

Plasma Transfusion

Evidence-based clinical practice guidelines

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Plasma transfusion

- US: approximately 4 million units of plasma transfused per year
- 150% increase over last 25 years
- Other nations with advanced health care systems transfuse similar (or slightly lower) amounts of plasma
- Many recognized adverse effects of plasma: viral transmission, TRALI, etc...

Why develop plasma transfusion practice guidelines?

- Guidelines identify best clinical practices
- Guidelines provide useful and needed information to those in your specialty as well as related specialties
- If stakeholders are deeply involved, guidelines can promote more acceptance of these practices
- Guidelines can also stimulate research initiatives into areas where evidence addressing efficacy is lacking.....

Practice guidelines as a “ratchet”

Evidence from clinical studies



Evidence-based guidelines are
developed/revised



Guidelines inform study designs



Studies improve quality of evidence



Typical “guidelines” for plasma transfusion

- Massive transfusion
- Active bleeding
- Multiple coag factor deficiency with (risk of) bleeding
 - Warfarin reversal
 - Liver disease
- Single coag factor deficiency without concentrate available
- Plasma exchange

Recognized contra-indications to plasma transfusion

- Volume replacement/expander
- Nutritional supplement
- When warfarin can be reversed with Vit K
- When recombinant/virus-inactivated products are available
- When INR is < 1.7
- Unfortunately, guideline compliance is often limited...

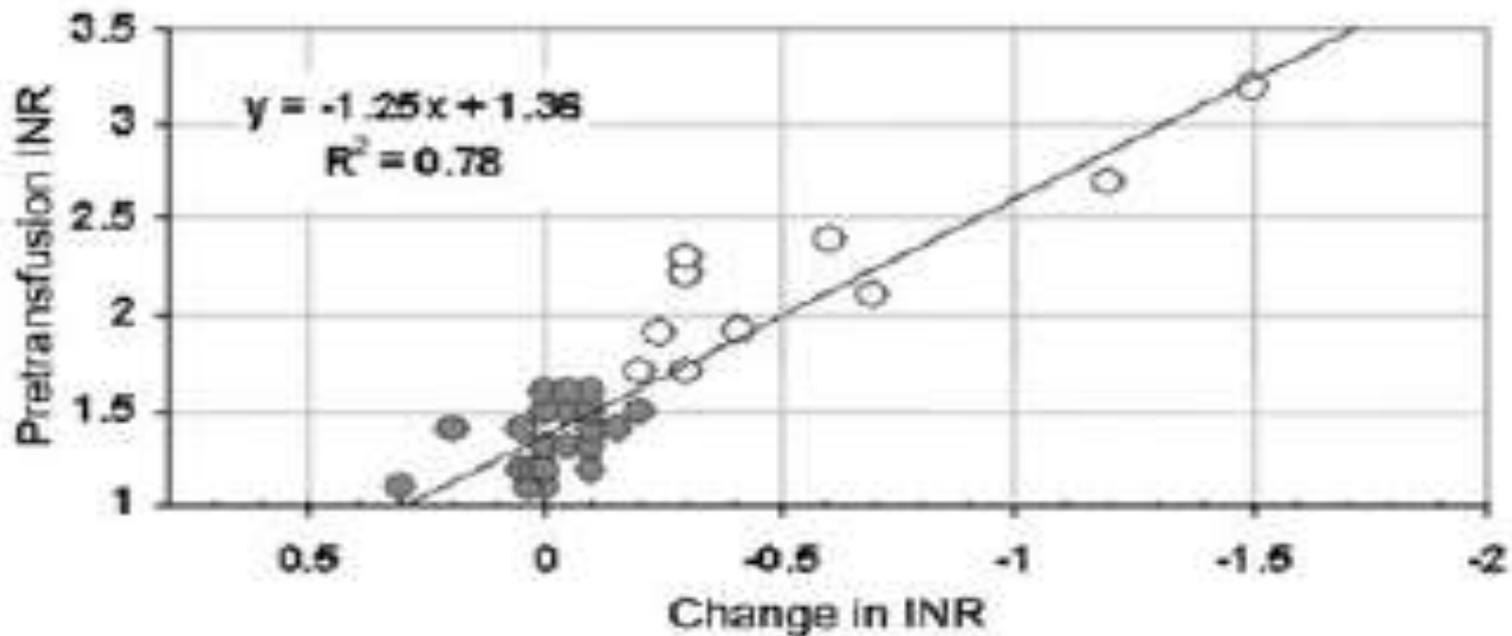


Fig. 1. Changes in recipients' INRs after transfusions of FFP that were within guidelines (INR, 1.6; ○; n= 10 units) compared to transfusions of FFP outside guidelines (●; n= 68 units). Only 20 filled circles appear in the figure because 48 additional results were overlapping.

Fresh frozen plasma is ineffective for correcting minimally elevated international normalized ratios

■ Results

- Minimally prolonged INRs decreased with treatment of the underlying disease alone (FFP had no impact).
- With an observed analytic variation of 3.2%, a significant change in the INR following FFP transfusion is expected only at an INR of > 1.7.

■ Conclusion

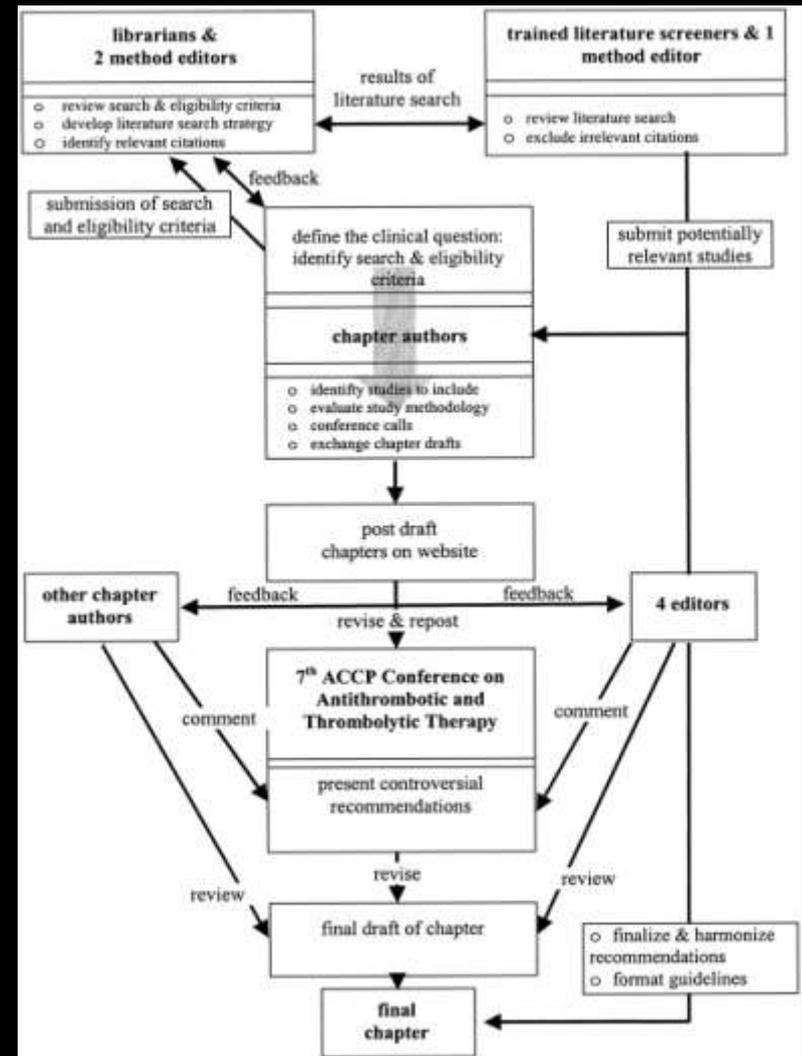
- Transfusions not meeting current FFP guidelines do not reliably reduce the INR.
- However, 20-30% of transfusions were outside guidelines

