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)

Acknowledgements

Co-Authors/Collaborators

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

Expert Panel/Reviewers

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

Evidence-based Synthesis Program (ESP)

Disclosure

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the Portland VA Medical Center funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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 erythropoeisis 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

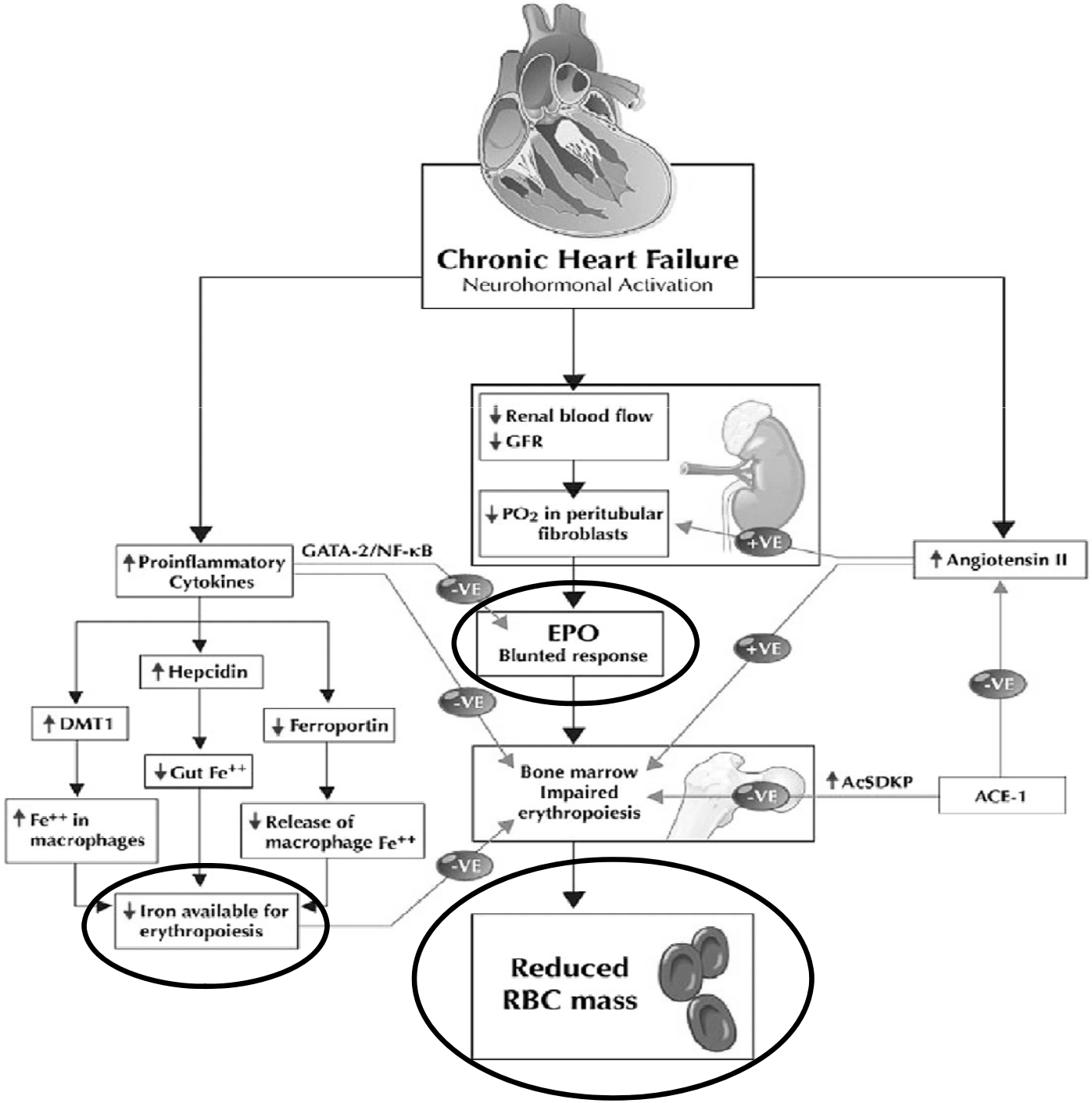
- The mechanism for poor outcomes may be unrelated to underlying CHD and myocardial ischemia

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

Sabatine M, Circ, 2005



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

JACC
Journal of the American College of Cardiology

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…"

Ngo K et al, Cochrane Database Sys Rev, 2010

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 darbepoeitin
  - 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)

