
**THE DARTMOUTH INSTITUTE
FOR HEALTH POLICY & CLINICAL PRACTICE**



Where Knowledge Informs Change

**An evidence-based review of pharmaceutical
interventions to limit the systemic
inflammatory response in cardiac surgery**

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for the International

Consortium for Evidence Based Perfusion (ICEBP)

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Centre, Barbados; The Dartmouth Institute for Public Health Policy and
Clinical Practice, Lebanon, NH, USA;

Disclosures



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Disclosures: R. Clive Landis

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Medicor International
Point Care Technologies

Mission:

- The International Consortium for Evidence-Based Perfusion (ICEBP) is a partnership and collaboration between perfusion societies, medical societies, clinicians and industry to improve continuously the delivery of care and outcomes for our patients.

Vision:

- To achieve this mission, we will focus our energies in two principle areas:
 - Registry
 - Create an international perfusion registry and facilitate its implementation
 - Identify gaps between current and evidence-based clinical practice
 - Guidelines
 - Review, comment, and/or endorse evidence-based guidelines concerning the practice of cardiopulmonary bypass
 - Collaborate with medical societies in the development of guidelines concerning the practice of cardiopulmonary bypass
- In order to succeed, the ICEBP will foster communication amongst its membership through a web portal, scientific conference, and internal and external publications.

Guideline Writing Subcommittee

- The mission of the guideline writing subcommittee is to develop evidence-based clinical practice guidelines for cardiovascular perfusion.
 - Methodology used by the American College of Cardiology/ American Heart Association (ACC/AHA)
 - Written and subsequently updated to remain concurrent with the medical literature.
 - Adoption of these guidelines in practice would be tracked through the clinical registry subcommittee.

Guideline Writing Subcommittee

- Guidelines
 - Involvement of representatives from each of the participating perfusion organizations in the guideline writing subcommittee should reduce any unanticipated hurdles for the endorsement of any given guideline.
 - Submitted to the participating perfusion organizations for their review and endorsement

What are the steps?

- Evaluate the peer-reviewed medical literature in a rigorous and consistent fashion
- Focus expertise on specific topics
- Develop an informed opinion regarding effectiveness and assign levels of evidence
- Formulate a “finding” and a written summary for publication



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Added by administrator, last edited by Robert Baker on Oct 12, 2008 (view change)
Labels: (None) EDIT

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 - [Registry Subcommittee](#)
 - [Scientific Sessions](#)
 - [Guidelines Subcommittee](#)
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- Links**
- [Community Exchange](#)
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Announcements

New!! 11th October 2008.

TAMPA MEETING ONLY 4 DAYS TO GO!

The ICEBP meeting will be an opportunity for perfusionists intersted in developing guildiens for perfusion practice to get involved in the Guideline Writing Subcommittee.

We look forward to seeing as many of our colleagues at teh meeting as possible.

FEEDBACK FROM OUTCOMES MEETING

The ICEBP was given a priomnant postion at the recent OUTCOMES meeting. Clive Landis presented an exciting lecture on the rebirth of the systemic inflammatory response and the way that we should or could examine and develop our undersatanding of it. This was followed by two abstract presentations, one from Clive and one from me, on our guideline

Where is the ICEBP Guideline Initiative going?

- Two paths
 - ICEBP Subcommittee
 - Inflammatory Response Guidelines
 - Evaluation of guidelines
 - Collaborative Guidelines Writing
 - STS
 - SCA

2009 Update to Society of Thoracic Surgeons Blood Conservation Practice Guidelines

Victor A. Ferraris, M.D., Ph.D. (Chair), Siby Saha, M.D., M.B.A., David Royston, M.D., Bruce Spiess, M.D., Jonathan Waters, M.D., Lawrence T. Goodnough, M.D., Linda Shore-Lesserson, M.D., Aryeh Shander, M.D., George Despotis, M.D., Jeremiah R. Brown, Ph.D., John W. Hammon, M.D., C. David Mazer, M.D., **Kenneth Shann, C.C.P., Rob Baker, C.C.P.**, Donald S. Likosky, Ph.D., Eugene A. Hessell, II, M.D., **Daniel J. FitzGerald, C.C.P., L.P.**, Kevin H.T. Teoh, M.D.

An evidence-based review of pharmaceutical interventions to limit the systemic inflammatory response in cardiac surgery

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for the International

Consortium for Evidence Based Perfusion (ICEBP)

Objectives

- Cardiac operations with cardiopulmonary bypass cause a systemic inflammatory response, which can lead to organ injury and postoperative morbidity.
- The ICEBP has undertaken the first ever evidence based review of pharmaceutical interventions aimed at curbing the systemic inflammatory response.

