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

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\(^1\) 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 concerns3-5

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

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\(^1\)Sweeting (2005); \(^2\)Bradburn (2005); \(^3\)Vandermere (2004); \(^4\)Ioannidis (2007); \(^5\)Pitrou (2009); \(^6\)Fergusson (2006); \(^7\)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…

Surgical Patient Encountered

Physician choice of agent…

Complex / more risky procedure?

Aprotinin

Less complex procedure?

Comparator

100% 0%

0% 100%

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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