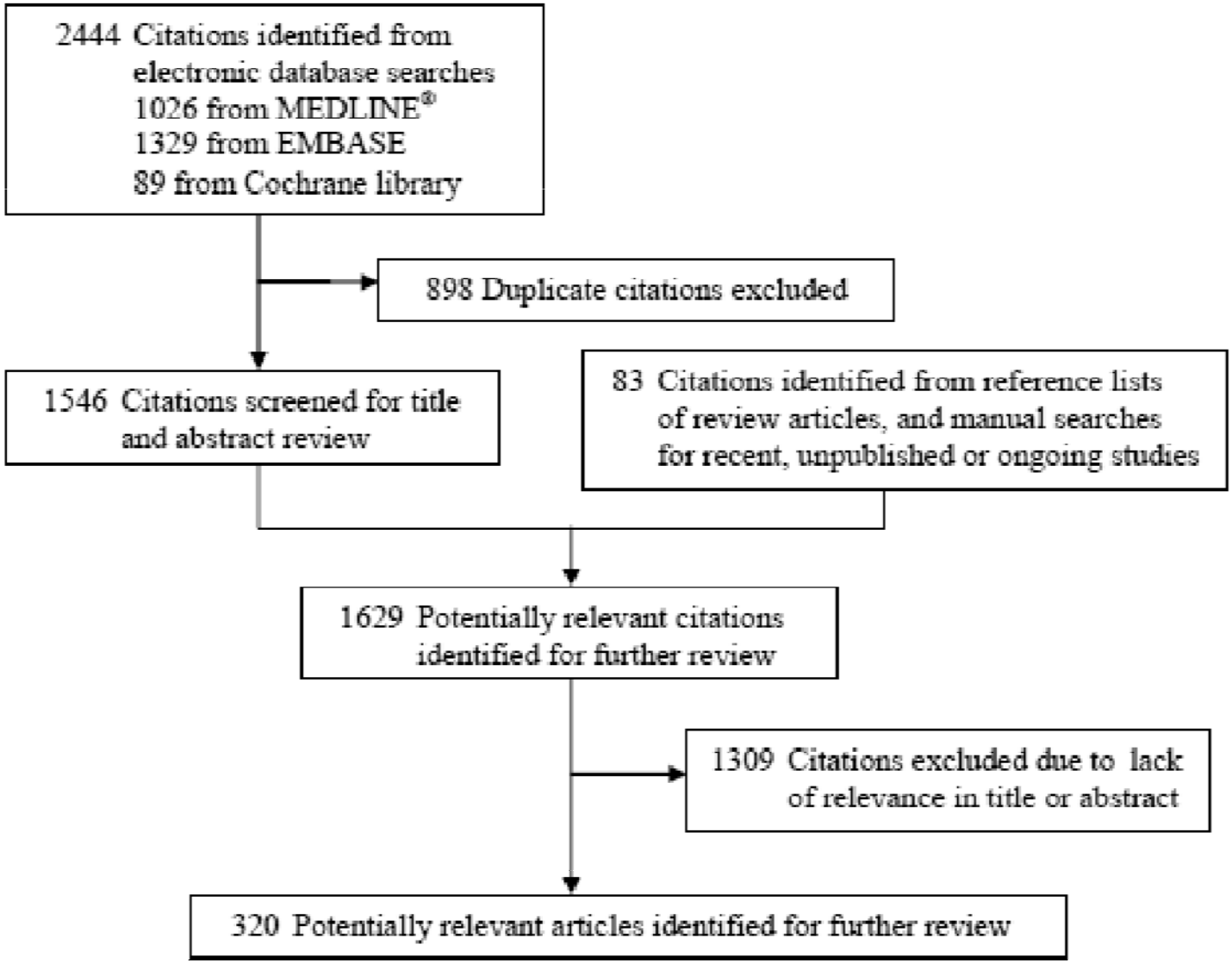
Study selection

- Transfusions – included observational studies
  - Except cardiac surgery

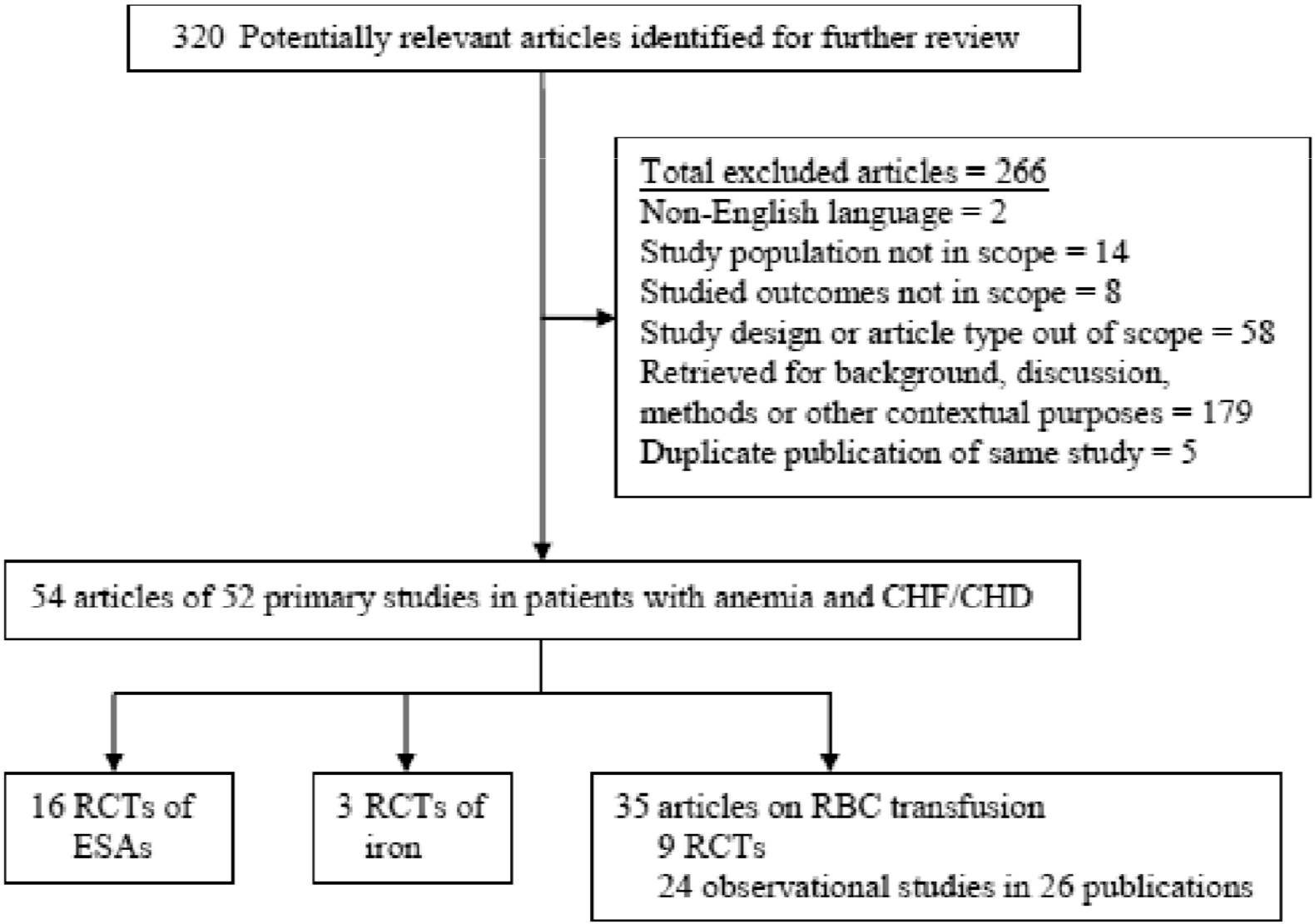
Search

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

Literature Flow – Anemia and CHF



Literature flow, continued

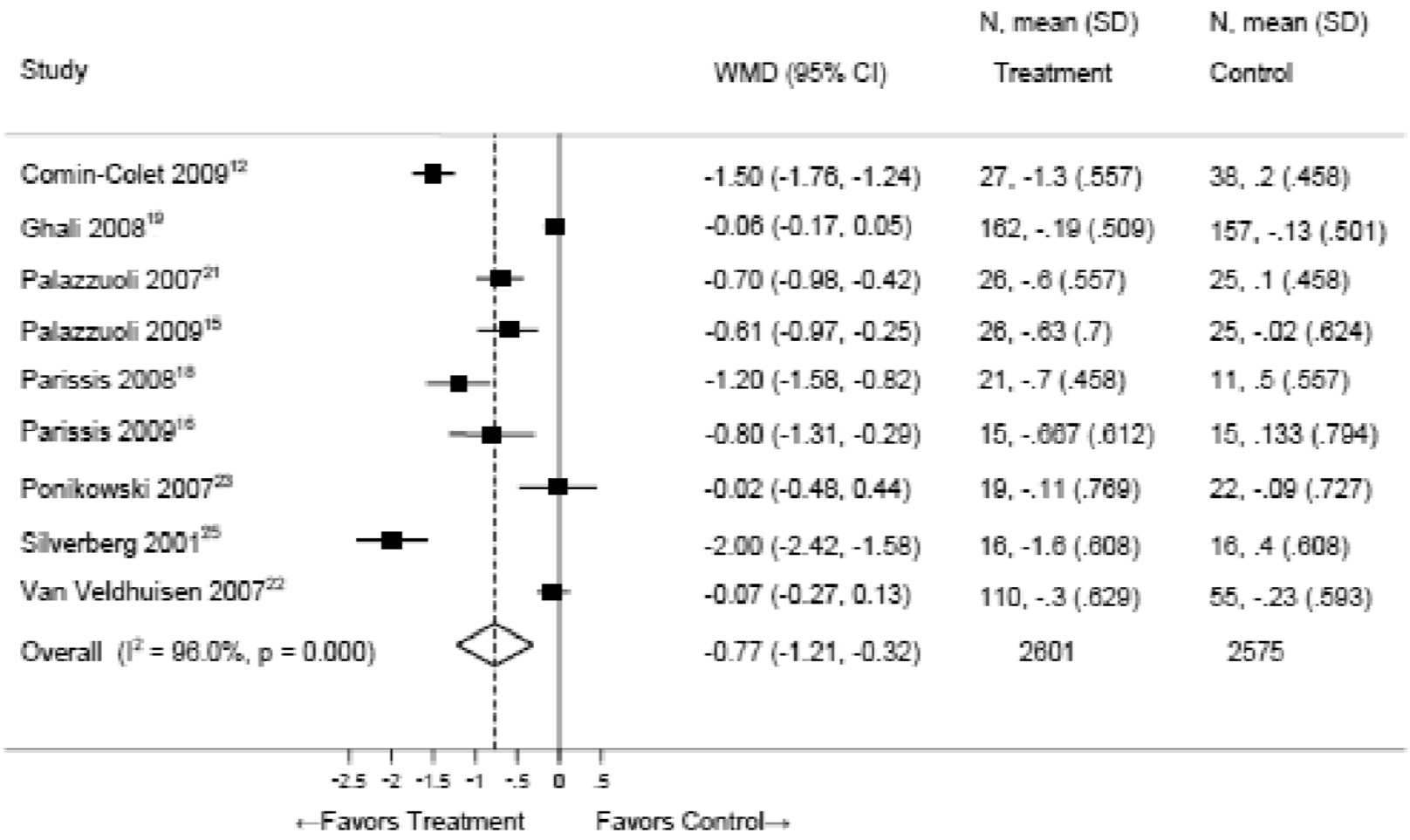


Erythropoiesis stimulating agents