Search Strategy

Search 1: (((("thoracic surgery"[TIAB] NOT Medline[SB]) OR "thoracic surgery"[MeSH Terms] OR cardiac surgery[Text Word]) OR (((("cardiopulmonary bypass"[TIAB] NOT Medline[SB]) OR "cardiopulmonary bypass"[MeSH Terms] OR ("coronary artery bypass"[TIAB] NOT Medline[SB]) OR "coronary artery bypass"[MeSH Terms] OR "Heart-lung machine"[MeSH Terms]) OR (((("heart valves"[TIAB] NOT Medline[SB]) OR "heart valves"[MeSH Terms] OR valve[Text Word]) OR valves[All Fields] OR valvular[All Fields]) AND ("surgery"[Subheading] OR "operative surgical procedures"[Text Word] OR "surgical procedures, operative"[MeSH Terms] OR "surgery"[MeSH Terms] OR surgery[Text Word]))) AND (#19) Limits: Humans, Randomized Controlled Trial, English

Search 2: (aprotinin OR dexamethasone OR steroids OR cortisol OR aspirin OR tranexamic acid OR aminocaproic acid) AND ((Inflammation OR cytokines OR interleukin OR tnf OR (tumor necrosis factor) OR (leukocyte count) OR granulocytes OR immunoelectrophoresis OR monocytes OR (cell adhesion molecules) OR leukocyte OR aprotinin OR dexamethasone OR steroids OR cortisol OR aspirin OR tranexamic acid OR aminocaproic acid) AND (cardiac surgery OR (((("cardiopulmonary bypass"[TIAB] NOT Medline[SB]) OR "cardiopulmonary bypass"[MeSH Terms] OR ("coronary artery bypass"[TIAB] NOT Medline[SB]) OR "coronary artery bypass"[MeSH Terms]) OR (valve OR valves OR valvular) AND and surgery))) AND ((Humans[Mesh]) AND (English[lang]) AND (Randomized Controlled Trial[ptyp]))

Search 3: (("thoracic surgery"[TIAB] NOT Medline[SB]) OR "thoracic surgery"[MeSH Terms] OR cardiac surgery[Text Word]) OR (((("cardiopulmonary bypass"[TIAB] NOT Medline[SB]) OR "cardiopulmonary bypass"[MeSH Terms] OR ("coronary artery bypass"[TIAB] NOT Medline[SB]) OR "coronary artery bypass"[MeSH Terms] OR "Heart-lung machine"[MeSH Terms]) OR (((("heart valves"[TIAB] NOT Medline[SB]) OR "heart valves"[MeSH Terms] OR valve[Text Word]) OR valves[All Fields] OR valvular[All Fields]) AND ("surgery"[Subheading] OR "operative surgical procedures"[Text Word] OR "surgical procedures, operative"[MeSH Terms] OR "surgery"[MeSH Terms] OR surgery[Text Word])))

Search 4: (("complement activation"[MeSH Terms] OR complement activation[Text Word]) OR ("complement system proteins"[MeSH Terms] OR complement system proteins[Text Word]) OR complement[Text Word]) OR ("kallikreins"[MeSH Terms] OR kallikrein[Text Word]) or (inflammatory[All Fields])

Systematic search of the literature ...

randomised drug trials
inflammatory response
1970 - 2008

645 papers

Exclusion criteria ...

pediatric
off-pump, valve, other CT procedures

Incl No meta-analyses met inclusion criteria

measure at least one inflammatory marker

Optional: measure organ function to

heart, lung, brain, kidney, gut

17 papers

ACC/AHA guidelines

1. Two independent reviewers
2. Any conflicts resolved by third reviewer

ACC/AHA clinical recommendations

Table 1. Classification scheme used to summarize clinical recommendations (taken from the the AHA/ACC Manual for Guideline Writing Committees at http://circ.ahajournals.org/manual/manual_11step6.shtml).

Estimate of Certainty (Precision) of Treatment Effect	Class I	Class IIa	Class IIb	Class III
		Benefit >>> Risk Procedure/Treatment SHOULD be performed/ administered	Benefit >> Risk Additional studies with focused objectives needed IT IS REASONABLE to perform procedure/ administer treatment	Benefit ≥ Risk Additional studies with broad objectives needed; Additional registry data would be helpful IT IS NOT UNREASONABLE to perform procedure/ administer treatment
Level A Multiple (3-5) population risk strata evaluated General consistency of direction and magnitude of effect	<ul style="list-style-type: none"> o Recommendation that procedure or treatment is useful/effective o Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> o Recommendation in favor of treatment or procedure being useful/effective o Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> o Recommendation's usefulness/efficacy less well established o Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> o Recommendation that procedure or treatment not useful/effective and may be harmful o Sufficient evidence from multiple randomized trials or meta-analyses
Level B Limited (2-3) population risk strata evaluated	<ul style="list-style-type: none"> o Recommendation that procedure or treatment is useful/effective o Limited evidence from single randomized trial or non-randomized studies 	<ul style="list-style-type: none"> o Recommendation in favor of treatment or procedure being useful/effective o Some conflicting evidence from single randomized trial or non-randomized studies 	<ul style="list-style-type: none"> o Recommendation's usefulness/efficacy less well established o Greater conflicting evidence from single randomized trial or non-randomized studies 	<ul style="list-style-type: none"> o Recommendation that procedure or treatment not useful/effective and may be harmful o Limited evidence from single randomized trial or non-randomized studies
Level C Very limited (1-2) population risk strata evaluated	<ul style="list-style-type: none"> o Recommendation that procedure or treatment is useful/effective o Only expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> o Recommendation in favor of treatment or procedure being useful/effective o Only diverging expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> o Recommendation's usefulness/efficacy less well established o Only diverging expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> o Recommendation that procedure or treatment not useful/effective and may be harmful o Only expert opinion, case studies, or standard-of-care

