# FDA Cardiology and Renal Drugs Advisory Committee

September 21, 2006

TRASYLOL® (aprotinin injection)

Risk-Benefit Review

Bayer Pharmaceuticals Corporation

# Introduction and Overview of Sponsor's Presentation

**Michael Rozycki, PhD**
**Director, US Regulatory Affairs**
**Bayer Pharmaceuticals Corporation**

# Presentation Overview

- Methodological considerations of 2 recently published observational studies
- Discussion of clinical data and risk-benefit of aprotinin in Coronary Artery Bypass Graft surgery (CABG)
- Conclusion: clinical data and post-marketing experience supports a favorable risk-benefit profile for aprotinin when used according to labeling

# Approval of Trasylol® For Use In CABG Surgery

- US NDA approved December 28, 1993 for repeat CABG and primary CABG at risk for high degree of blood loss
  - sNDA-004 approved August 28, 1998
    - Indication expanded to current (primary and repeat CABG)
    - Addition of Boxed Warning for hypersensitivity
- Clinical trial efficacy and safety data from 45 global Bayer randomized controlled CABG trials in 4413 patients (full-dose aprotinin or placebo)

# Bayer's Actions in Response to Observational Studies

- Communicated with FDA and global regulatory authorities
- Notified healthcare providers
- Conducted comprehensive review of data
- Revised investigator brochure and informed consent for clinical trials
- Provided expert evaluation of publication methodologies to regulatory authorities

# Presentation Outline

**Methodological Considerations: RCTS and Two Recent Observational Studies of Aprotinin**

**Robert W. Makuch, PhD**
Professor, Biostatistics
Yale School of Public Health

**Review of Clinical Data**

**Pamela Cyrus, MD**
Vice President, US Medical Affairs
Bayer Pharmaceuticals Corporation

**Risk-Benefit Summary**

**Jerrold Levy, MD**
Director, Cardiothoracic Anesthesiology
Emory University Hospital

# Additional Expert Consultants Available in the Audience Today

| | |
|---|---|
| Frank Adkinson, MD | Johns Hopkins University |
| Tomas Berl, MD | University of Colorado |
| Bernard Chaitman, MD | St. Louis University School of Medicine |
| Steven Cohen, D.Sc. | Massachusetts College of Pharmacy and Health Sciences |
| George Despotis, MD | Washington University School of Medicine |
| Wulf Dietrich, MD | German Heart Center, Munich |
| Marc Fisher, MD | University of Massachusetts Medical School |
| Tim Goodnough, MD | Stanford University School of Medicine |
| Allan S. Jaffe, MD | Mayo Clinic College of Medicine |
| Neil Blumberg, MD | University of Rochester |

# Additional Expert Consultants Available in the Audience Today

| | |
|---|---|
| John H. Lemmer, Jr., MD | Oregon Health and Science University |
| Barry Massie, MD | University of California, San Francisco |
| David Royston, MD | Harefield Hospital, UK |
| Donald B. Rubin, PhD | Harvard University |
| Peter K. Smith, MD | Duke University School of Medicine |
| Samy Suissa, PhD | McGill University, Canada |
| David Warnock, MD | University of Alabama School of Medicine |
| Andrew Whelton, MD | Johns Hopkins University |

# Methodological Considerations: RCTS and Two Recent Observational Studies of Aprotinin

**Robert W. Makuch, PhD**

**Professor, Biostatistics**

**Yale School of Public Health**

# Considerations in Evaluating Clinical Data

- Hierarchy of evidence
  - RCTs (Balance known and unknown confounders)
  - Cohort, case control, observational, and case series
- Baseline comparability
- Patient population
- Outcome definitions
- Analytic methods and Interpretation
- Consistency of reports based on the same data
- Replication of findings using different data