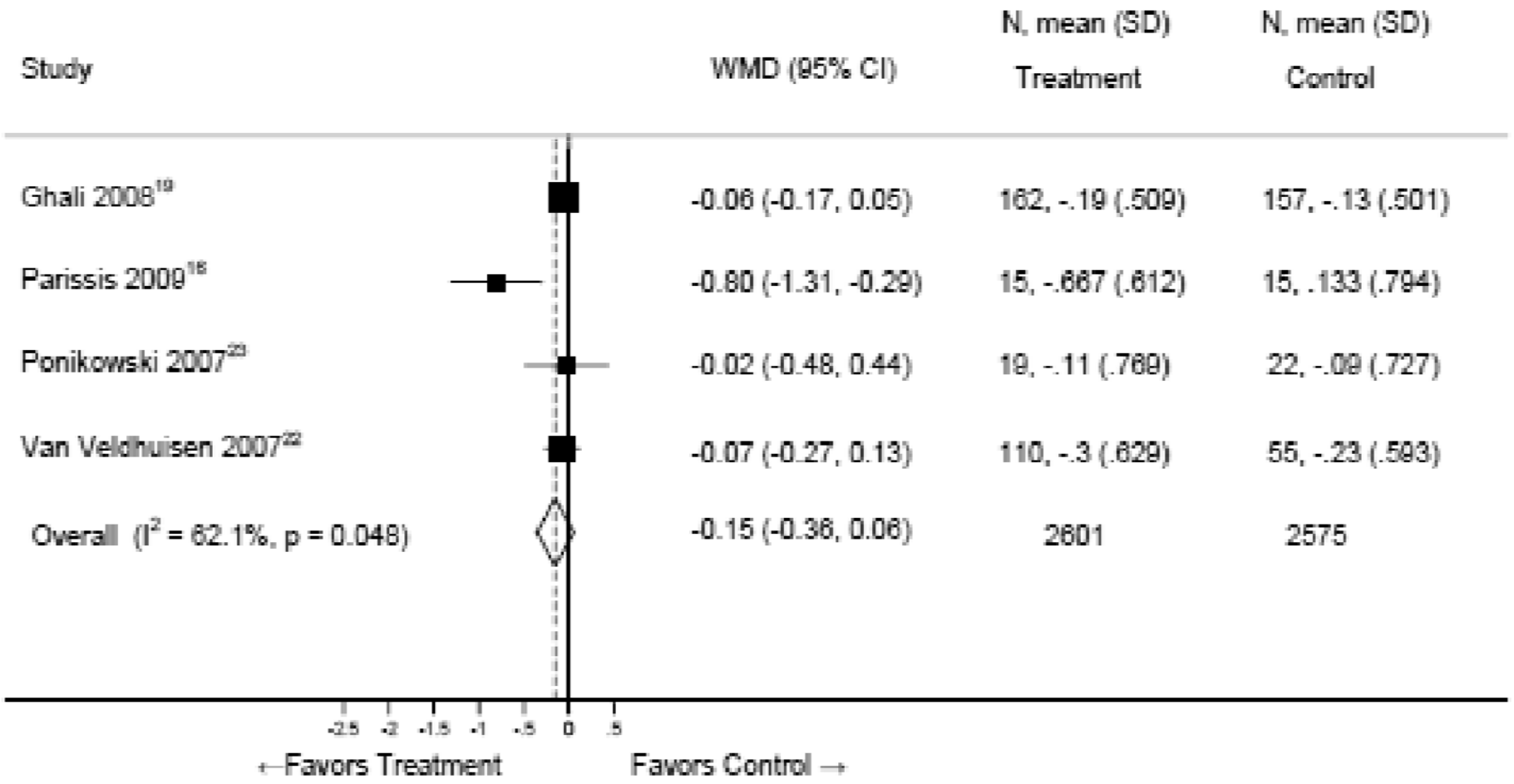
Erythropoiesis stimulating agents

- 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

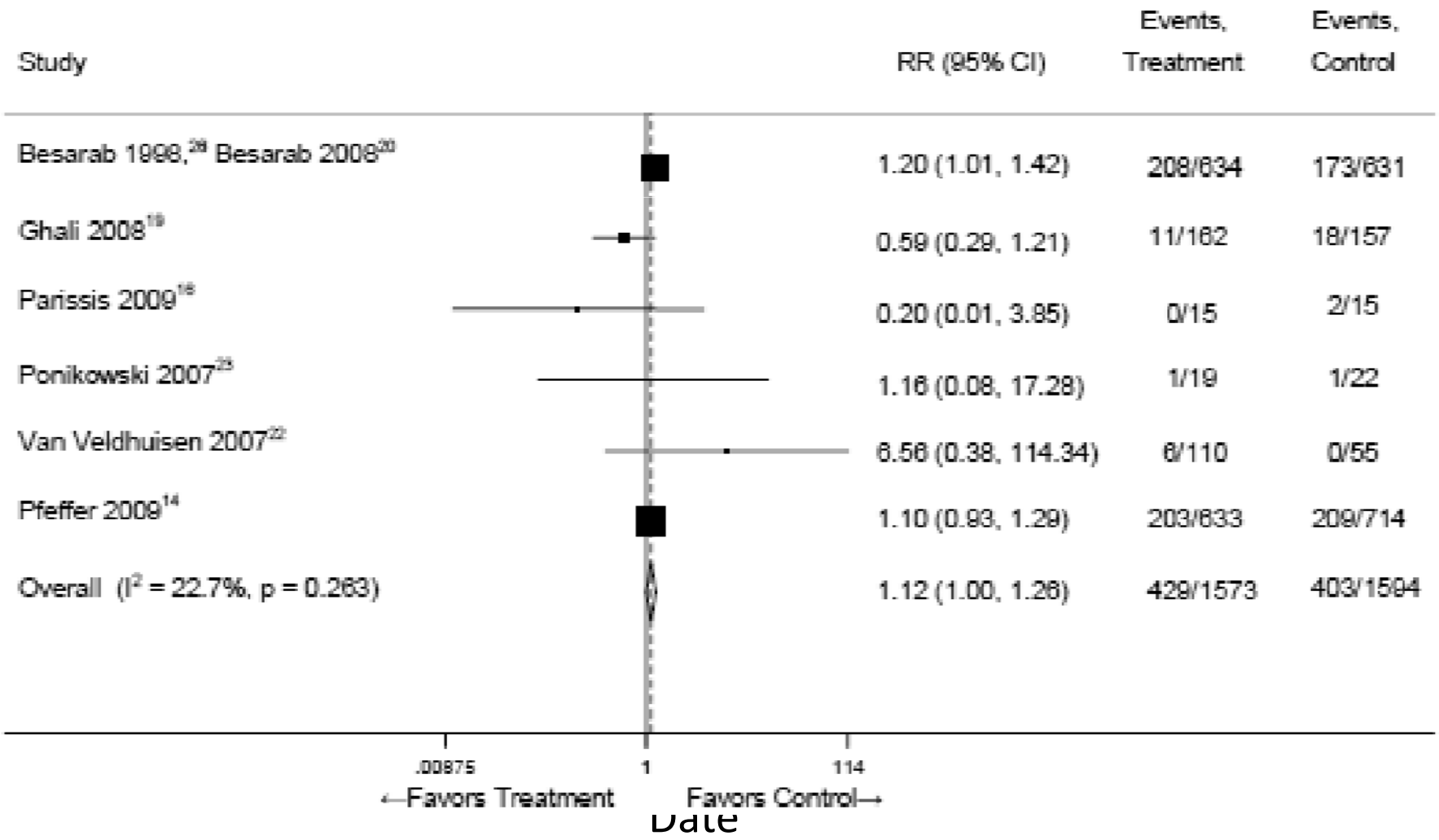
Change in NYHA scores in CHF patients: mean difference comparing ESA to control group



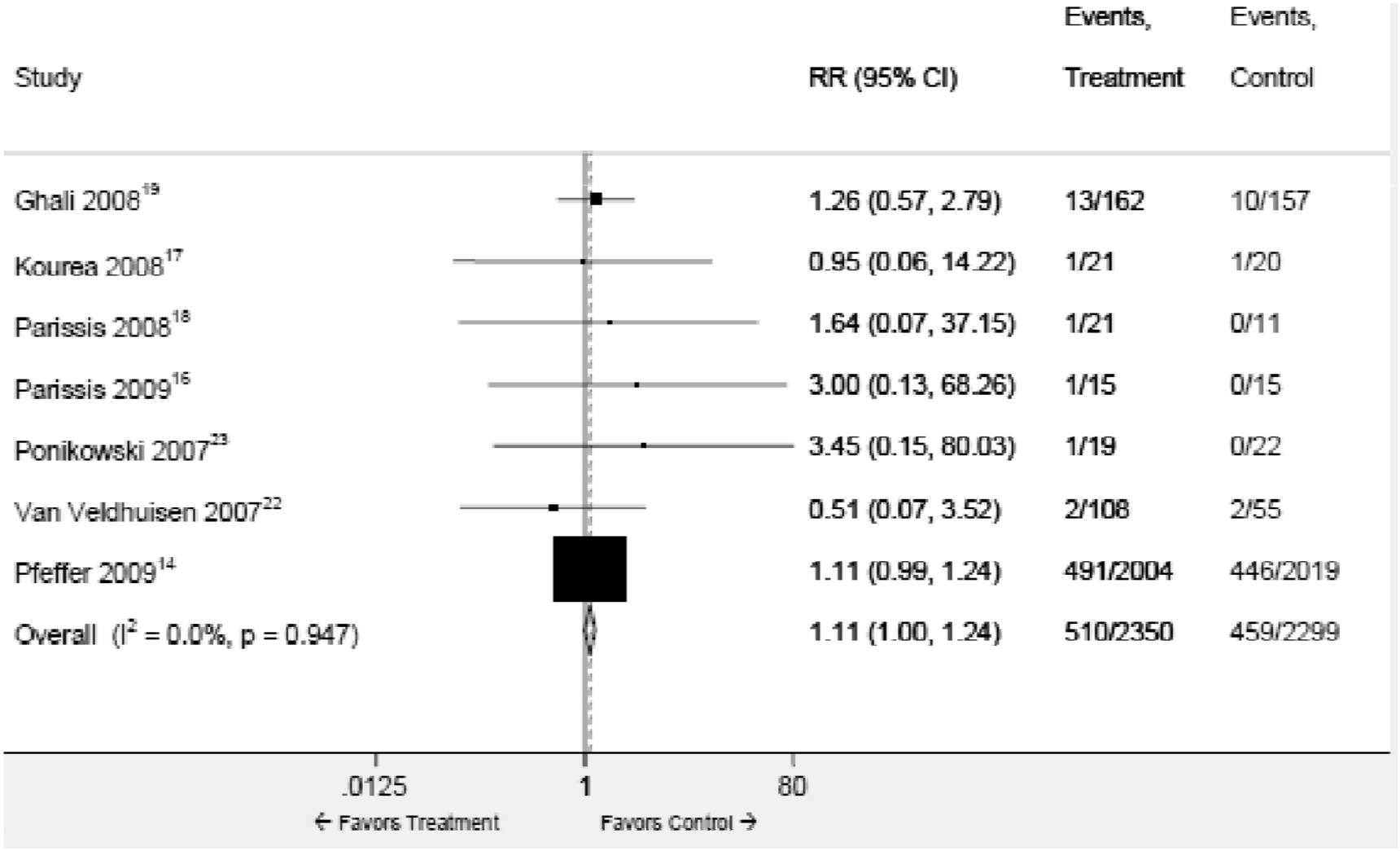
Change in NYHA scores in CHF patients – studies with low risk of bias, excluding studies with duplicate patient populations: mean difference comparing ESA to control



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

Studies by size	**N**
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: Epoeitin 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.

Studies of iron	**N**
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)
- 1st 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