ACC/AHA clinical recommendations

Class of Recommendation:

Class I should do

Class IIa good idea

Class IIb uncertain - not a bad idea

Class III Do not do, could be harmful

ACC/AHA clinical recommendations

Level of Evidence:

- A Multiple randomised trials
- B Single randomised trial
- C Case report / expert opinion

Provisional recommendations

Methylprednisolone:

20/23 in favor

4/6 organ protective

Class IIa, Evidence Level A

Provisional recommendations

Hydrocortisone / Cortisol:

3/3 in favor

2/2 organ protective

Class IIa, Evidence Level B

Provisional recommendations

High Dose Aprotinin:

12/18 in favor

3/5 organ protective

Class III, Evidence Level A

Provisional recommendations

Low Dose Aprotinin:

2/11 in favor

1/6 organ protective

Class III, Evidence Level A

Provisional recommendations

Lysine Analogs (tranexamic acid, ϵ -amino caproic acid):

2/4 in favor

2/4 organ protective

Class III, Evidence Level B

Provisional recommendations

Atorvastatin:

0/1 in favor

-- organ protective

Class III, Evidence Level C

Conclusions

- Less than a third of all clinical trials actually measured an inflammatory marker
- Less than 4% could demonstrate any linkage between drug effects on the inflammatory response *and organ function*
- Steroids were the only category of drugs for which lukewarm evidence for efficacy existed, but may be adversely linked to hyperglycemia and should not be used in patients with an infection
- Safety concerns with antifibrinolytic drugs and the removal of aprotinin from the market may have further narrowed available options

Conclusions

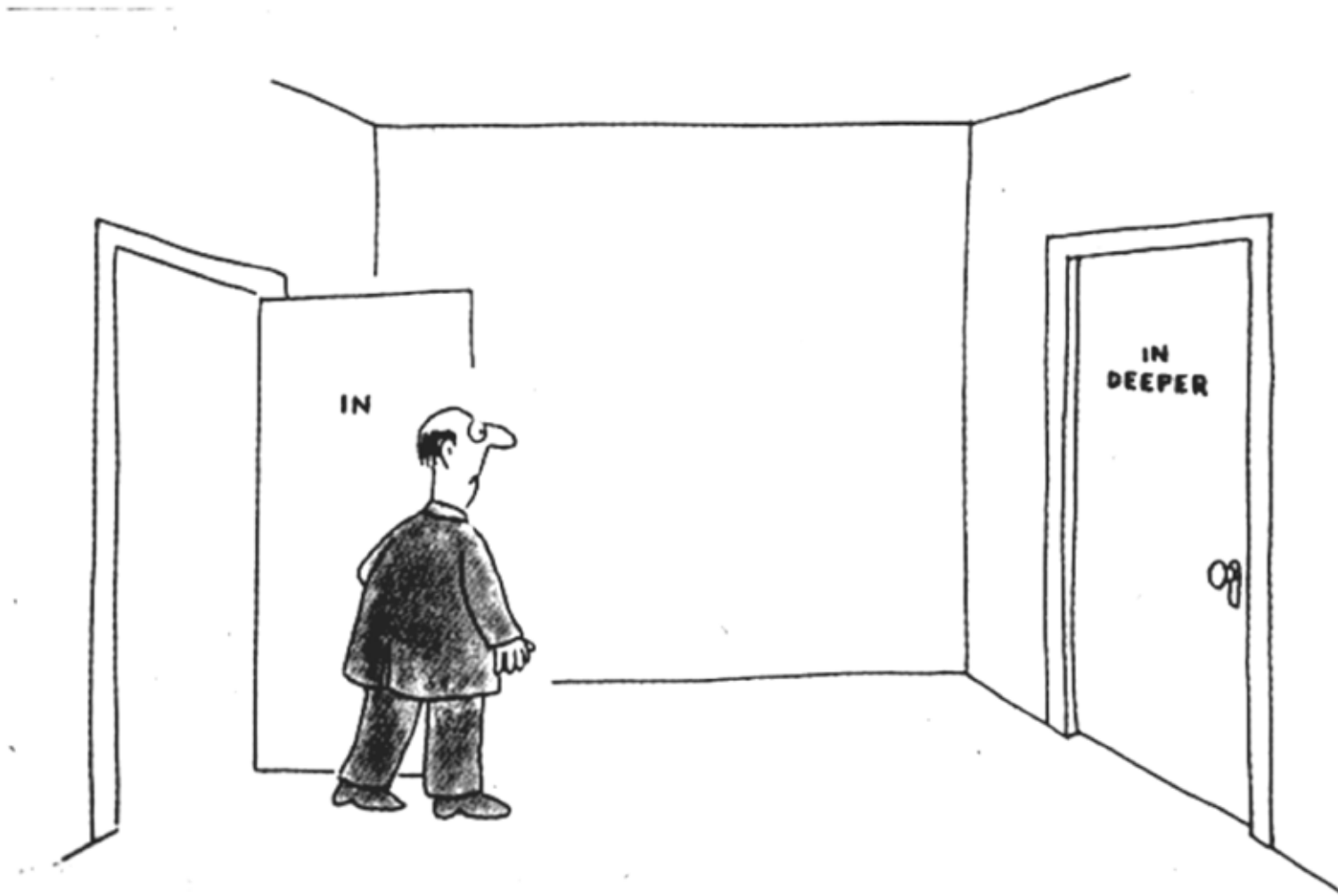
The evidence base is minimal

Most studies do not measure a single inflammatory marker

No meta-analyses

Only Methylprednisolone merited a Class IIa clinical recommendation based on multiple randomised trials