Approaches to developing guidelines

- Literature reviews
- Consensus conferences
- Systematic reviews
 - A key component of evidence-based medicine
- Explicit, transparent systematized approaches for deriving practice guidelines from study evidence
 - **GRADE**: Grading of Recommendations, Assessment, Development, and Evaluation

GRADE:

a widely-accepted transparent methodology for developing evidence-based practice guidelines



CHEST
The Cardiopulmonary and Critical Care Journal

Organizations that have endorsed GRADE

World Health Organization
Endocrine Society
American College of Chest Physicians
Up To Date
Agenzia Sanitaria Regionale, Bologna-Italy
Ministry of Health and Long-Term Care,
Ontario-Canada
Surviving Sepsis – International
Arztliches Zentrum für Qualität in der Medizin-
Germany
American Thoracic Society- USA
American College of Physicians-USA
The Cochrane Collaboration-International
European Society of Thoracic Surgeons-
International
British Medical Journal
Journal of Infection in Developing Countries-
international
Agency for Healthcare Research and Quality-
USA
Society of Critical Care Medicine-USA
National Institute for Clinical Excellence-UK
Norwegian Knowledge Centre for the Health
Services
The UPenn Center for Evidence-Based Practice
German Center for Evidence-Based
Nursing
Evidence-Based Nursing Sudtiroil-Italy
Society for Vascular Surgery-USA
BMJ Clinical Evidence
EBM Guidelines-Finland/International
Polish Institute for EBM
European Respiratory Society (ERS)-
Europe
Japanese Society for Temporomandibular
Joint-Japan
National Board of Health and Welfare-
Sweden
COMPUS at the Canadian Agency for
Drugs and Technologies in Health-
Canada
Infectious Diseases Society of America-
USA

Major steps for developing guidelines using GRADE

1. Assemble the guidelines review group
2. Formulate the clinical question(s)
3. Perform a thorough search of the relevant literature followed by a systematic review and statistical analysis
4. Prepare evidence-based guidelines following the explicit step-by-step methodology of the GRADE system

The Guidelines Group

AABB CTMC

- Jeff Carson, UMDNJ
- Rob Davenport, U Michigan
- Mary Jo Drew, ARC
- Mark Fung, U Vermont
- Marilyn Hamilton, CMHC
- John Hess, U Maryland
- Anne Eder, ARC
- John Roback, Emory
- Bruce Sachais, U Penn
- Toby Silverman, CBER FDA
- John Waters, U Pittsburgh

AABB staff

- Theresa Wiegmann
- Aaron Lyss

Outside stakeholders

- Stephen Caldwell, UVA (AASLD)
- Naomi Luban, CNMC (AAP)
- Jeremy Perkins, Walter Reed (military)
- Aryeh Shander, MSSM (ASA)
- Ed Snyder, Yale (ASH)
- Christopher Tormey, Yale (ASH)

Consultants

- Ben Djulbegovic, Moffitt
- Victor Montori, Mayo
- Hassan Murad, Mayo

Questions with FFP transfusion

1. Should plasma transfusion be used (vs. no plasma) in patients requiring massive transfusion?
2. Should a plasma:RBC transfusion ratio $\geq 1:3$ (vs. $< 1:3$) be used in patients requiring massive transfusion?
3. Should plasma transfusion (vs. no plasma) be used in patients undergoing surgery without massive transfusion?
4. Should plasma transfusion (vs. no plasma) be used for patients with anticoagulation-related intracranial haemorrhage?
5. Should plasma transfusion (vs. no plasma) be used to reverse anticoagulation in patients without intracranial haemorrhage?
6. Should plasma transfusion (vs. no plasma) be used in medical patients who are not bleeding, not undergoing surgery, or massive transfusion?