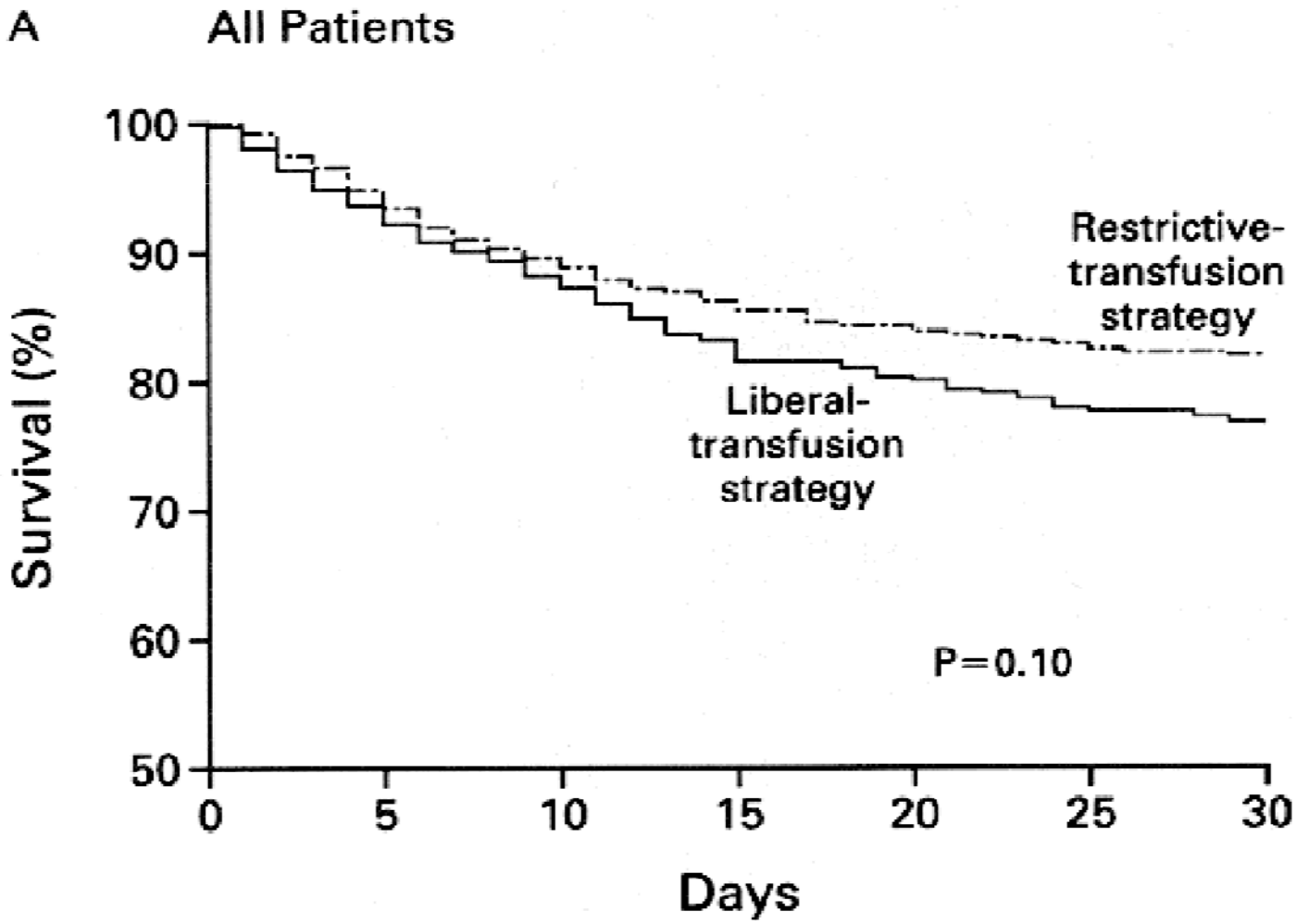
- 9 controlled trials
  - 2 in medical populations
  - 4 in cardiac surgery
  - 3 in non-cardiac surgery
- 24 observational cohort studies
  - 21 in medical populations
  - 3 in non-cardiac surgery

TRICC Trial

- Hebert PC et al – NEJM 1999
  - Multicenter (all in Canada) RCT (unblinded), 60 day f/u
  - 838 ICU pts, all w/ hgb ≤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.

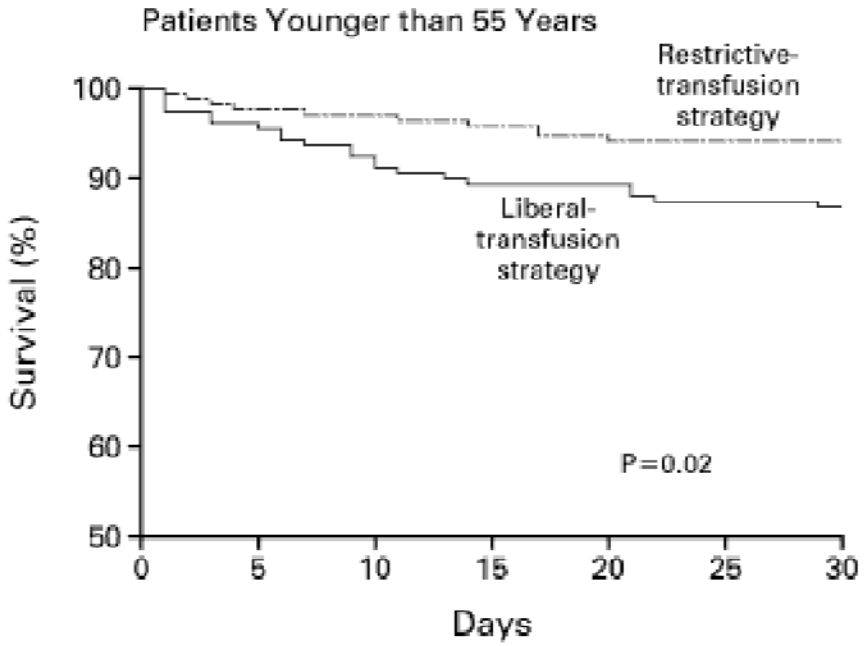
TRICC Trial - Outcomes

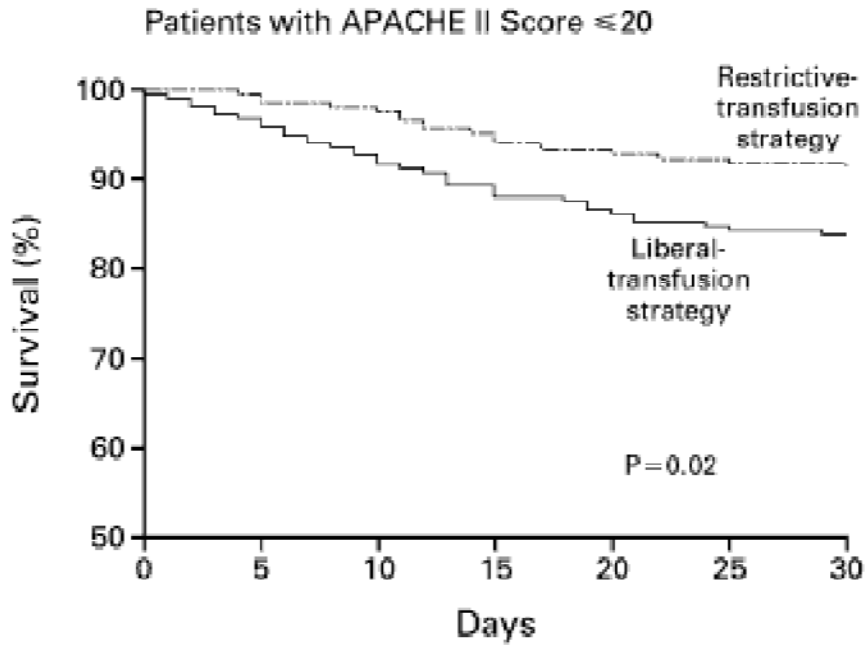
Outcome	R	L	
30d mortality	18.7%	23.3%	RRR 20%, p=0.11
Hospital mortality	22.2%	28.1%	RRR 21%, p=0.05
MODS, adjusted	10.7	11.8	NS
Cardiac events	13.2%	21.0%	NS
Pulmonary comps	25.4%	29.0%	NS
Infectious comps	10.0%	11.9%	NS
LOS, ICU (d)	11.0	11.5	NS
LOS, hospital (d)	34.8	35.5	NS

