Association of increased mortality with aprotinin administration in cardiac surgery? Bias-adjusted meta-analysis of randomized and observational studies

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Background: Aprotinin use in Cardiac Surgery

- **Cardiac surgery → bleeding → transfusions**
  - large consumer of RBCs each year in Canada and the US [1]
  - Infection risk (HBV, HCV, HIV) associated with RBC transfusions
  - Goal: minimization exposure to allogeneic RBCs

- **Aprotinin:**
  - **Enhances clotting**; FDA-approved in 1993
  - **Shown effective to reduce blood loss** in dozens of placebo controlled RCTs.[2,3,4,5]
  - **Active comparators?** RCTs also have been conducted which suggest a benefit versus primary comparators tranexamic acid and aminocaproic acid

[1] Chiavetta (1984); [2] Henry (2007); [3] Fergusson (2005); [4] Sedraykan (2001); [5]Munoz (1997).

Aprotinin Safety (1987-2006)

- Several dozen RCTs performed in this time frame; none associated with increased safety risks for aprotinin. Meta-analyses also did not find any clearly increased safety risks for death or other measures (MI, stroke, renal outcomes). [3,5,6]

- In 2006, suggestive observational data:
  - Mangano (NEJM, JAMA)[1,2]
  - Large multi-armed propensity-adjusted cohort study suggesting increased risks of above outcomes compared to no intervention (not so for TXA, ACA)

- Similar observational studies since reported, some also suggestive of concerns[3-5]

[1] Mangano D (2006); [2]Mangano (2007); [3]Karkouti (2006); [4]Schneeweiss (2008); [5]Shaw (2008)

ISSUE 1:

Differential findings between designs.
Such discrepancies complicate interpretation for physicians.
What are the issues, and how to resolve?

Safety Data Meta-Analyses with RCT Data: Problems?

- **RCTs are sometimes…**
  - of limited help for safety comparisons (issues of power and rarity of events[1-3]);
  - inadequately reported in journal articles:
    - limited reporting space, insufficient level of detail, non-disclosure of events below a certain threshold, etc[4-6]

- **Need to re-visit the evidence hierarchy for this purpose?**

- **Some suggest inclusion of observational studies in meta-analyses is worth consideration.[7,8]**
  - e.g. efficacy analyses lacking RCT data

- **Methods to combine studies of different designs with bias adjustments are available.[9-11] (just infrequently used)**