Figure 1: Study Flow

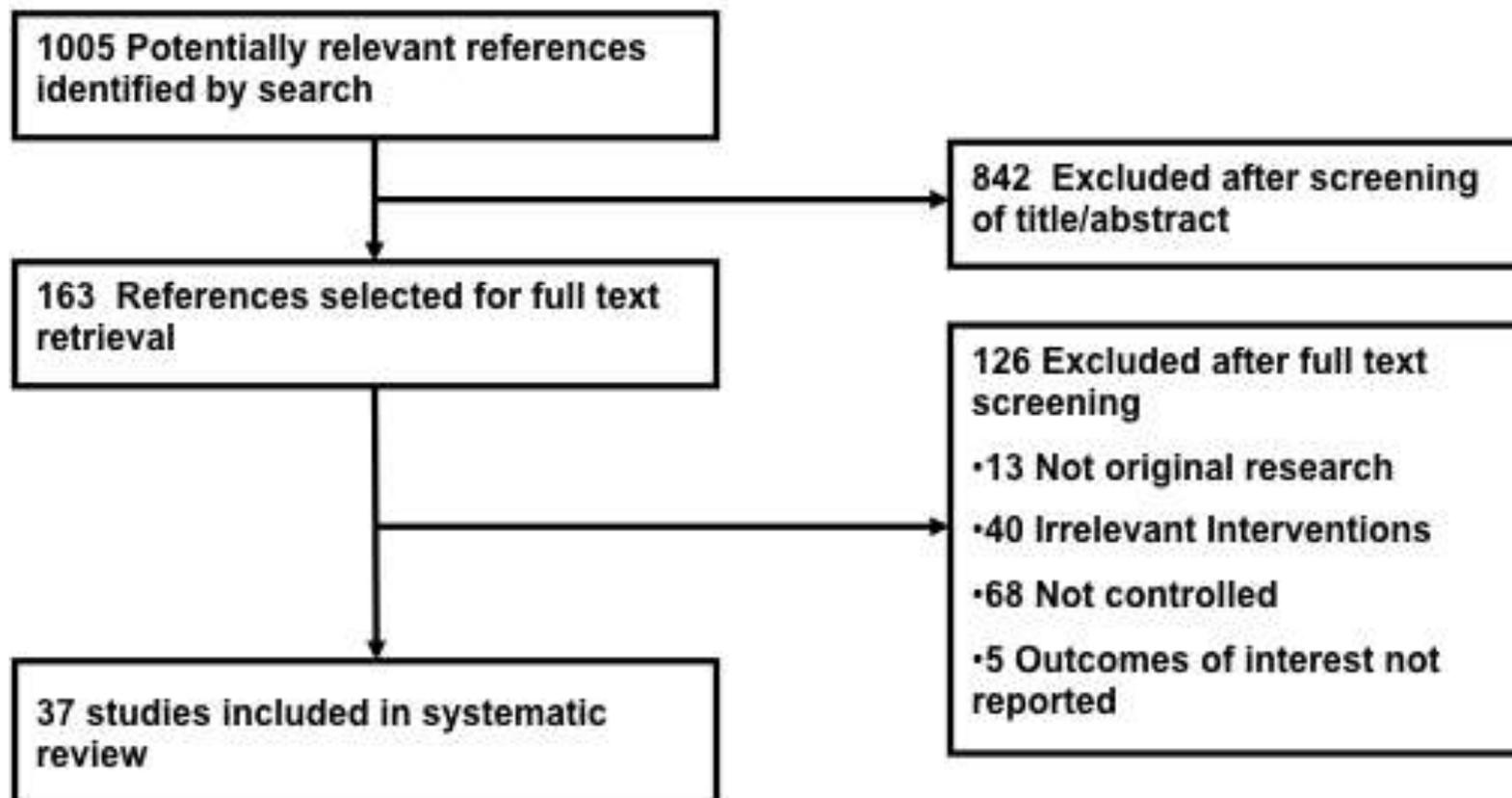
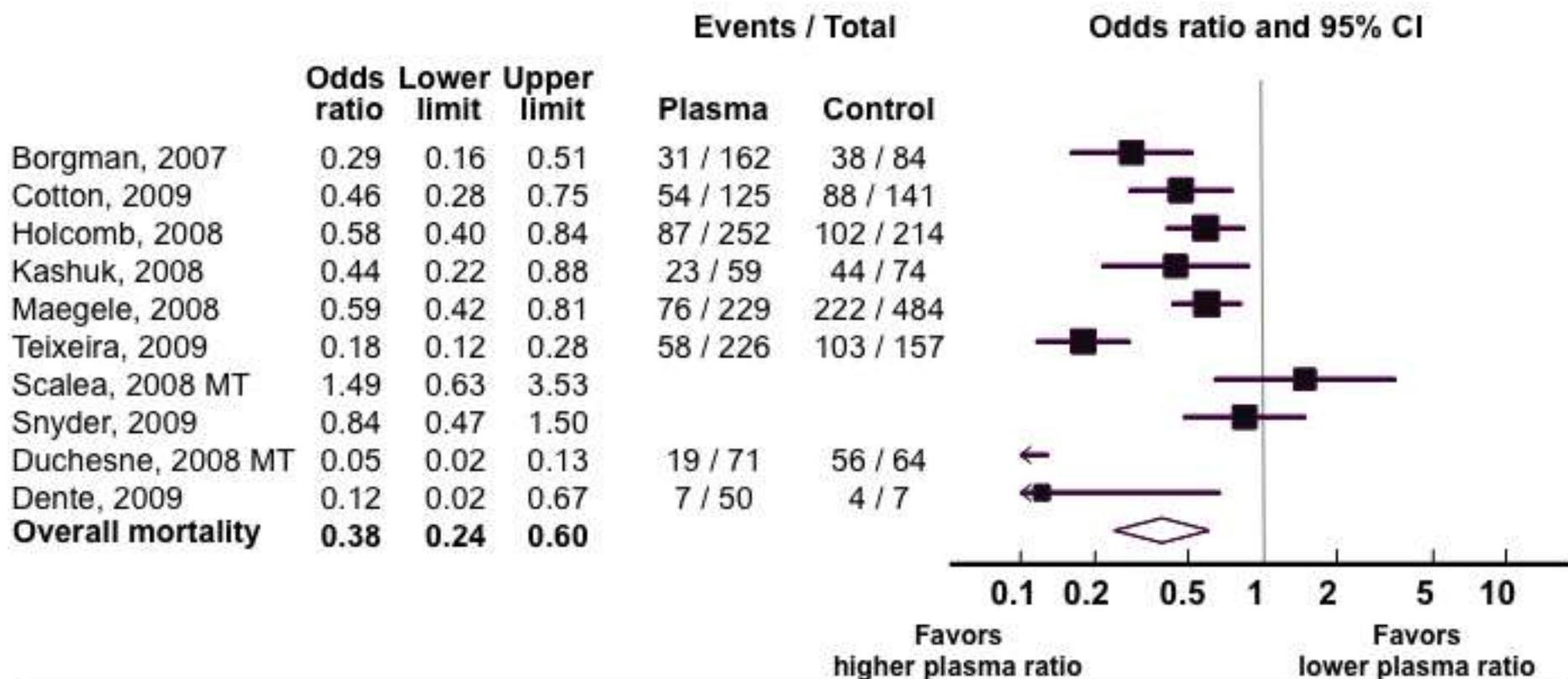


Table 2: Study description

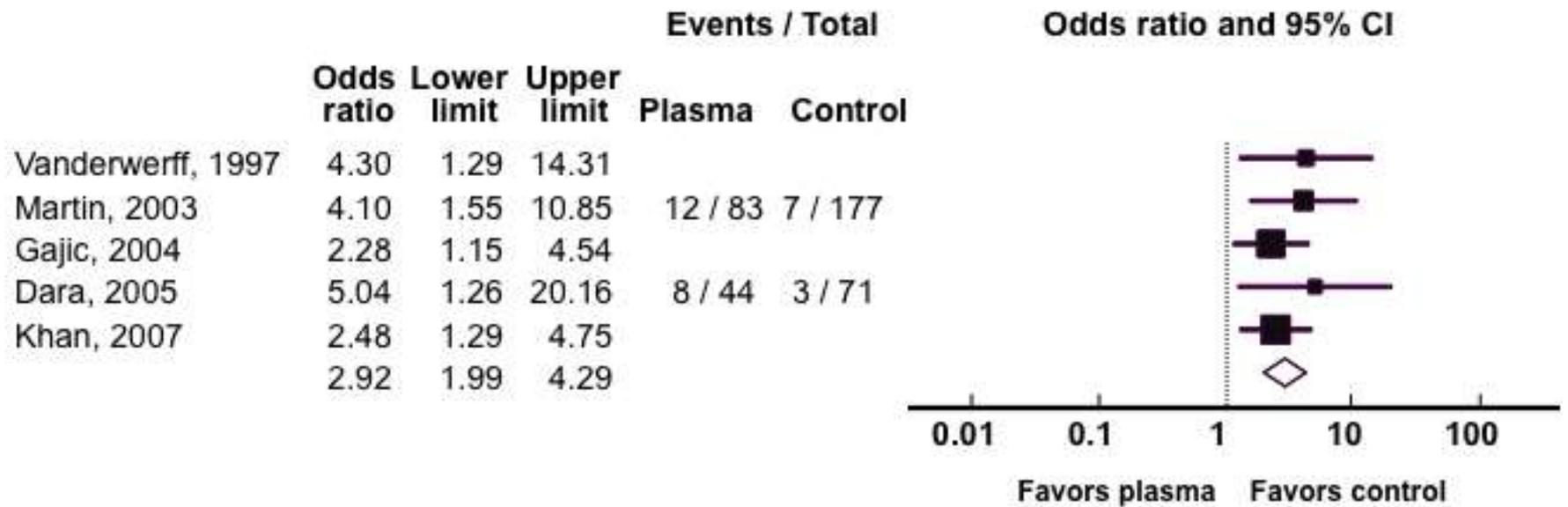
Randomized studies											
Author, Year	Number of patients	Mean Age (years)	Female (%)	Comorbidities	Liver Disease	Operative Status	Anti-coagulation	Follow-up	Intervention	Control	
Gazzard, 1975 ⁷⁴	20	26	N R	Acetaminophen overdose and coagulopathy	Yes	No	No	7 d	plasma 300 ml/6hr until PT ratio normalize	No treatment	
Mannucci, 1976 ⁴⁷	21	NR	N R	Cirrhosis/ hepatitis	Yes	Needle biopsy	No	365 d	plasma 12ml/kg	Prothrombin complex 25 Units/ml	
Belcher, 1984 ⁴⁸	73	53	7	Elderly, Cardiac surgery	No	Yes	No	180 d	Plasma Protein fraction	Hydroxy ethyl Starch	
Boughton, 1984 ⁴⁹	10	42	N R	20 to 70% burns	NR	No	No	21 d	plasma	Human Plasma Protein Fraction	
Leese, 1987 ⁷⁵	198	59	52	Severe acute pancreatitis, no coagulopathy	No	No	No	105 d	plasma 2 U Daily for 3 days.	albumin solution	
Hedstrand, 1987 ⁶¹	275	69	55	Elderly, elective surgery (abdominal, hip, knee and others), in need of blood transfusion	No	Yes	No	14 d	plasma	6% Macrodex & Ringerdex	
Martinowitz, 1990 ⁵⁰	40	60	28	Cardiopulmonary bypass patients who received prophylactic plasma postoperatively	No	Yes	No	1 d	plasma	Fresh packed cells	