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

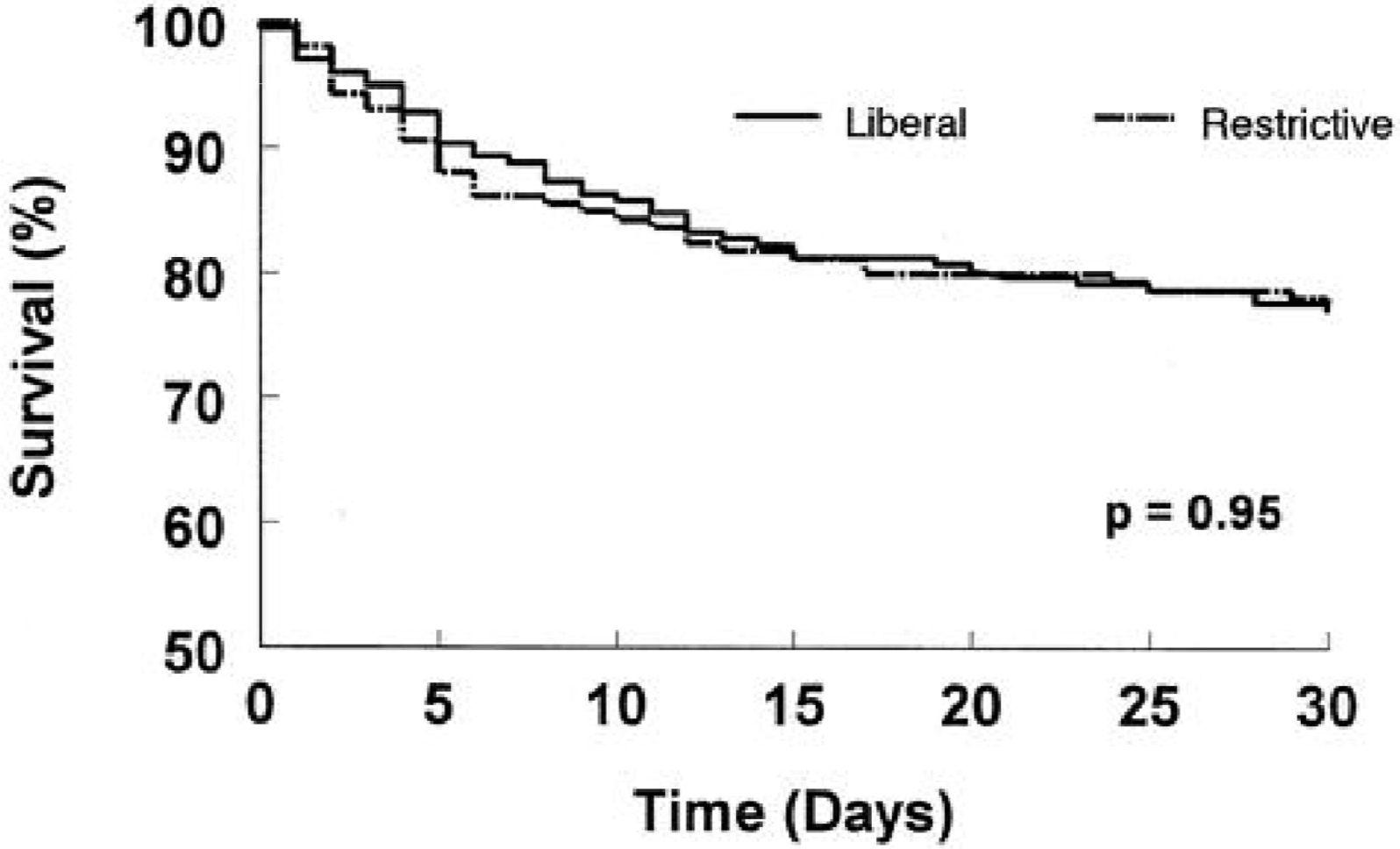
- A restrictive transfusion policy (goal hgb >7 g/dL) is safe in critically ill pts, including those being mechanically ventilated
- Withholding transfused RBCs may actually be beneficial, particularly in younger and less critically ill pts

That still leaves the question of cardiovascular disease…

- TRICC trial – subgroup analysis
  - 357 pts w/ 1º or 2º 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

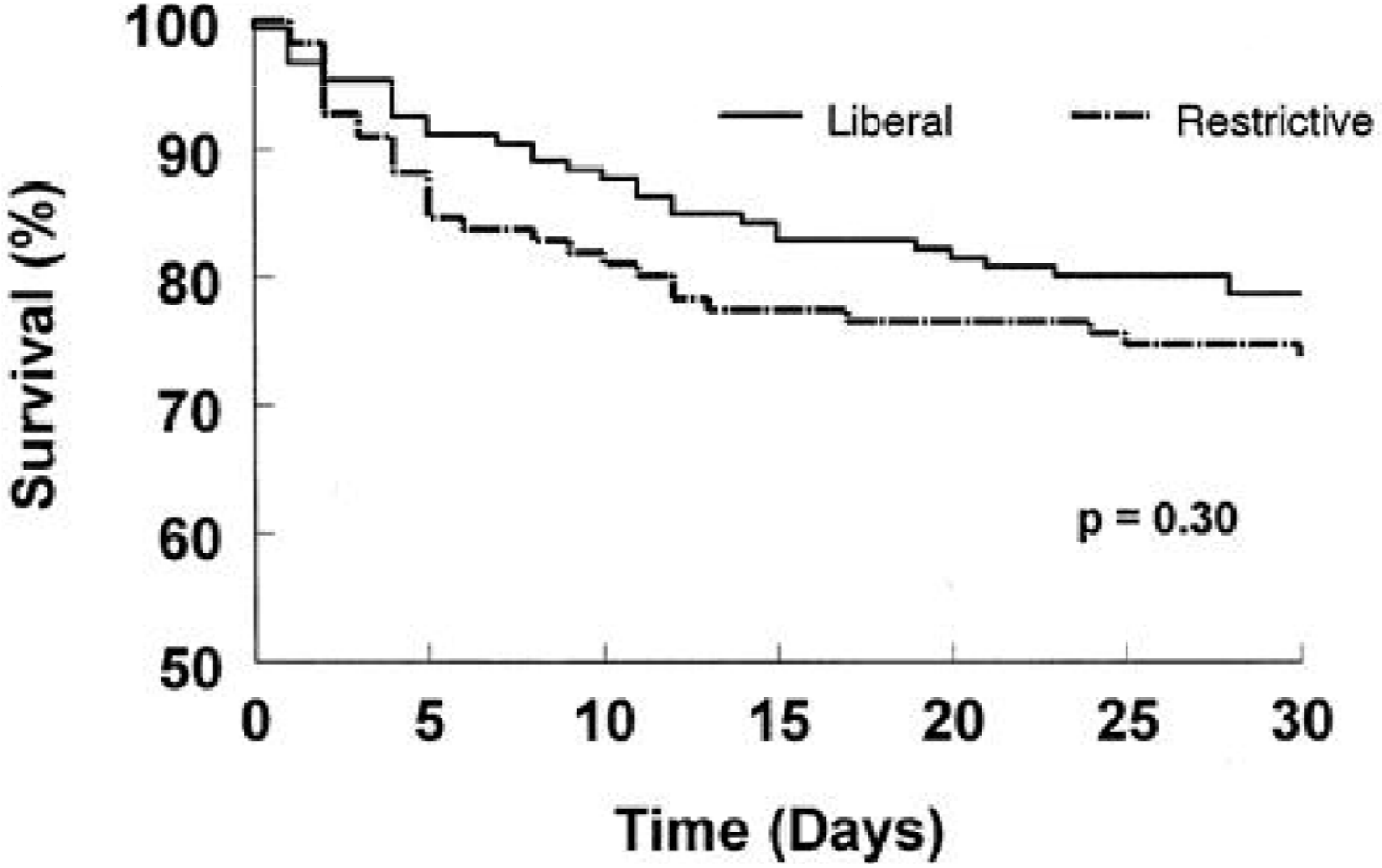
- Cardiovascular disease patients

Outcome		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

Outcome	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 ≤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.

