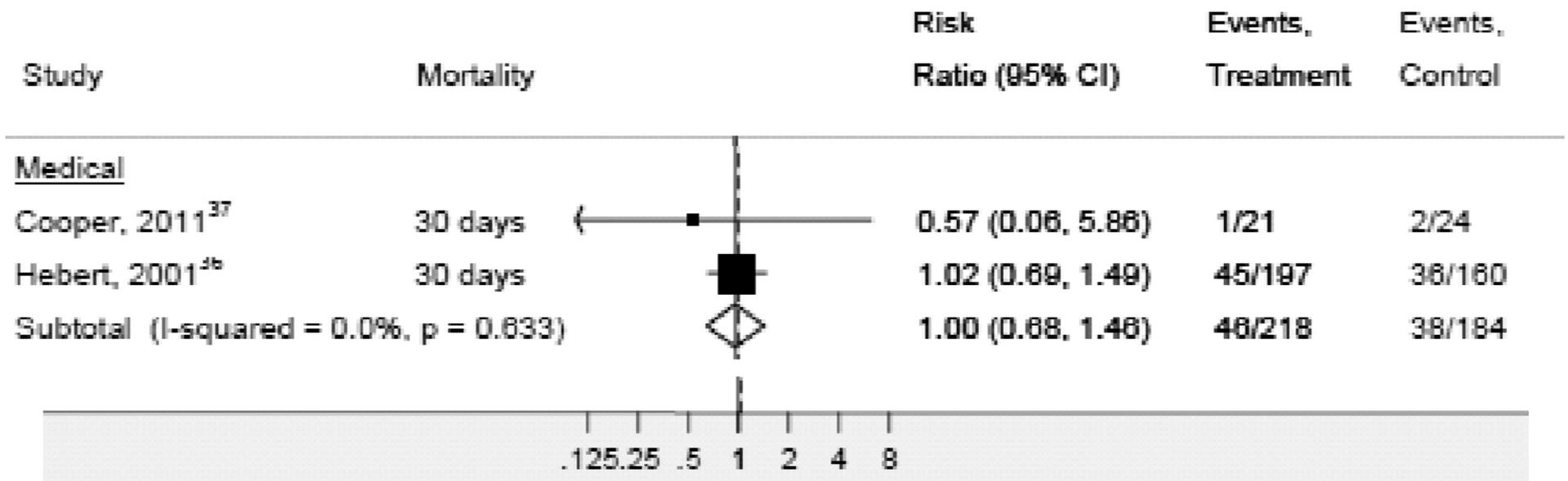
# CRIT trial – Cooper 2011

<u>Outcome</u>		R	L	
Mortality, in-hospital	8%	5%		NS
Death/MI/CHF, in-hospital	13%		38%	p=0.046
CHF, in-hospital		8%	38%	p=0.03
Mortality, 30 d		8%	5%	NS
Death/MI/CHF, 30 d	20%	60%		p=0.02

**Also no significant difference in recurrent ischemia or LOS (hospital or CCU)**

**Cooper HA et al, Am J Cardiol 2011; 108: 1108.**

# Meta-Analysis – 30 d Mortality Transfusion in Medical Populations



# Perioperative Transfusion in CV Disease

- FOCUS trial – hip fracture repair
  - Multicenter RCT in US and Canada 2004-2009
  - 2016 pts  $\geq$  50 yrs old undergoing hip fracture repair w/:
    - Known CVD (IHD hx, consistent ECG, CHF, PVD, CVA/TIA) OR
    - RFs (HTN, DM, dyslipidemia, smoking, Cr  $\geq$  2.0)
  - Intervention
    - Liberal strategy – transfuse at hgb  $<$ 10, 1 unit at a time
    - Restrictive strategy – transfuse 1 unit at a time upon development of signs/sx of anemia (cardiac CP, CHF, tachycardia/hypotension unresponsive to IVF) or at discretion of MD if hgb  $<$ 8