Figure 2: Mortality, massive transfusion



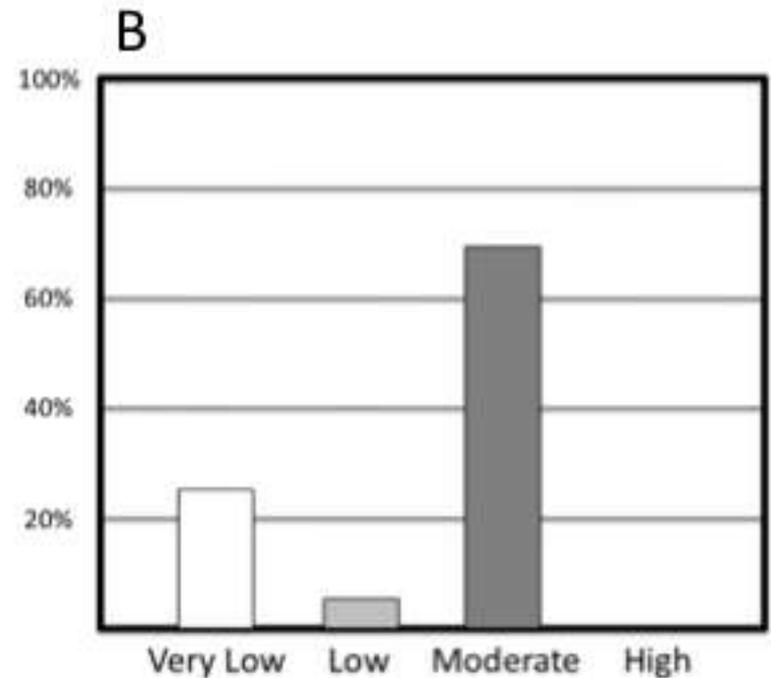
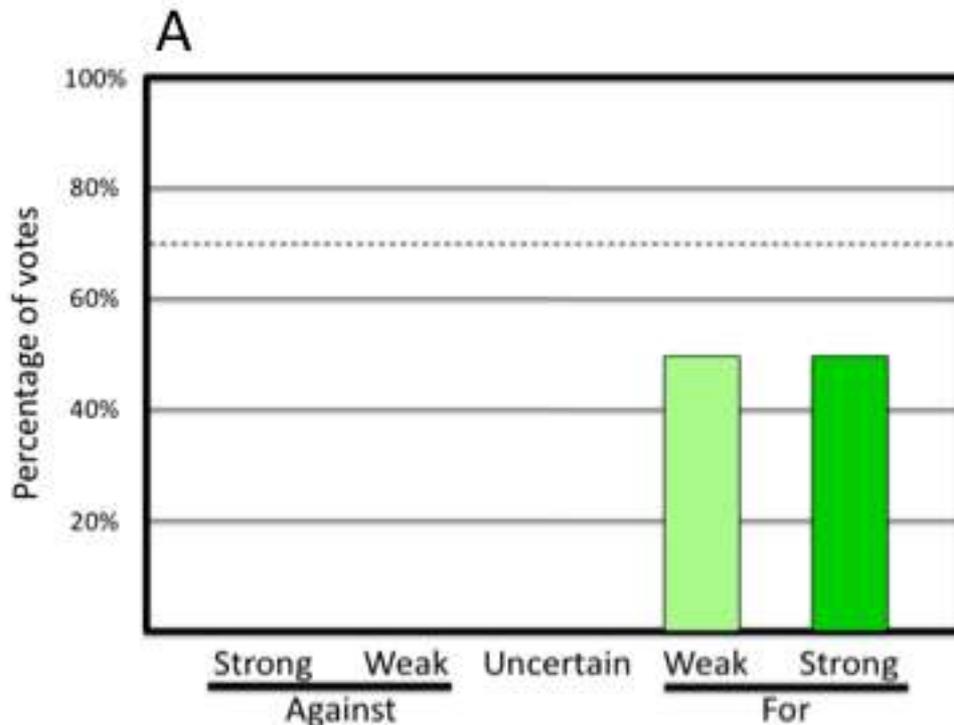
Meta Analysis

Figure 5: Acute lung injury



Recommendation: We suggest that plasma be transfused to trauma patients requiring massive transfusion

Quality of evidence = **Moderate**



Quality of Evidence

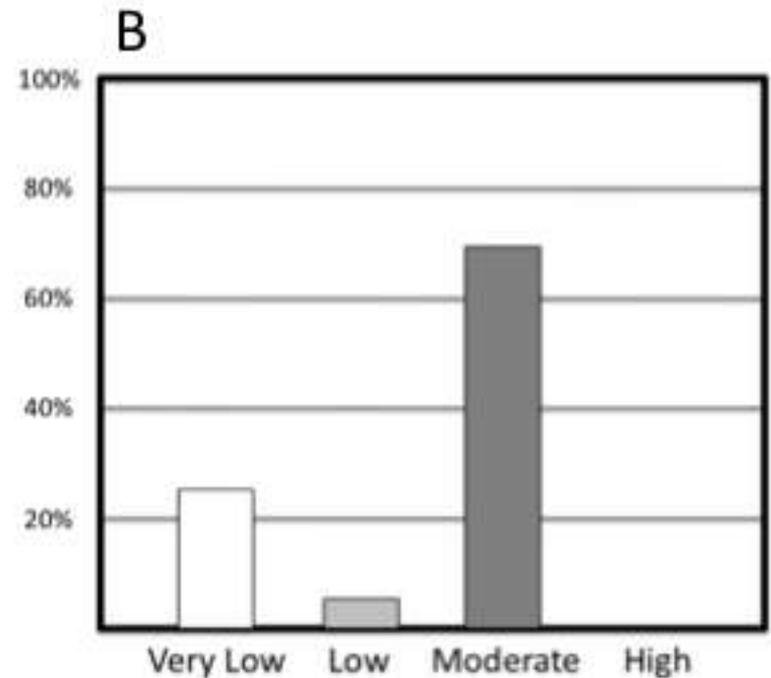
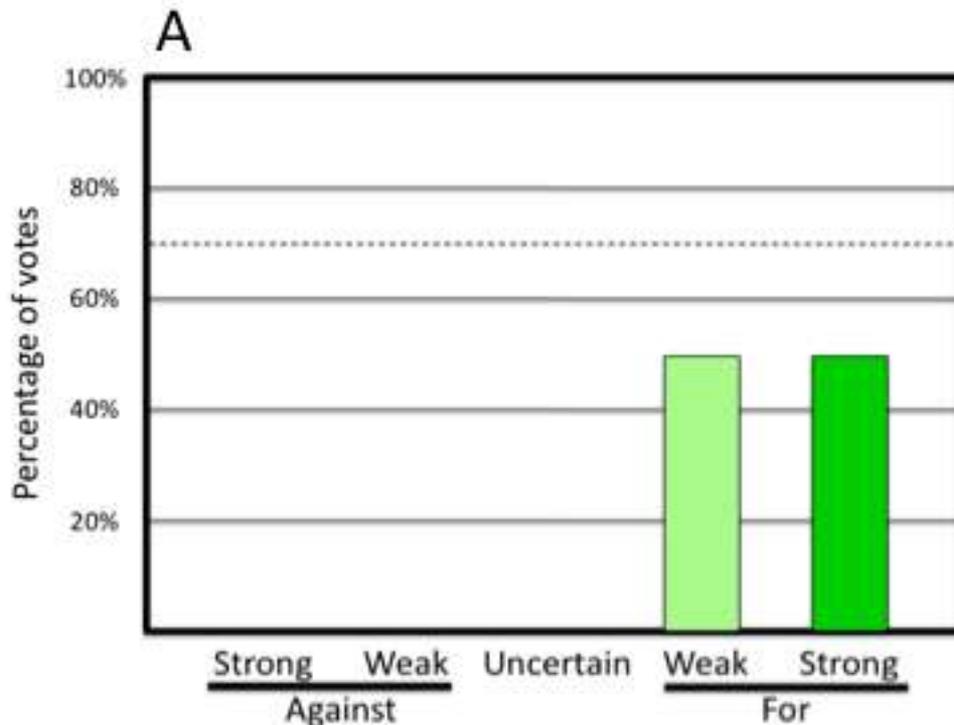
- The extent of confidence that an estimate of effect is correct, i.e. represents the “truth”
 - **High:** Considerable confidence in the estimate of effect. Future research is unlikely to change the estimate of the health intervention’s effect.
 - **Moderate:** Further research is likely to have an important impact on confidence in the estimate, and may change the estimate of the health intervention’s effect.
 - **Low:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
 - **Very low:** Any estimate of effect is very uncertain.