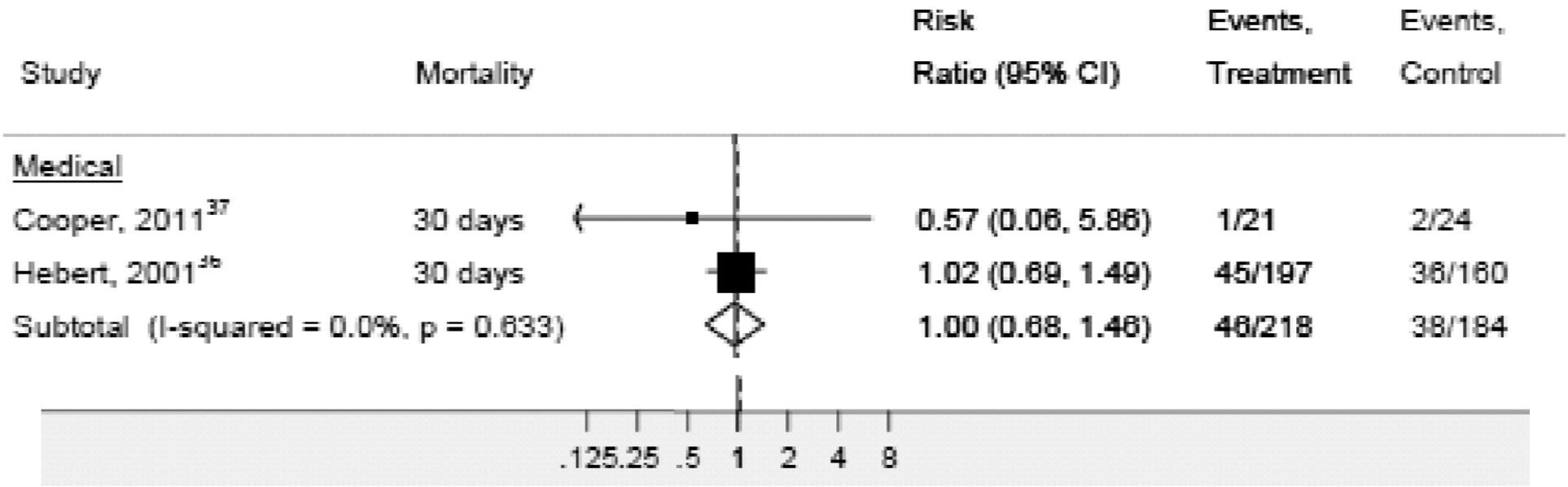
CRIT trial – Cooper 2011

Outcome		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 ≥ 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 ≥ 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

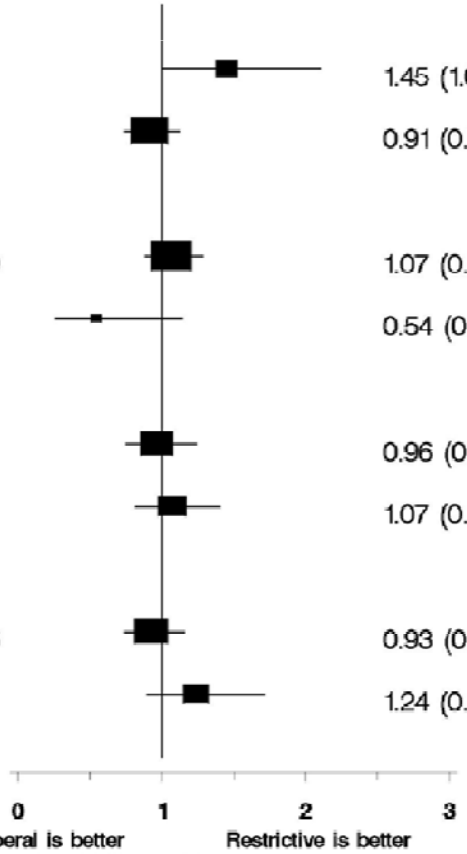
Outcome	R	L	OR
Death/can't walk 10 ft, 60 d	34.7%	35.2%	1.01 (0.84-1.22)
Mortality, 60 d	6.6%	7.6%	1.17 (0.75-1.83)
Death/MI/UA, in-hospital	5.2%	4.3%	0.82 (0.48-1.42)
MI, in-hospital	3.8%	2.3%	0.60 (0.30-1.19)
CHF, in-hospital	3.5%	2.7%	0.77 (0.39-1.50)