**Carson JL et al, NEJM 2011; 365: 2453.**

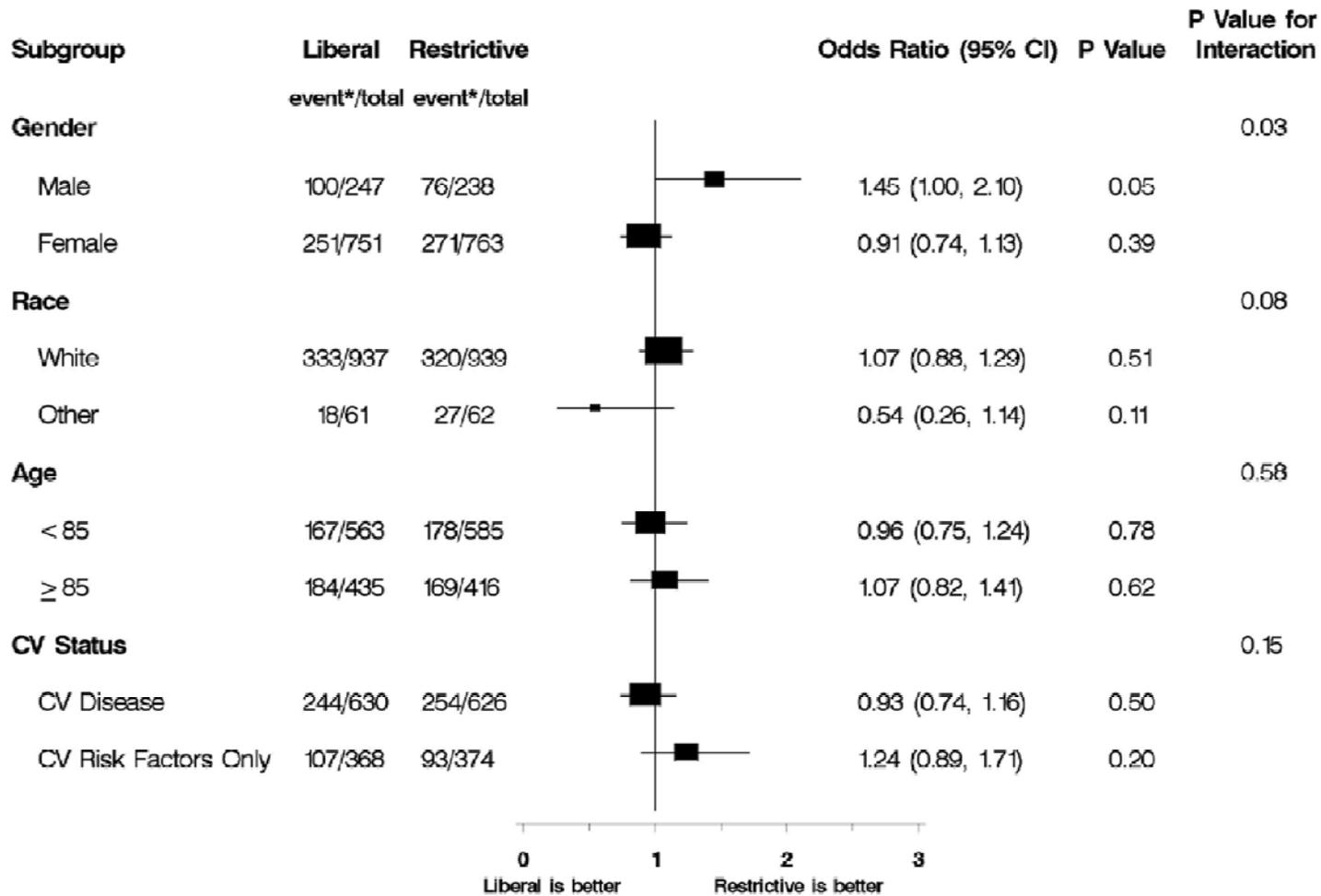
# FOCUS trial

<u>Outcome</u>	R	L	OR
Death/can't walk 10 ft, 60 d	34.7%	35.2%	1.01 (0.84-1.22)
Mortality, 60 d	6.6%	7.6%	1.17 (0.75-1.83)
Death/MI/UA, in-hospital	5.2%	4.3%	0.82 (0.48-1.42)
MI, in-hospital	3.8%	2.3%	0.60 (0.30-1.19)
CHF, in-hospital	3.5%	2.7%	0.77 (0.39-1.50)

Also no significant difference in CVA/TIA, pna, wound infection, VTE, need for repeat operation, ICU transfer, LOS, ADL/IADL scores

Carson JL et al, NEJM 2011; 365: 2453.