Reveals need to define criteria for carrying out such studies in future



IN

IN
DEEPER

Meta-analysis on the anti-inflammatory effects of aprotinin

Background

- It is important to define the extent, and any limitations, of potential anti-inflammatory regimens used in cardiac surgery in order to guide the rational combination of drugs to suppress the systemic inflammatory response.
- Aprotinin (Trasylol) is an anti-fibrinolytic agent with reported anti-inflammatory properties.

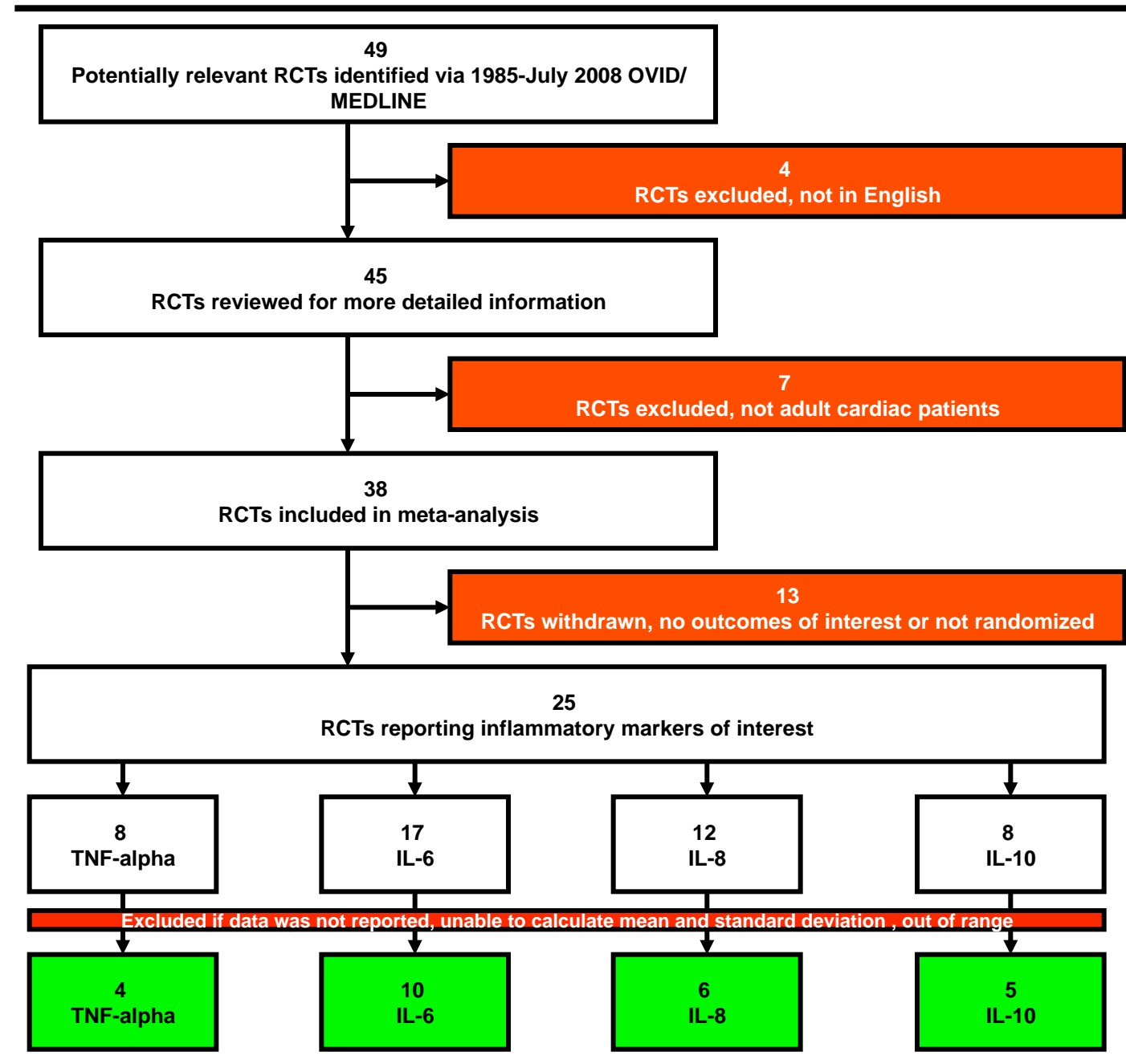
Methods

- We investigated the published data on aprotinin's effect on acute phase protein and cytokine levels in cardiac surgery patients.
- Two independent reviewers graded each paper and collected information on inflammatory markers.
- RevMan 4.3 statistical software was used to calculate and plot the weighted mean difference between placebo and aprotinin groups.