Strength of Recommendation

- Confidence that adherence to recommendations will do more good than harm).
 - **Strong:** indicating the judgment that most well informed people will make the same choice. The terminology “**We recommend...**” is used for these situations.
 - **Weak:** indicating the judgment that a majority of well informed people will make the same choice, but a substantial minority will not. “**We suggest...**” is used in these situations.
 - **Uncertain:** indicating that the panel made no specific recommendations for or against interventions, or made recommendations only in the context of research. “**We cannot recommend for or against...**”

Recommendation: We suggest that plasma be transfused to trauma patients requiring massive transfusion

Quality of evidence = **Moderate**



Recommendation: We **cannot recommend** for or against transfusion of plasma at a plasma:RBC ratio of $\geq 1:3$ in trauma patients during massive transfusion

Quality of evidence = **Low**

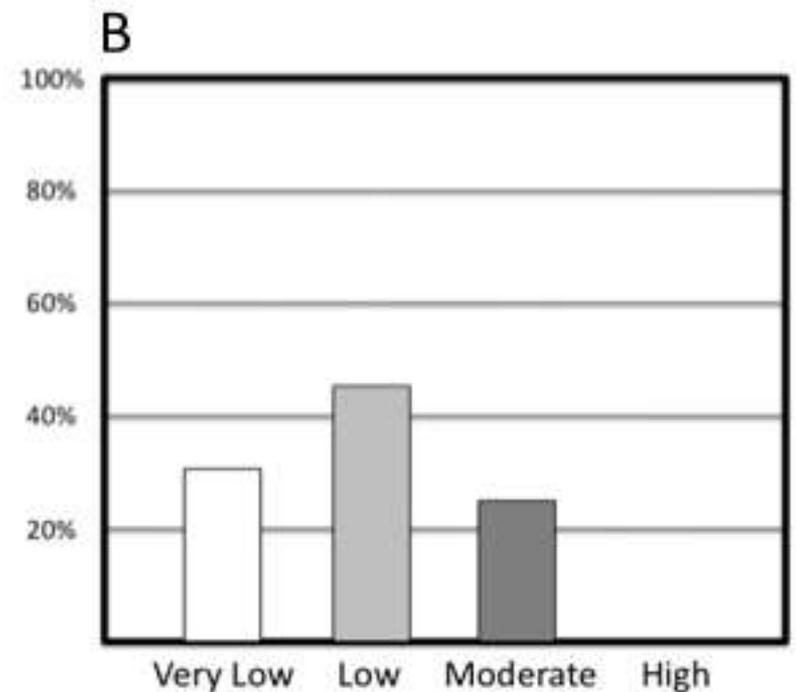
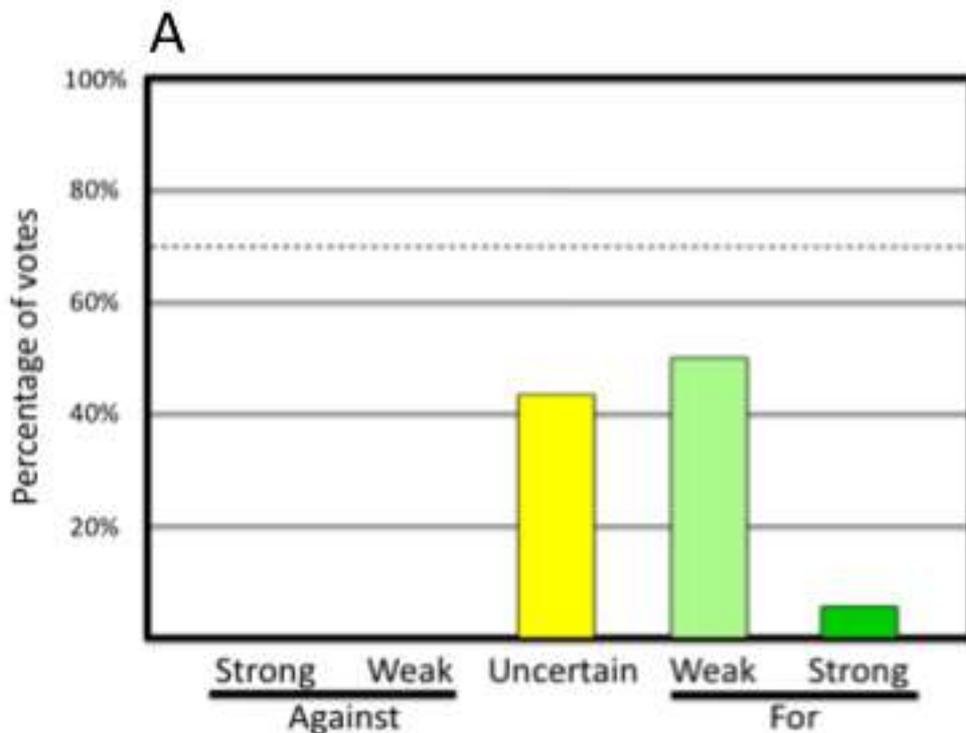
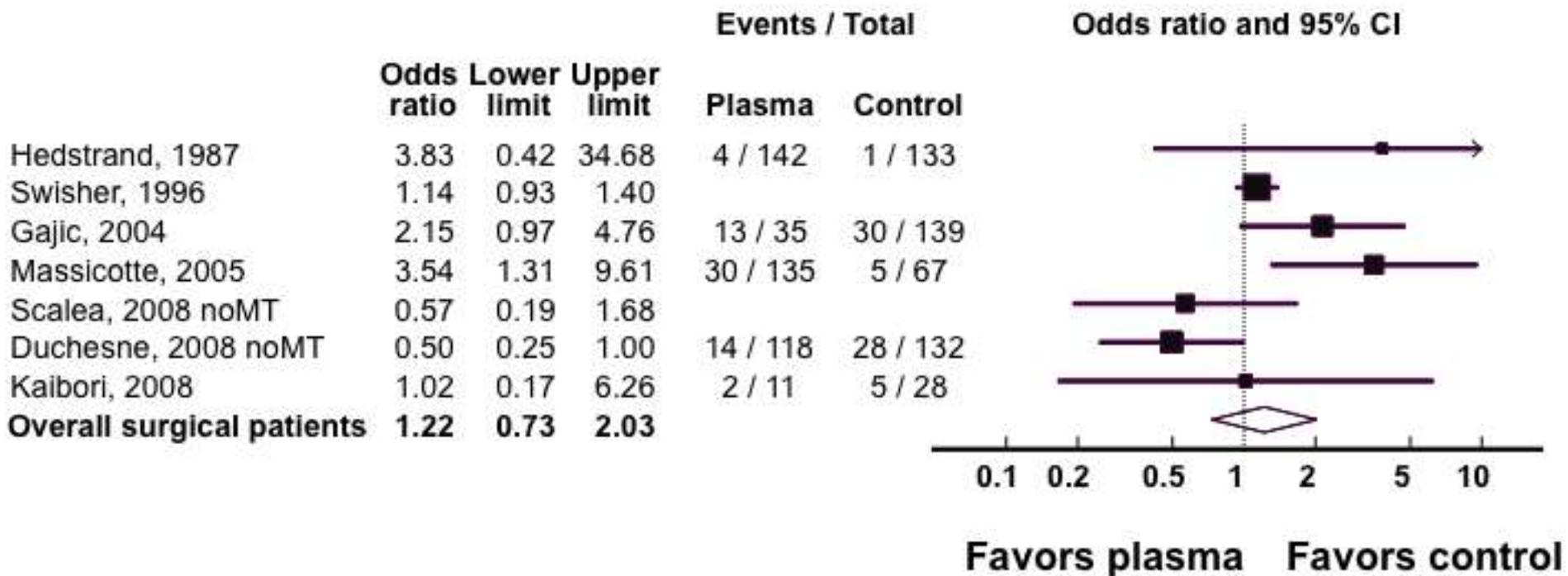