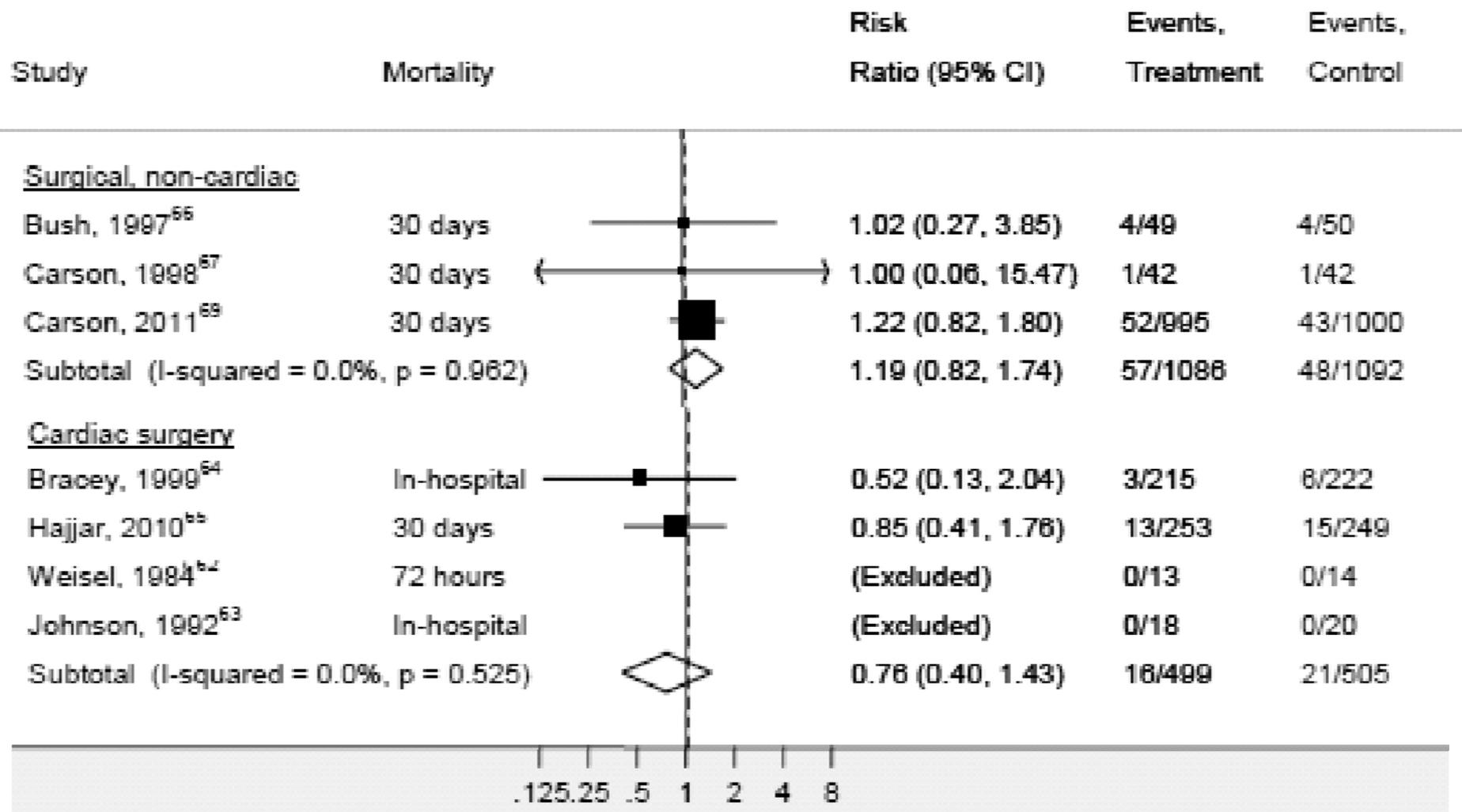
# FOCUS trial



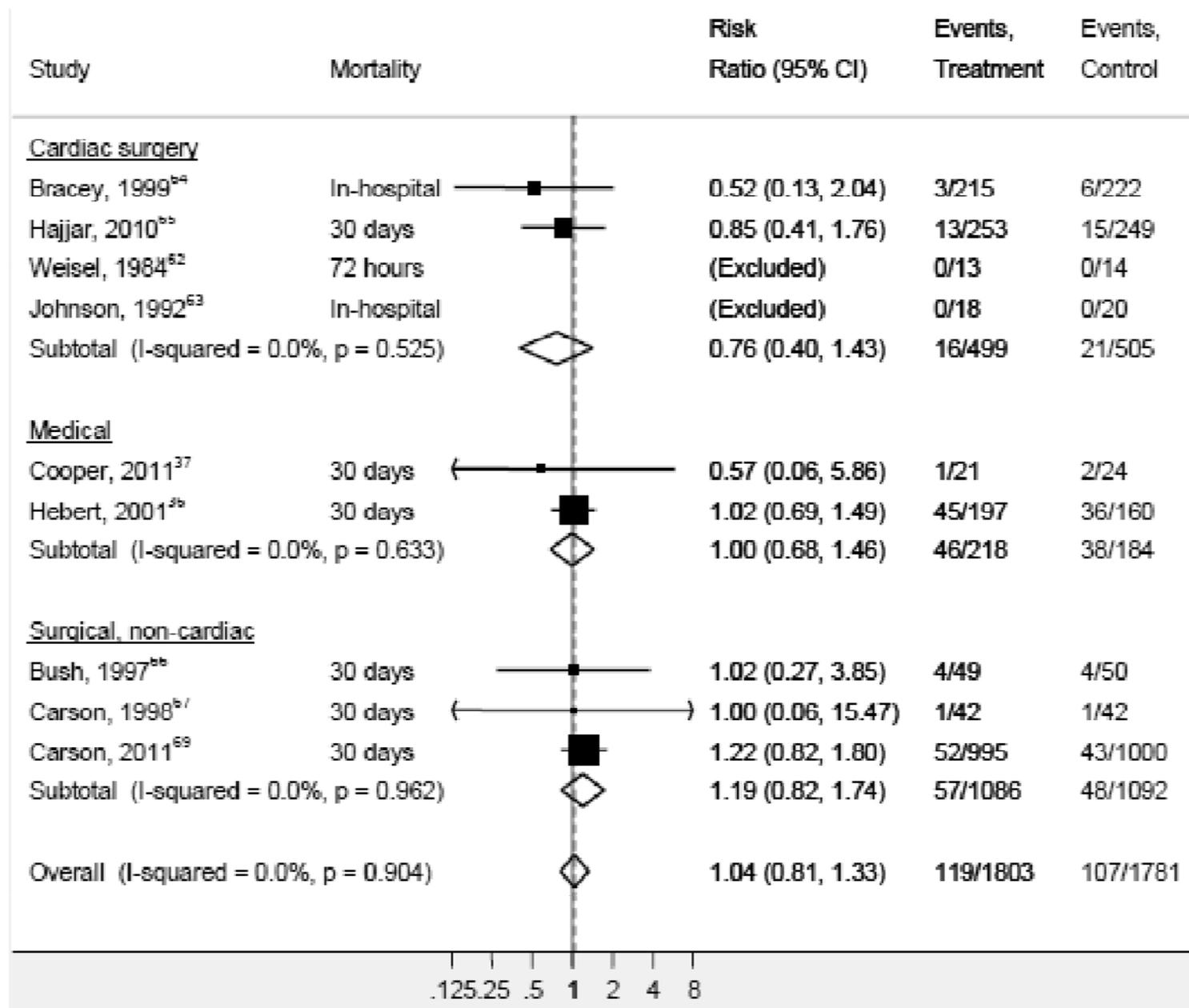
\*Death or inability to walk independently at 60-Day Follow-Up

Carson JL et al, NEJM 2011; 365: 2453.

# Meta-Analysis – 30 d Mortality Transfusion in Surgical Populations



# Meta-Analysis – All Populations



# Observational Studies of Transfusion in IHD

- PCI setting – 9 studies, ~2000-39,000 pts
  - Transfusion associated with higher mortality in 8 of 9 (no difference in 9<sup>th</sup>)
    - Finding was consistent in both bleeding and non-bleeding transfused cohorts

# Observational Studies of Transfusion in IHD

- ACS/AMI populations – 12 studies
  - Outcomes w/ transfusion at any hgb/hct level (overall) - reported in 9 studies
    - Higher mortality in 8 of 9 studies (no difference in the last one)