Methods

- Randomized placebo-controlled trials published between 1985 and 2007
 - adult cardiac surgery
 - tumor necrosis factor-alpha (TNF-alpha)
 - interleukin-6 (IL-6)
 - interleukin-8 (IL-8)
 - interleukin-10 (IL-10)
- 2 endpoints for consistent biomarker measurement:
 - Post-protamine (nearest sample following protamine administration)
 - Post-operative (nearest sample following surgery within 24 hours)

Figure 1: RCT Selection



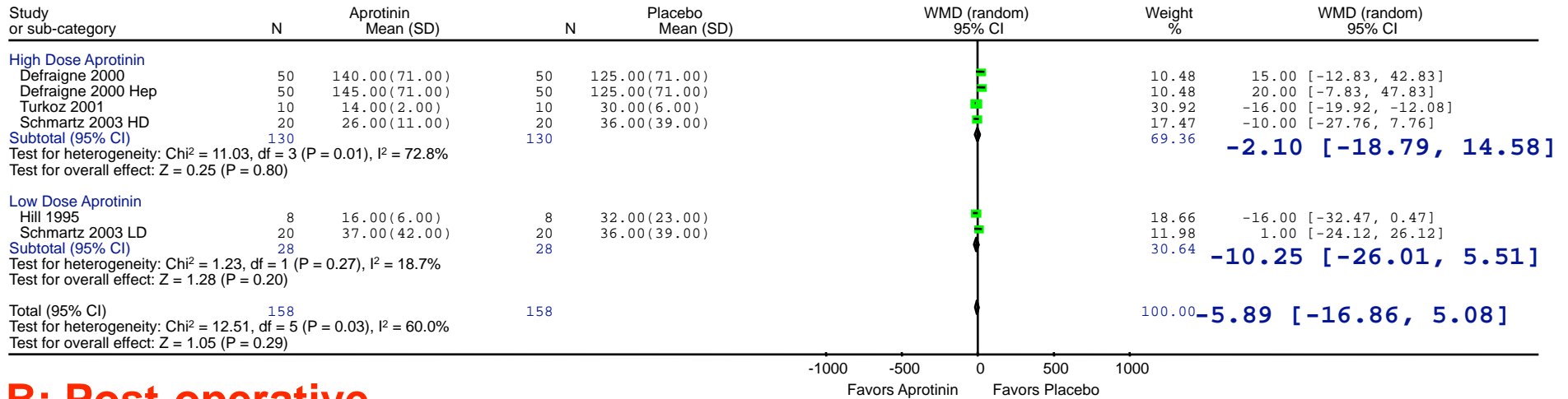
Results

- 25 studies met the review criteria
- None of the inflammatory markers reviewed were reduced by high dose aprotinin treatment
- Low dose aprotinin significantly reduced IL-10 (an *anti-inflammatory* cytokine) levels post-protamine administration
-41.3 pg/mL; 95%CI: -59.5, -23.1)

Figure 2: TNF-alpha

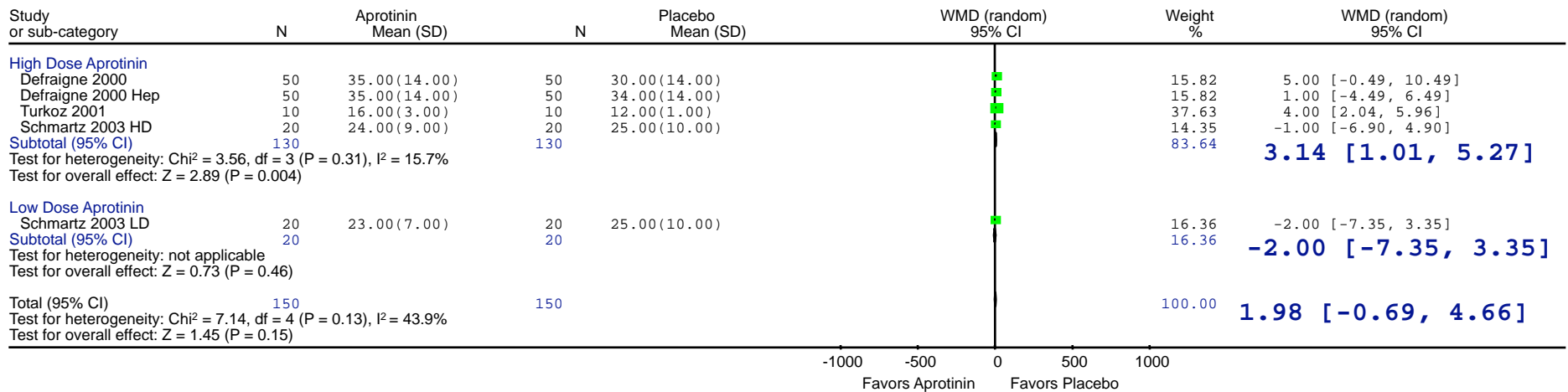
A: Post-Protamine

Review: Aprotinin Inflammation
 Comparison: TNF-alpha: Aprotinin vs. Placebo
 Outcome: Post Protamine TNF-alpha Levels