Figure 3: Mortality, surgical patients



Recommendation: We **cannot recommend** for or against transfusion of plasma for patients undergoing surgery in the absence of massive transfusion.

Quality of evidence: **Very Low**

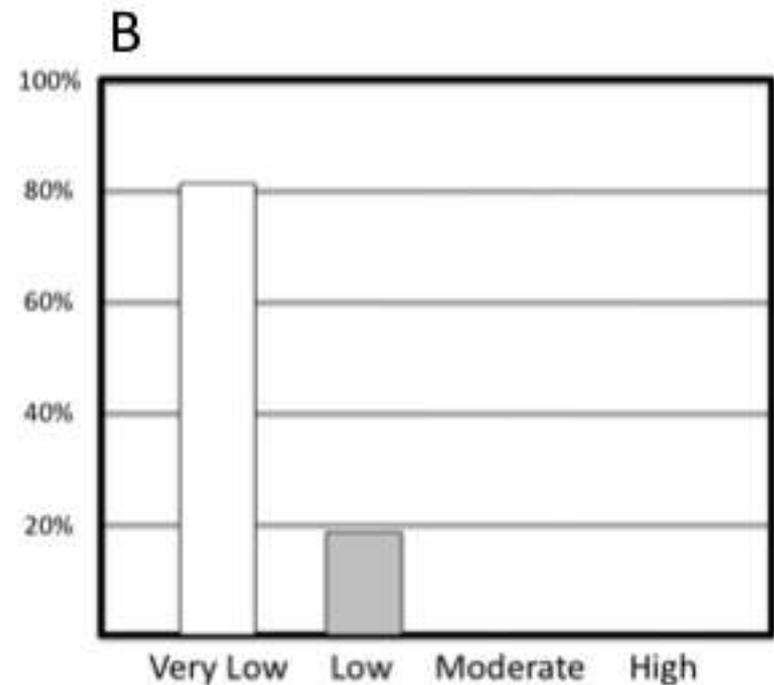
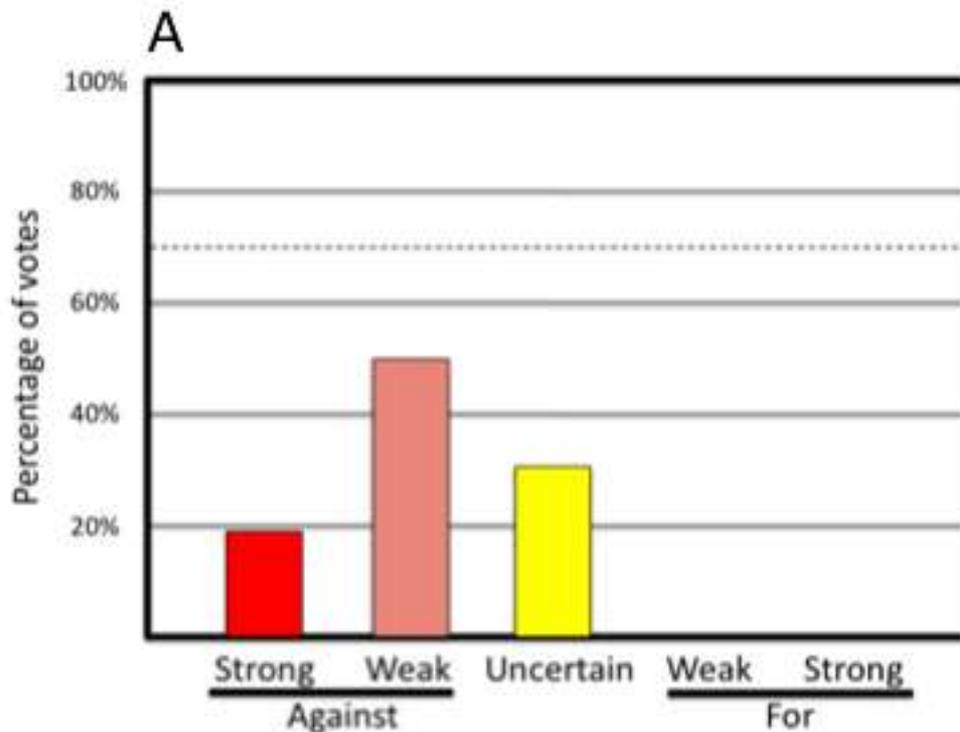
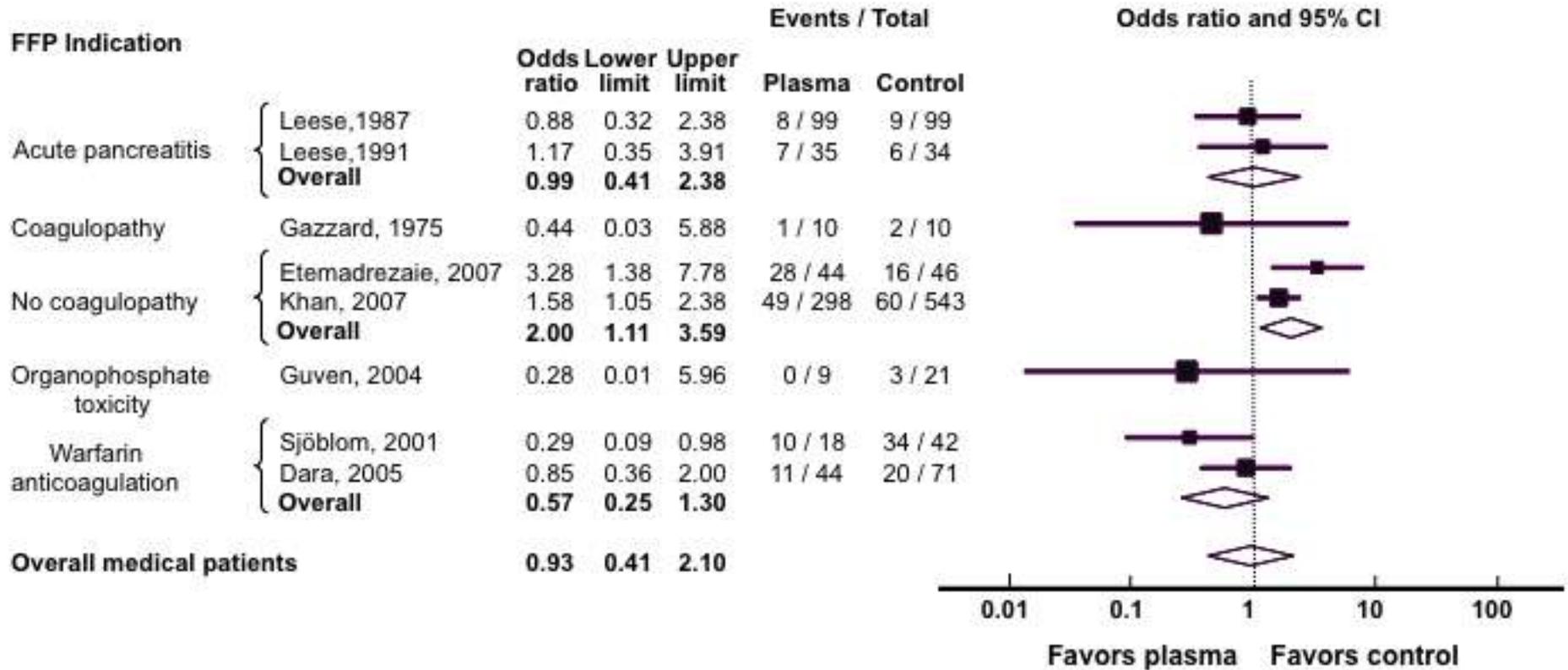