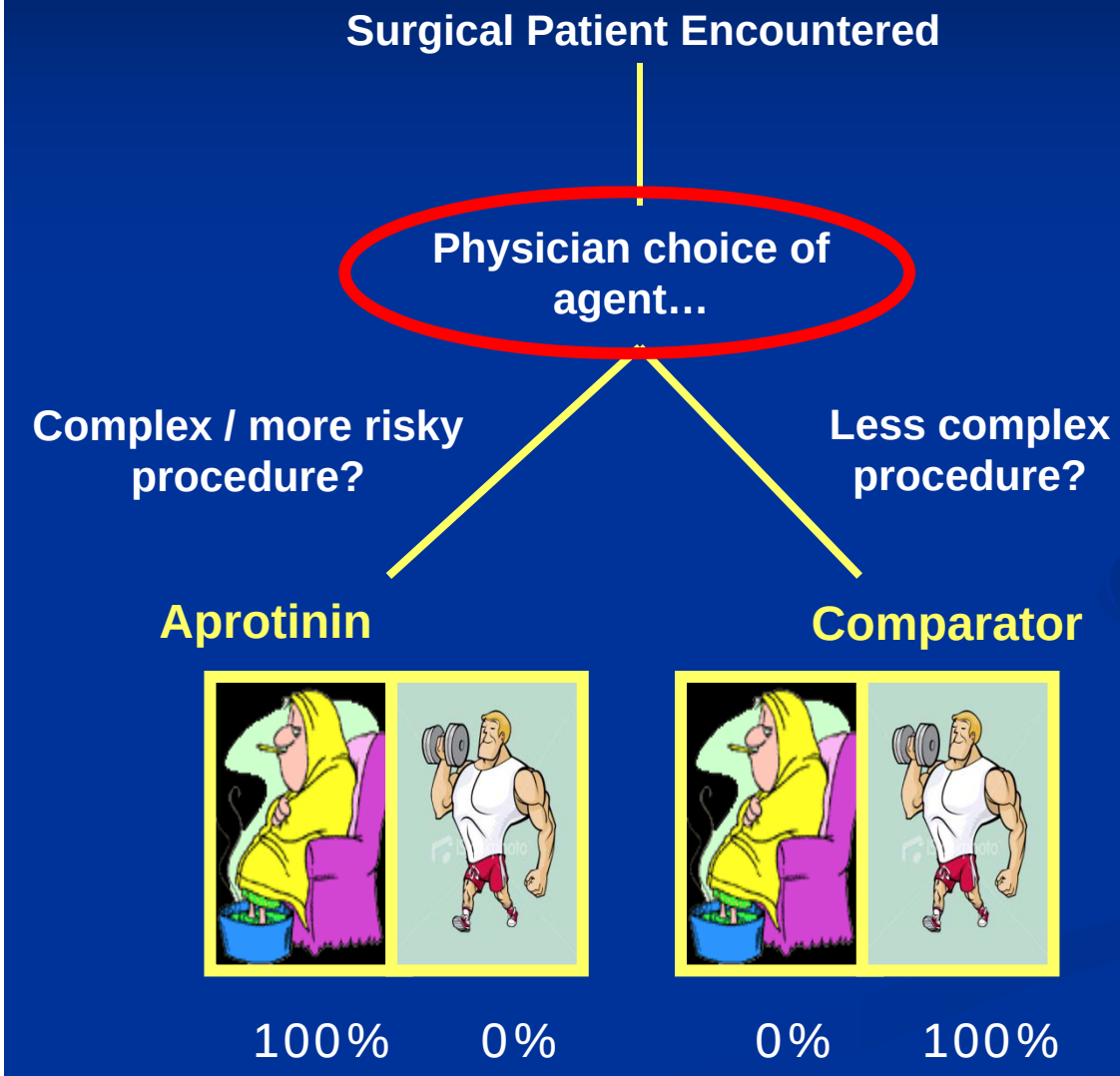
[1]Sweeting (2005); [2]Bradburn (2005); [3]Vandermere (2004); [4]Ioannidis (2007); [5]Pitrou (2009); [6]Fergusson (2006); [4]; [7]Shrier (2007); [8]Chou & Helfand (2005); [9]Eddy (2002); [10]Wolpert (2006); [11]Turner (2008)

ISSUE 2:

Past syntheses of aprotinin data limited by reporting quality and limited power of RCTs?

Could addition of observational data to meta-analyses be helpful?

Primary Concern with Observational Studies of Aprotinin? Selection bias…



ISSUE 3:

Aprotinin has rep for greater efficacy in complex cases versus alternatives.

Thus… sickest patients undergoing trickiest surgeries get aprotinin.

Safety analyses biased against aprotinin?

Wish to Address Issues 1-3 in a Comprehensive Analysis…HOW?

- **Bias adjusted meta-analysis:**
  - i.e. synthesize all data from both designs
  - account for between group differences in patient groups at the individual study level:
    - Meta-regression of key risk factors, + expert derived bias adjustments

- **How to derive bias adjustments?**
  - **RCTs, propensity matched cohort studies** not subjected to adjustments (unless evidence of imbalances)
  - Other observational studies assessed; presentation of blinded Table 1's for each study presented to expert
  - Questions to the expert:
    - "Does one of the groups have greater baseline risk of death? Which?
    - "What are the MIN, MAX influences on risk of death that could result???"

The available evidence, and how it was synthesized:

Available Literature:

- Aprotinin vs. no therapy: 77 studies (65 RCTs, 12 Obs)
- Aprotinin vs TXA: 26 studies (18 RCTs, 8 Obs)
- Aprotinin vs ACA: 12 studies (6 RCTs, 6 Obs)

- **Overall, >70 studies excluded due to insufficient AE reporting**

- **For the 21 studies bias assessed, most judged to be biased against aprotinin. Reasons: med histories, comorbidities, severity of illness.**

Sequential Analysis Pursued:

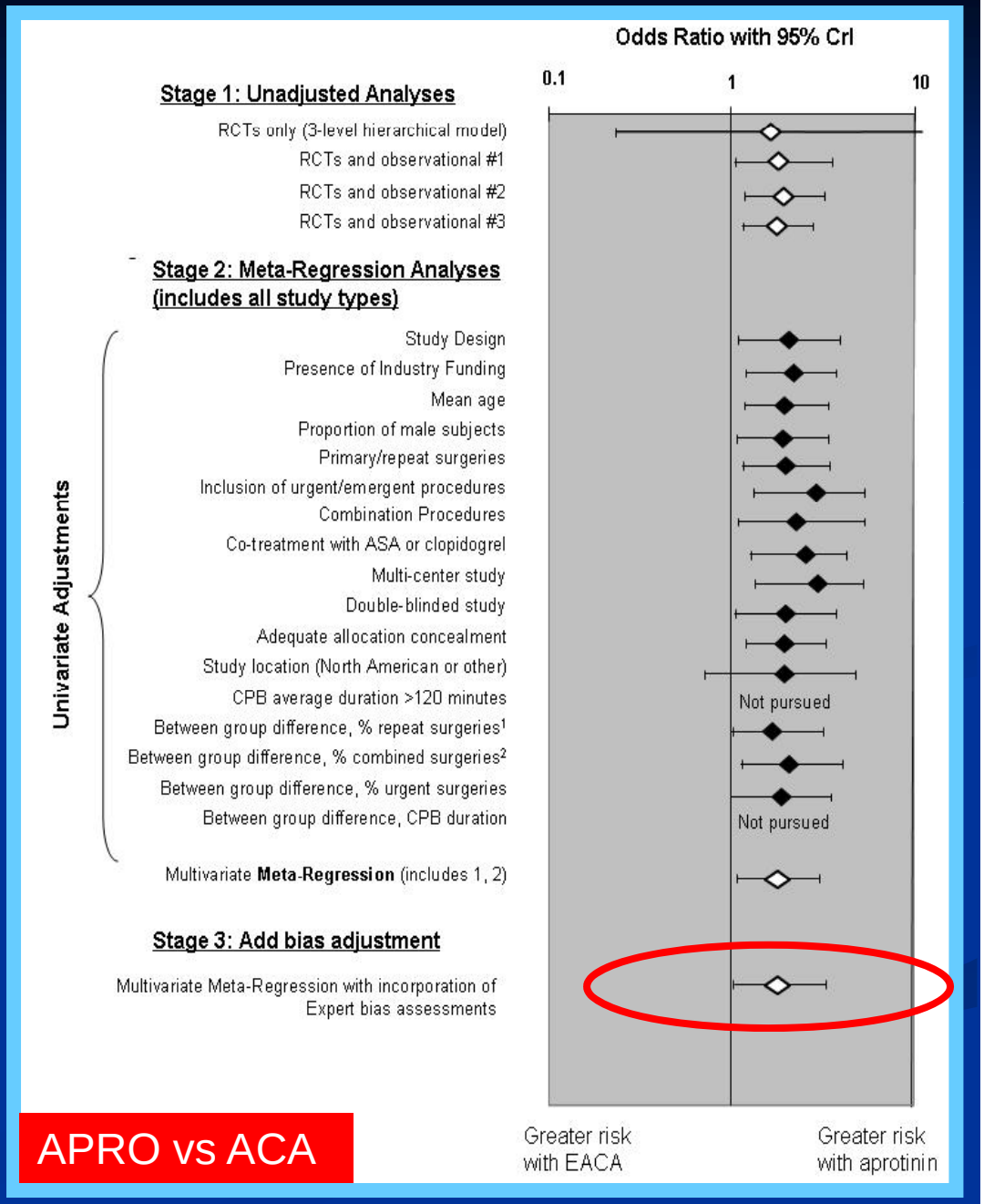
- Stage 1: Pool RCTs only; then RCTs along with observational data
- Stage 2: Meta-regression analysis of RCTs with observational data
- Stage 3: Where needed, bias adjustment of observational studies incorporated along with meta-regression analysis

Summary of Findings, Mortality:

For comparisons of APRO vs no therapy and APRO vs TXA, results were inconclusive

For APRO vs ACA, only 6 RCTs had data, and 4 were < 50 subjects per group.

Once observational data added, comparisons across all stages suggested greater risk with APRO, even after bias adjustment (OR 1.67, 95% CrI 1.05 – 3.06).



Summary of Findings:

- **Clinical:**
  - Aprotinin does not appear less safe than no therapy, but:
  - may be less safe than one of the lysine analogues (ACA)

- **Methods:**
  - For ACA analysis, adding observational studies offset a paucity of RCT data. (Potential pro for efficacy analyses also)
  - Bias adjustments caused only slight increases in uncertainty, small shifts in point estimates.
    - More research needed regarding approaches to bias assessment: # of assessors? Best approach to derive? How many biases to account for?
  - More applications in the literature are needed to increase familiarity of researchers with these ideas

Thank You

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