B: Post-operative

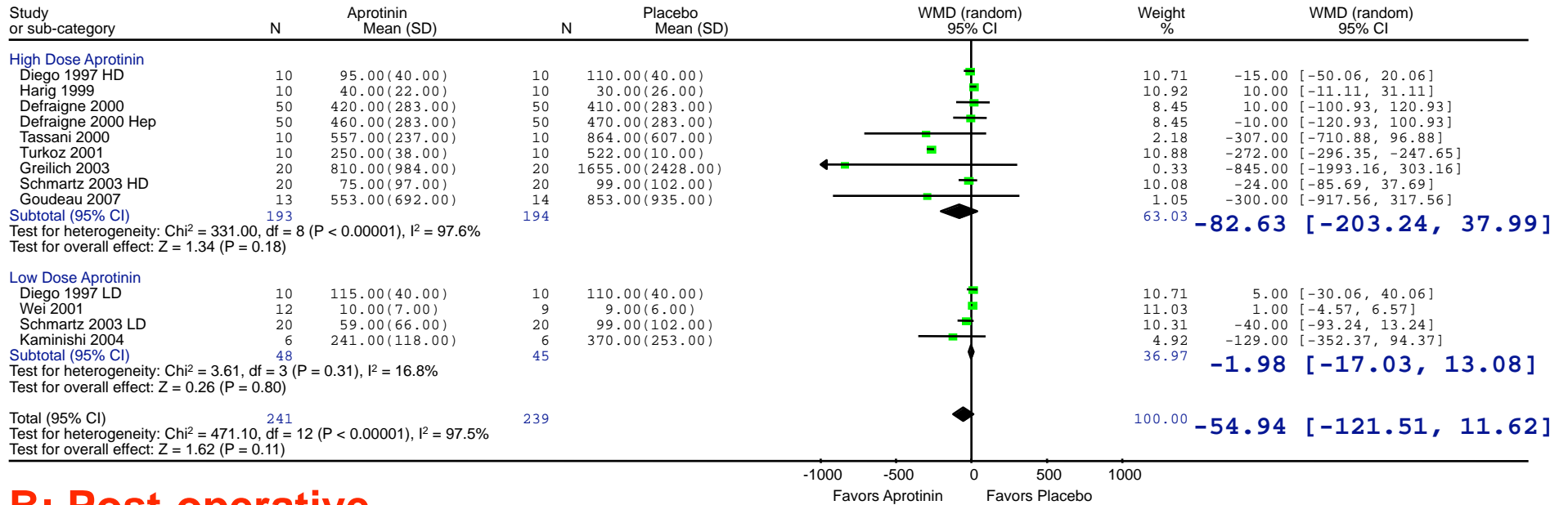
Review: Aprotinin Inflammation
 Comparison: TNF-alpha: Aprotinin vs. Placebo
 Outcome: Postoperative Day 1 TNF-Alpha Levels



A: Post-Protamine

Figure 3: IL-6

Review: Aprotinin Inflammation
 Comparison: IL-6: Aprotinin vs. Placebo
 Outcome: Post Protamine IL-6 Levels



B: Post-operative

Review: Aprotinin Inflammation
 Comparison: IL-6: Aprotinin vs. Placebo
 Outcome: Postoperative Day 1 IL-6 Levels