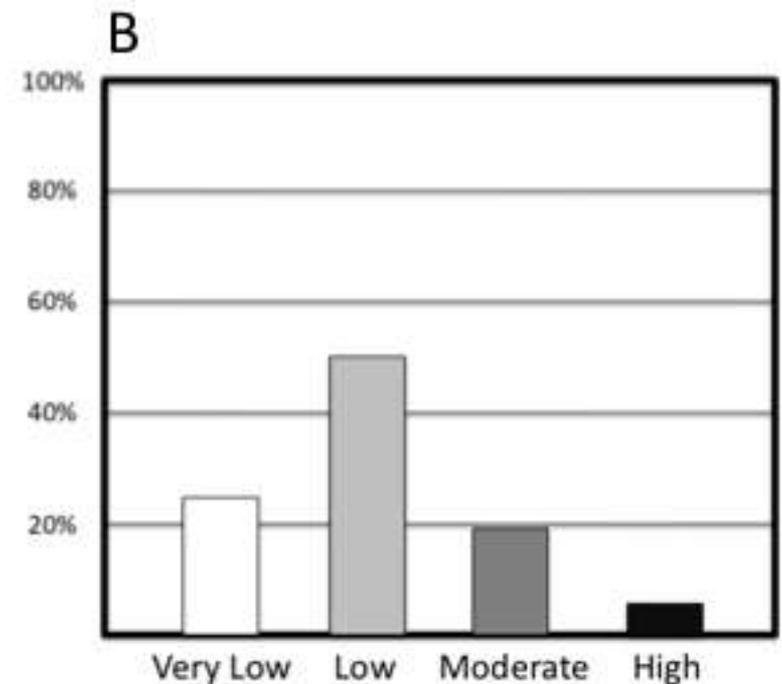
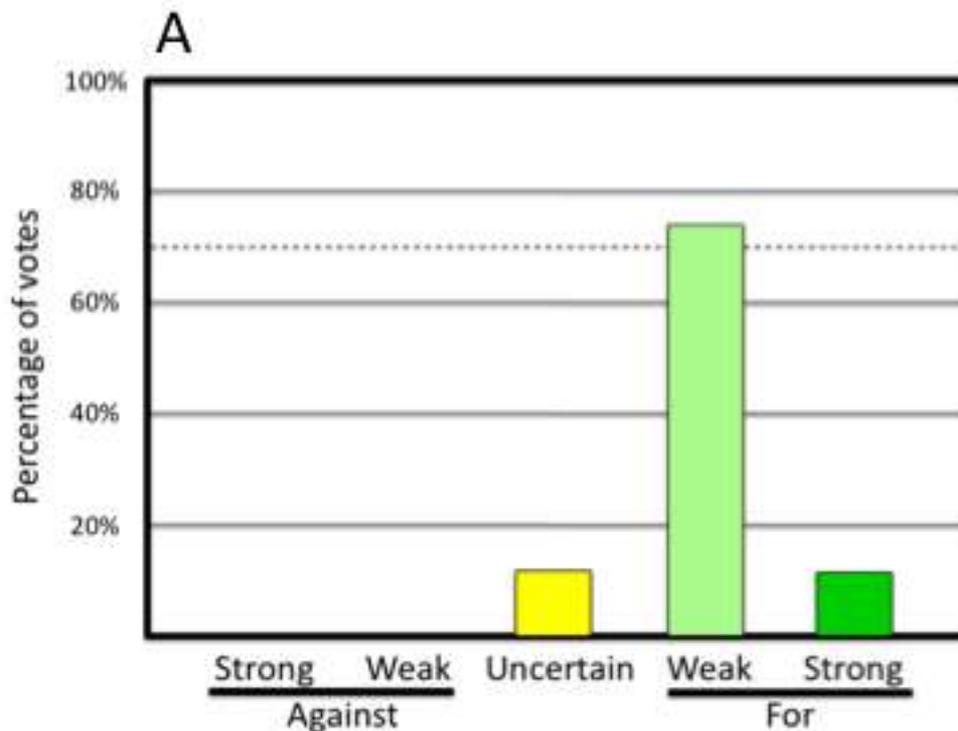
Figure 4: Mortality, medical patients