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

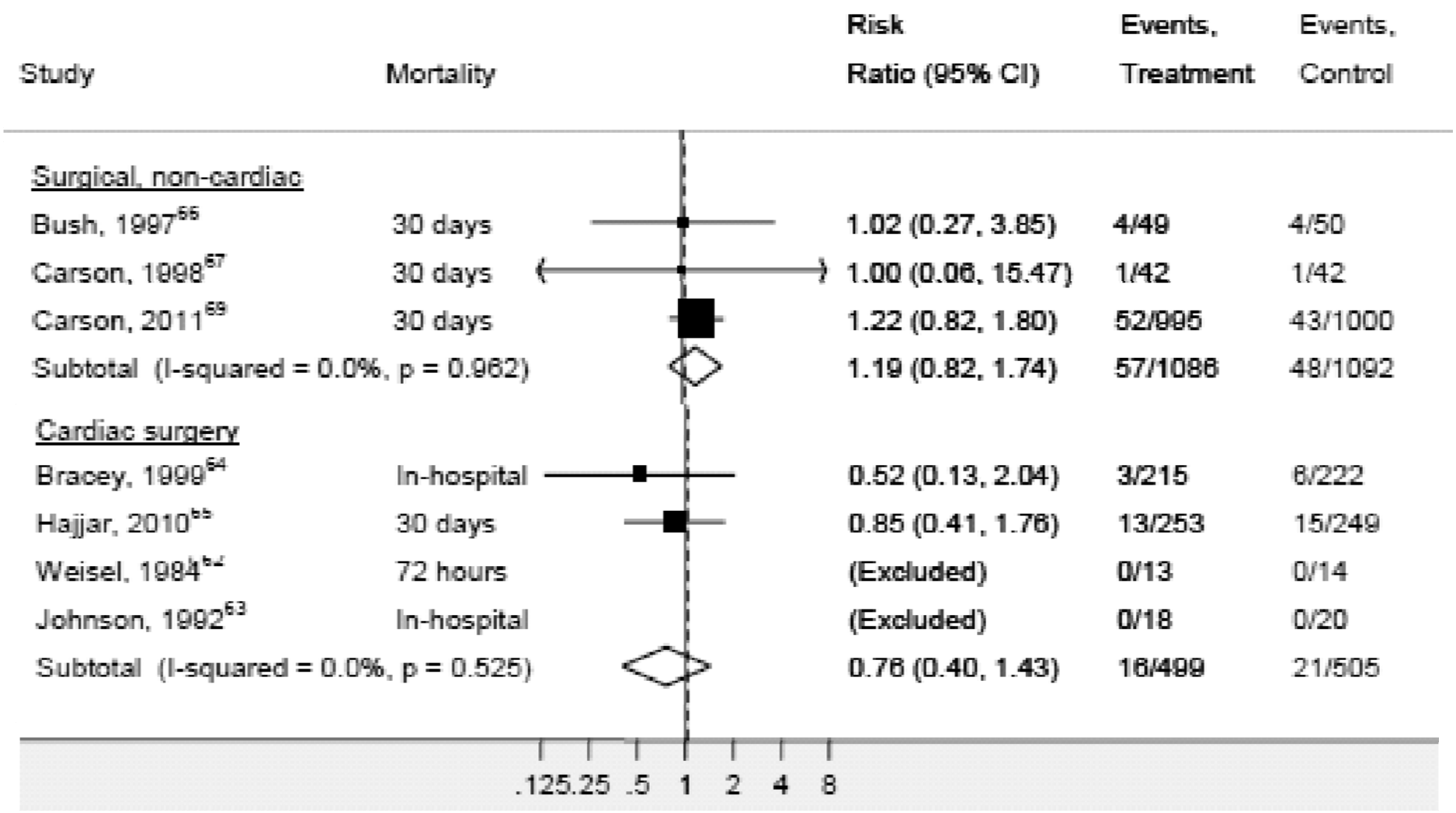
Subgroup	Liberal event*/total	Restrictive event*/total	Odds Ratio (95% CI)	P Value	P Value for Interaction
Gender					0.03
Male	100/247	76/238	1.45 (1.00, 2.10)	0.05	
Female	251/751	271/763	0.91 (0.74, 1.13)	0.39	
Race					0.08
White	333/937	320/939	1.07 (0.88, 1.29)	0.51	
Other	18/61	27/62	0.54 (0.26, 1.14)	0.11	
Age					0.58
< 85	167/563	178/585	0.96 (0.75, 1.24)	0.78	
≥ 85	184/435	169/416	1.07 (0.82, 1.41)	0.62	
CV Status					0.15
CV Disease	244/630	254/626	0.93 (0.74, 1.16)	0.50	
CV Risk Factors Only	107/368	93/374	1.24 (0.89, 1.71)	0.20	



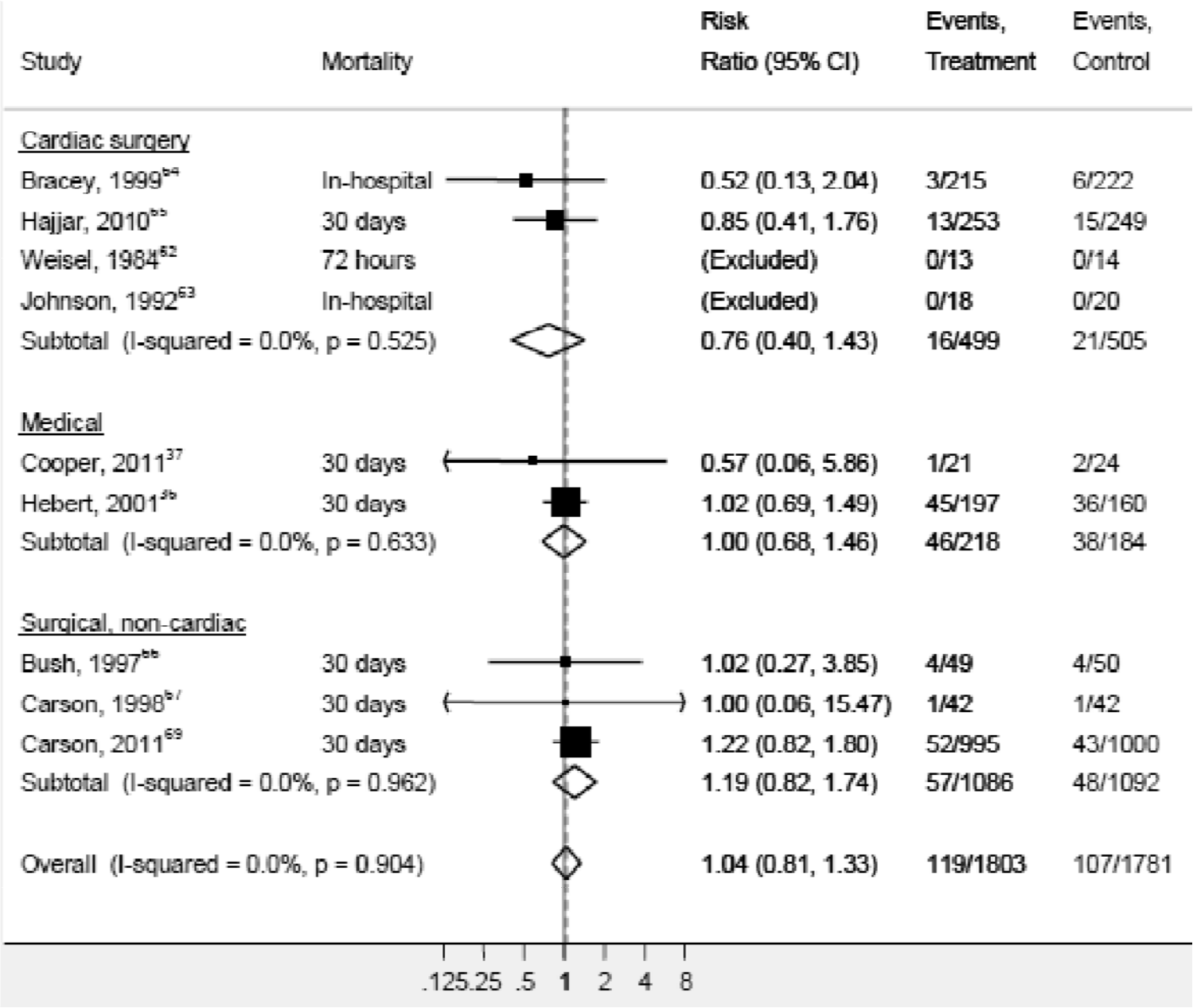
*Death or inability to walk independently at 60–Day Follow–Up

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 9th)
    - 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 NSTE-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 NSTE-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/ NSTE-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 NSTE-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 ≈ 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).

Carson J et al, Ann Int Med, 2012

Future studies

- RED-HF
  - Target of 2600 pts symptomatic CHF and reduced LVEF
  - Results ≈ 2014
  - Darbepoetin titrated to hgb ≥ 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.hsrd.research.va.gov/publications/esp/