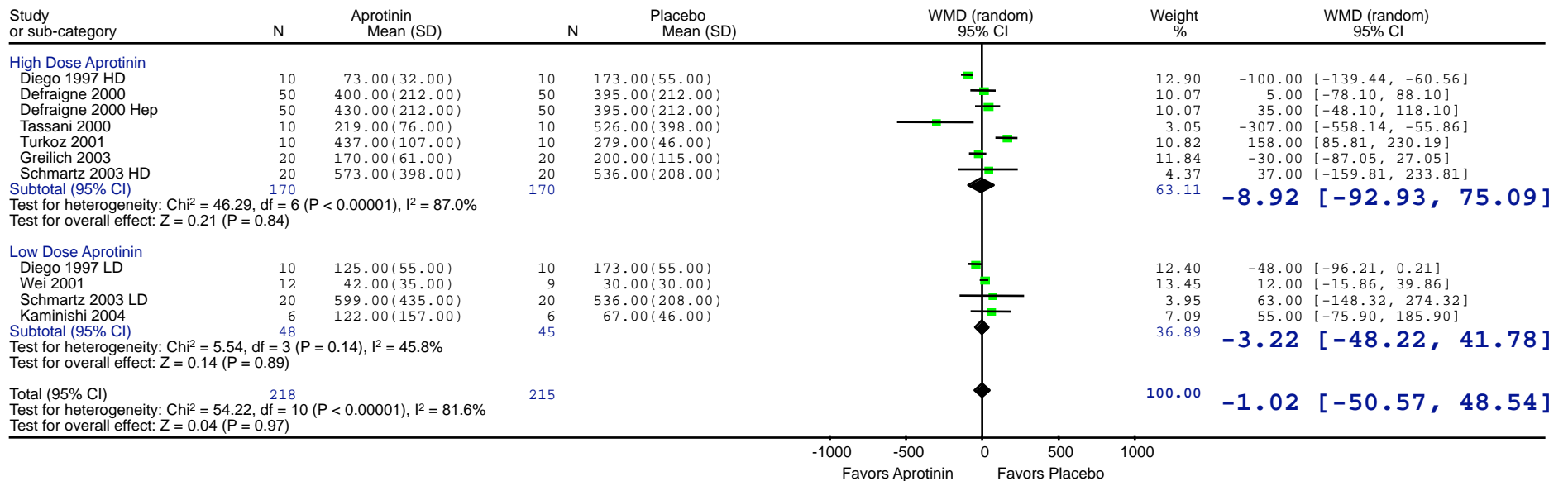
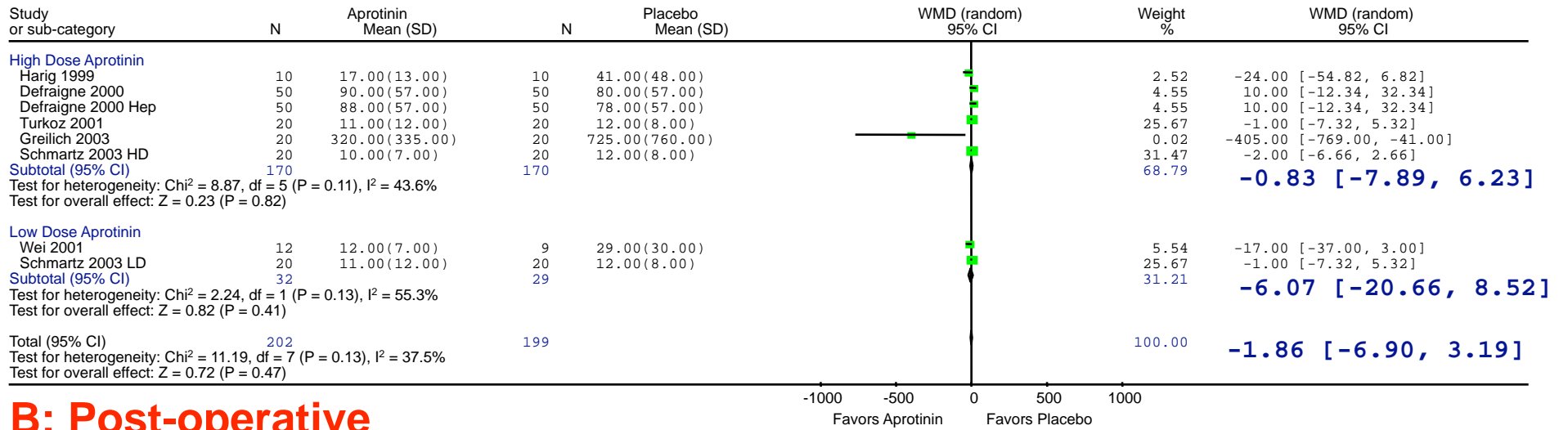


Figure 4: IL-8

A: Post-Protamine

Review: Aprotinin Inflammation
 Comparison: IL-8: Aprotinin vs. Placebo
 Outcome: Post Protamine IL-8 Levels



B: Post-operative

Review: Aprotinin Inflammation
 Comparison: IL-8: Aprotinin vs. Placebo
 Outcome: Postoperative Day 1 IL-8 Levels

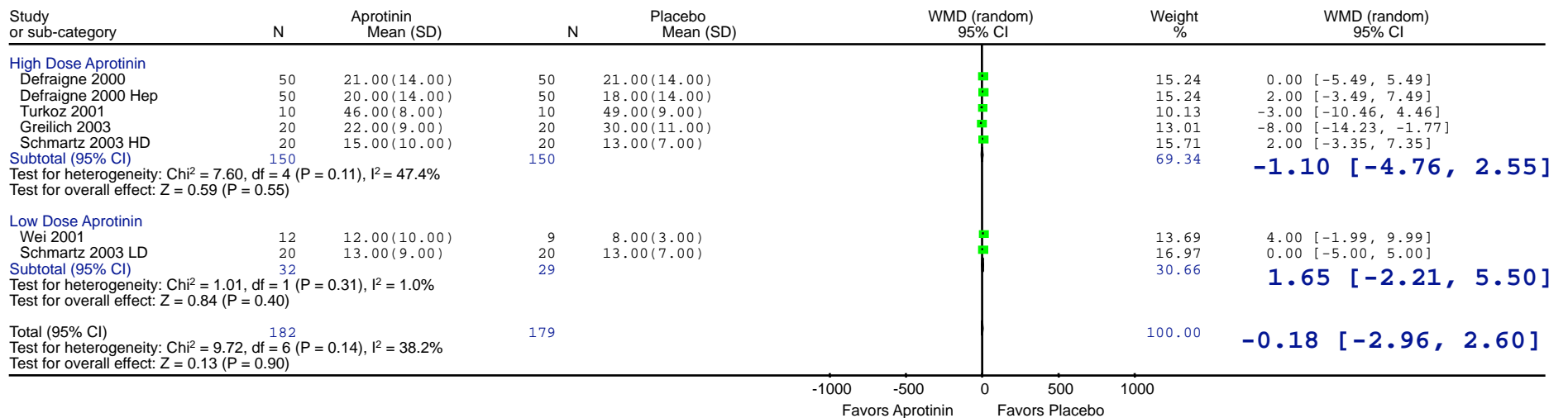
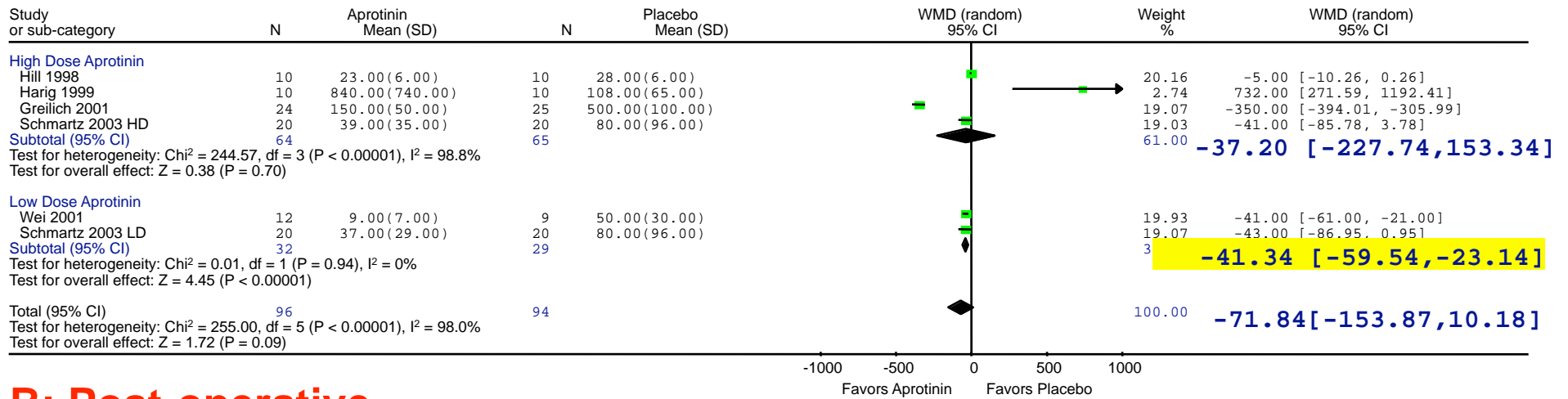