Meta Analysis

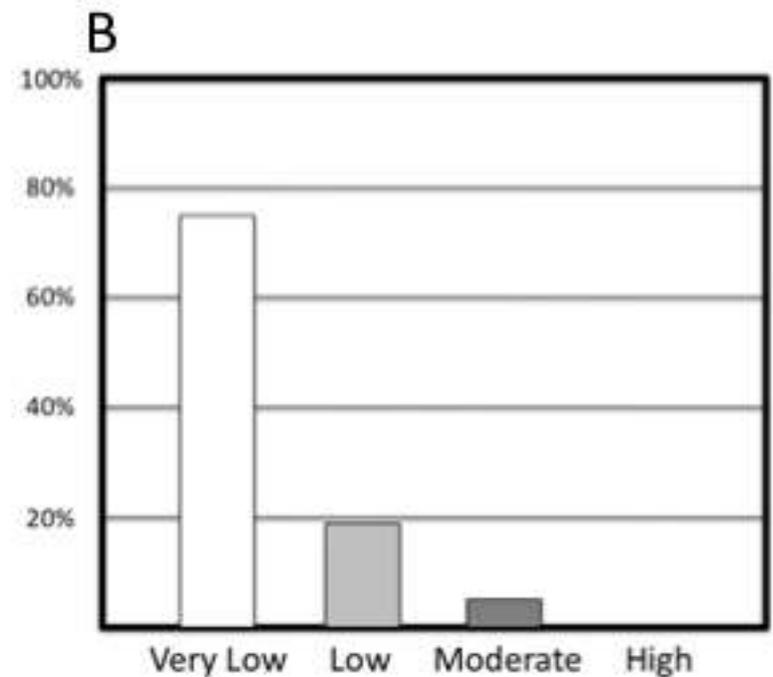
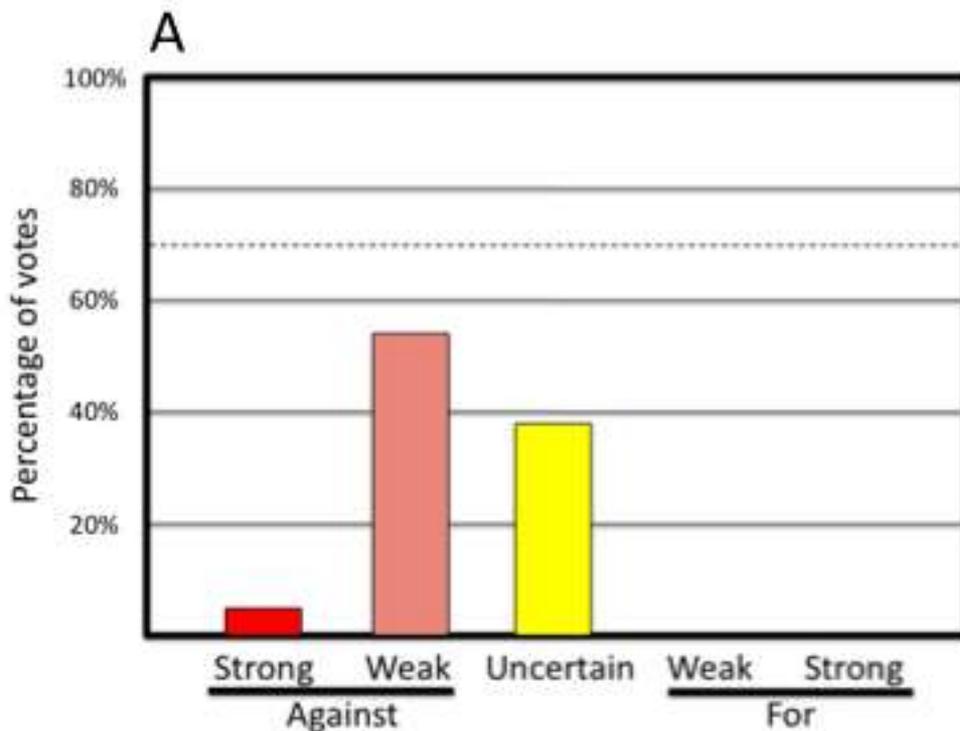
Recommendation: We suggest that plasma be transfused in patients with warfarin anticoagulation-related intracranial hemorrhage.

Quality of evidence: **Low**



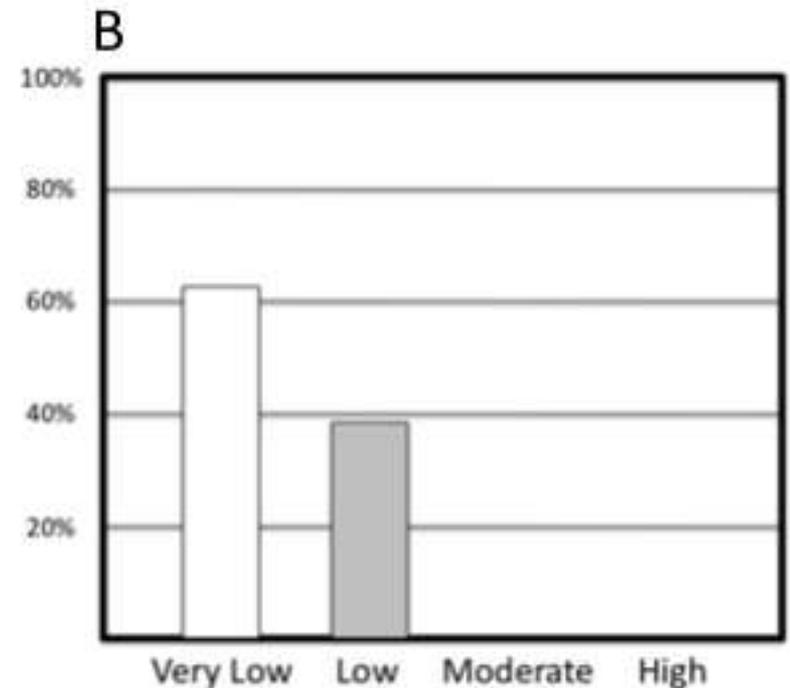
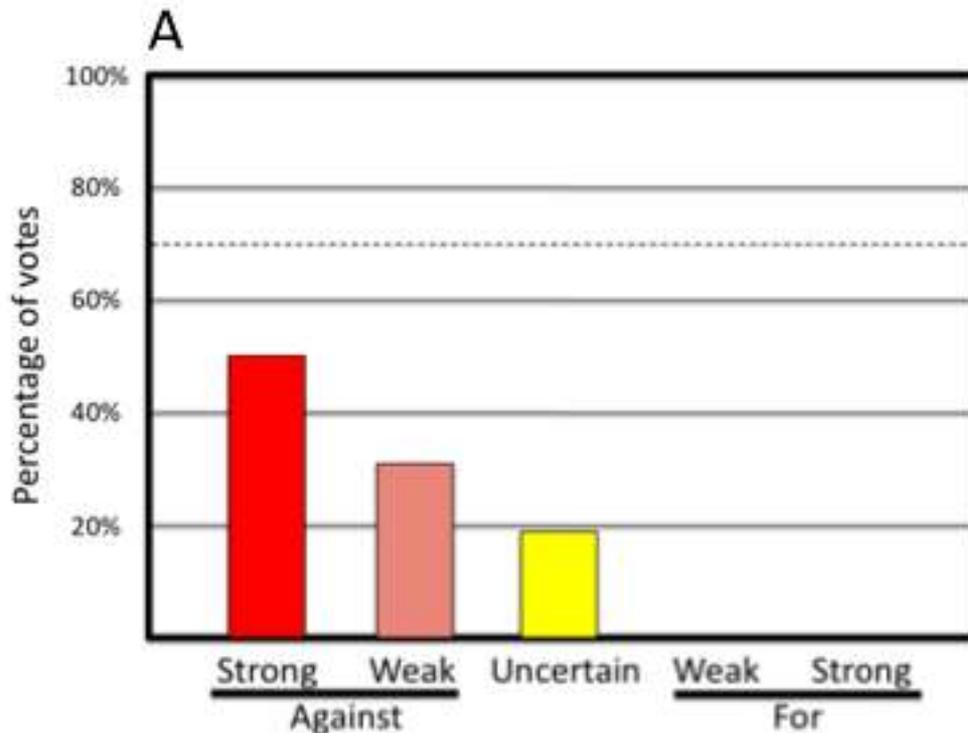
Recommendation: *We cannot recommend for or against transfusion of plasma to reverse warfarin in patients without intracranial hemorrhage.*

Quality of evidence: Very Low



Recommendation: *We suggest against plasma transfusion in the absence of massive transfusion, surgery, bleeding or overanticoagulation.*

Quality of evidence: Very Low



Conclusions

- Current indications for transfusion are based on limited evidence
- Clinical studies, and resulting guidelines, are improving but still have far to go
- In every scenario, the need for additional studies was identified
- In particular, there was an absence of studies that quantified plasma efficacy in patients with varying INRs
- Appropriately designed studies are expected to lead to stronger guideline recommendations