# Comparison of Three Data Sources

| | Multiple RCTs | Karkouti Study | Mangano Study |
|---|---|---|---|
| Randomized | Yes | No, matched | No, observational |
| Baseline Comparability | Yes | Yes (on observed covariates through matching) | Major imbalances |
| Patients Excluded | No | Yes (through matching) | Yes 691 patients |
| Sample size | 4413 | 898 | 4374 |
| Aprotinin exposed subjects | 2200 | 449 | 1295 |

# Comparison of Three Data Sources (cont'd)

| | Multiple RCTs | Karkouti Study | Mangano Study |
|---|---|---|---|
| Outcome Definitions | Prespecified | Prespecified | Prespecified, Different from previous studies of same database |
| Analysis | Standard | Propensity matching | "Propensity adjusted, multivariable logistic regression" |

# Karkouti Study

- Single-center observational comparison of aprotinin and tranexamic acid (TA) in high-transfusion risk cardiac surgery
- Aprotinin given only to high-transfusion risk patients (586 of 10,870 patients)
- Profound imbalances in pre-existing risk factors properly addressed by propensity score matching (N=449 each treatment)
  - The 898 = 2 x 449 matched patients were at very high risk
  - Proportion undergoing CABG is unknown
  - 23% of aprotinin-treated patients could not be matched
- Creatinine elevations due to aprotinin not inconsistent with results of RCTs

# Mangano Study: Significant Imbalances in Baseline Characteristics

| | No Treatment Cohort N = 1374 | | Aprotinin Cohort N = 1295 | | |
|---|---|---|---|---|---|
| | N | % | N | % | P value |
| Some college or above | 496 | 36.1 | 280 | 21.6 | <0.001 |
| Urgent or emergency surgery | 288 | 21.0 | 192 | 14.8 | <0.001 |
| Insulin-dependent diabetes | 78 | 5.7 | 116 | 9.0 | 0.001 |
| Hypertension | 824 | 60.3 | 905 | 70.0 | <0.001 |
| Angina | 1272 | 92.8 | 1136 | 87.8 | <0.001 |
| Congestive heart failure | 457 | 33.5 | 551 | 42.8 | <0.001 |
| Heart block | 176 | 12.8 | 224 | 17.3 | 0.001 |
| Carotid disease | 143 | 11.0 | 217 | 17.2 | <0.001 |
| Liver disease | 106 | 7.7 | 150 | 11.7 | <0.001 |
| Renal disease | 178 | 13.0 | 240 | 18.6 | <0.001 |
| Pulmonary disease | 238 | 17.4 | 326 | 25.3 | <0.001 |
| CABG | 31 | 2.3 | 148 | 11.4 | <0.001 |
| Valve disease | 167 | 12.3 | 326 | 25.4 | <0.001 |
| Valve surgery | 1 | 0.1 | 19 | 1.5 | <0.001 |
| PTCA | 138 | 10.1 | 223 | 17.3 | <0.001 |
| Intracoronary stent | 54 | 3.9 | 95 | 7.3 | <0.001 |
| Noncoronary angioplasty or stent | 20 | 1.5 | 40 | 3.3 | 0.002 |
| Current CABG and valve | 96 | 7.0 | 201 | 15.5 | <0.001 |
| Complex Surgery Stratum | 352 | 25.6 | 499 | 38.5 | <0.001 |
| Primary Surgery Stratum | 1022 | 74.4 | 796 | 61.5 | <0.001 |

# Mangano Study: Analytical Limitations

- Estimated propensity score was used as a variable in covariate adjustment rather than correct use to create matches or subclass bins
- No diagnostic displays or analyses to support claimed balance of covariates achieved by the use of propensity scores
- No diagnostic displays or analyses to support claimed balance of covariates achieved by propensity scores for each pair of treatment groups compared
- 410 subjects had missing covariate or propensity scores for renal outcome analysis (Table 2)
- 407 subjects had missing propensity scores for ischemic outcome analysis (Table 3)

# Mangano Study: Analytical Limitations

- Outcome variables were used to decide which covariates to include in the regression model; this introduces bias, at least in the significance levels
- With significant between-treatment imbalances in numerous baseline factors, regression modeling alone is known to be unreliable*
- Crude data were sometimes used where adjusted data should have been used
  - Dose-response assessment based on crude data that excluded 54% of aprotinin subjects

*e.g., Cochran W, Rubin D. Sankhya - A 1973;35(4):417-446.