Figure 5: IL-10

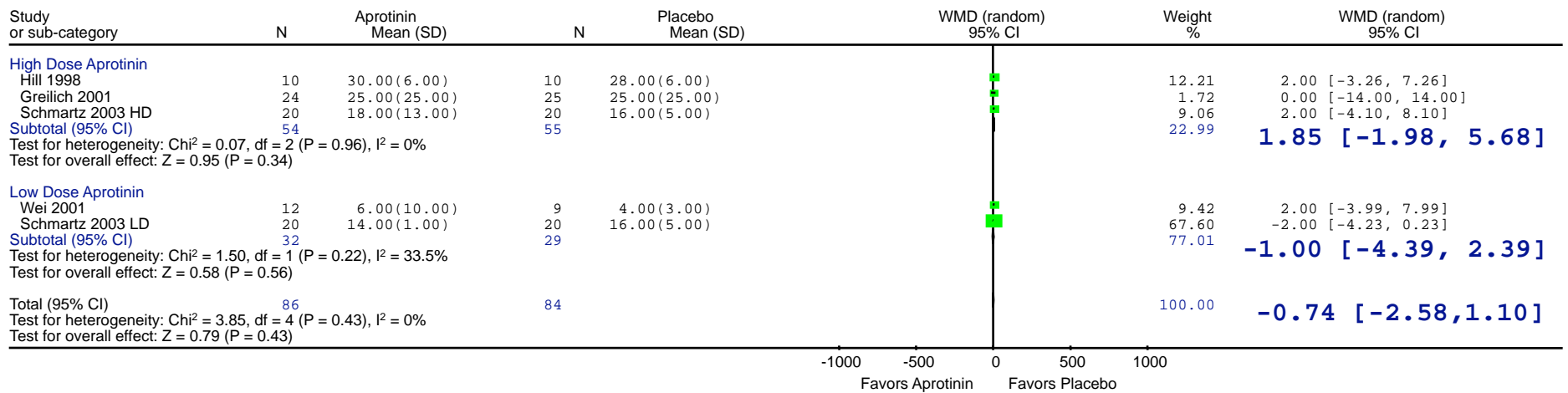
A: Post-Protamine

Review: Aprotinin Inflammation
 Comparison: IL-10: Aprotinin vs. Placebo
 Outcome: Post Protamine IL-10 Levels



B: Post-operative

Review: Aprotinin Inflammation
 Comparison: IL-10: Aprotinin vs. Placebo
 Outcome: Postoperative Day 1 IL-10 Levels



Conclusions

- We discovered that while aprotinin significantly reduced some markers immediately following protamine administration, it failed to show a sustained clinical benefit in reducing inflammation perioperatively.
- While recognizing that other host defense systems, such as coagulation and complement, contribute to the overall systemic inflammatory response, the weight of evidence does not support the use of aprotinin as an anti-inflammatory agent on its own. **Class III Level A**

Summary

- The evidence base for pharmaceutical intervention to reduce inflammation is minimal.
- Meta-analyses may be required for other agents
- Large scale, high quality trials are needed to measure efficacy with regard to inflammation and 90-day outcomes