# Observational Studies of Transfusion in IHD

- ACS/AMI populations – 12 studies
  - Outcomes w/ transfusion at hct <24-25% - reported in 6 studies
    - Improved survival in 2 studies
    - Mixed result in 1: Better survival in STEMI but not NSTEMI-ACS
    - No difference in mortality in 3 (2 showed a trend towards fewer deaths in transfused pts)

# Observational Studies of Transfusion in IHD

- ACS/AMI populations – 12 studies
  - Outcomes w/ transfusion at hct >30% - reported in 6 studies
    - Higher mortality in 4
    - Mixed result in 2:
      - Mortality higher in NSTEMI-ACS, but lower with transfusion in STEMI at hgb <12 g/dL (neutral at hgb >12)
      - No difference in mortality at hct 30-36% but increased mortality above hct 36% in 1

# Observational Studies of Transfusion in IHD

- ACS/AMI populations – 12 studies
  - Outcomes w/ transfusion at hct 25-30% - reported in 4 studies
    - Improved survival in 1
    - Mixed in 1 (improved survival w/ STEMI, worse w/ NSTEMI-ACS)
    - Neutral in 1
    - Increased mortality in 1
  - One additional study found higher mortality among all patients transfused at nadir hgb >8 g/dL (did not separate hgb 8-10 and >10 g/dL)

# Observational Studies of Transfusion

- CHF populations – 2 studies
  - Higher mortality w/ transfusion in 1
  - Lower mortality in the other

# Summary

## Observational Studies

- No benefit/possible harm with transfusion at hgb >10 g/dL (possible exception: STEMI)
- Mixed results but no clear benefit from transfusion at hgb down to 8-9 g/dL in NSTEMI-ACS
- Consistent evidence of increased mortality with transfusion in the unselected PCI population, at a mean nadir hgb 8-9 g/dL
- Higher incidence of death seen with transfusion in the setting of hemorrhage but may be higher still in non-bleeding patients
- No studies in stable CAD, and conflicting results seen in decompensated CHF

# Summary: ESA

- ESAs
  - No consistent, good-quality evidence for improved outcomes
  - Potential for serious harms, including thrombosis and mortality, especially in patients with chronic kidney disease

# Review design matters

- Our review differs from others in several ways:
  - Conducted additional analyses evaluating impact of study quality on results
  - Included studies of patients with advanced kidney disease if heart disease subgroup data reported
  - Included both CHF and CHD (though most studies were CHF)

# Implications: ESA

- Routine use of ESAs in patients with CHF is probably not warranted at this time
- For patients with comorbid chronic kidney disease, consider FDA recs that, if used at all, Hgb should be at least  $< 10$  g/dL

# Summary: Iron

- Iron
  - Most information from one large RCT
  - Improvement in short-term exercise tolerance and QOL
    - Most applicable to patients with NYHA III CHF and ferritin < 100
  - Long-term effects and effects on mortality/CV events unknown

# Implications: Iron

- Intravenous iron may be a promising adjunctive therapy in patients with symptomatic CHF and low ferritin, but further study is needed

# Summary: Transfusions

- Transfusions
  - More liberal transfusion protocols (trigger hgb 10g/dL) do not improve outcomes compared to more conservative protocols (trigger hgb  $\approx$  7-8 g/dL)
    - Evidence is stronger in surgical populations
    - Does not apply to actively symptomatic/unstable patients

# AABB Guidelines

- The AABB suggests adhering to a restrictive strategy in hospitalized patients with preexisting cardiovascular disease and considering transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less (Grade: weak recommendation; moderate-quality evidence).
- The AABB cannot recommend for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with the acute coronary syndrome (Grade: uncertain recommendation; very low-quality evidence).
- The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration (Grade: weak recommendation; low-quality evidence).

# Future studies

- RED-HF
  - Target of 2600 pts symptomatic CHF and reduced LVEF
  - Results  $\approx$  2014
  - Darbepoetin titrated to hgb  $\geq$  13 g/dL
- Still need long-term outcomes for iron, transfusion trials in ACS patients, ESA trials with less aggressive Hgb targets

# Evidence-based Synthesis Program (ESP)

## Questions?

If you have further questions,  
feel free to contact:

Devan Kansagara, MD, MCR  
kansagar@ohsu.edu

The full report and cyberseminar presentation is available on the ESP website:

<http://www.hsrp.research.va.gov/publications/esp/>