# Inconsistent Outcome Definitions: Heart Failure

Mangano, 2002 [page 1310]

Mathew et al, 2004 [page 1721]

Nussmeier et al, 2005 [page 508]

"If a ventricular assist device was used; if continuous inotropic support required for at least 24 hours; or if there was evidence of heart failure on autopsy"

Mangano, 2006 [page 354-5]

"required a cardiac output of less than 2.0 liters per minute associated with a pulmonary-artery occlusion pressure above 18 mm Hg, a central venous pressure above 12 mm Hg, an S3 gallop, or rales"


(1) Mangano DT, Tudor IC, Dietzel C. N Engl J Med 2006;354(4):353-65.
(2) Mangano DT. N Engl J Med 2002;347(17):1309-17.
(3) Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, et al. JAMA 2004;291(14):1720-9.
(4) Nussmeier NA, Mora-Mangano C, Fontes M, Schwann NM, Mangano DT. Tex Heart Inst J 2005;32(4):507-14.

# Broad Variability in Incidence of Myocardial Infarction Derived from the Same Database

| Event Type | Mangano et al 2002 | Mathew et al 2004 | Nussmeier et al 2005 | Mangano et al 2006 |
|---|---|---|---|---|
| Myocardial Infarction | 3.7% | 6.2% | 7.5% | 12-16% |


(1) Mangano DT, Tudor IC, Dietzel C. N Engl J Med 2006;354(4):353-65.
(2) Mangano DT. N Engl J Med 2002;347(17):1309-17.
(3) Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, et al. JAMA 2004;291(14):1720-9.
(4) Nussmeier NA, Mora-Mangano C, Fontes M, Schwann NM, Mangano DT. Tex Heart Inst J 2005;32(4):507-14.

# Abstract Inconsistent with Reported Results

Abstract, page 353

In propensity-adjusted, multivariable logistic regression (C-index, 0.72), use of aprotinin was associated with a **doubling in the risk of renal failure requiring dialysis among patients undergoing complex coronary-artery surgery (odds ratio, 2.59; 95 percent confidence interval, 1.36 to 4.95) or primary surgery (odds ratio, 2.34; 95 percent confidence interval, 1.27 to 4.31).**

Table 3, page 360

| Outcome Event | Predictors in Multivariable Logistic-Regression Model | Primary Surgery Odds Ratio (95% CI) | Complex Surgery Odds Ratio (95% CI) |
|---|---|---|---|
| Renal event§ | Aprotinin vs. control | 2.34 (1.27–4.31) | 2.59 (1.36–4.95) |

**§ A renal event was defined as either renal dysfunction or renal failure requiring dialysis.**

From Mangano et al, N Engl J Med 2006

# Summary

- The total sample size from RCTs was larger than that from observational studies. Randomized, well-controlled trials are the gold standard for assessing true treatment differences.
- Analytic methods to correct for baseline imbalances in the Karkouti study were generally appropriately applied.
- Analytic methods to correct for numerous and highly significant baseline imbalances in the Mangano study were incorrectly applied. Additional issues also were raised, leading to questionable validity of the findings.
- The Mangano study results should not be considered reliable.

# Trasylol® (aprotinin injection) Review of Clinical Data

**Pamela Cyrus, MD**
Vice President, US Medical Affairs
Bayer Pharmaceuticals Corporation

# Overview of Clinical Data

- US CABG Trials
- Efficacy in CABG
- Safety in CABG
  - Myocardial Infarction
  - Graft Patency
  - Congestive Heart Failure
  - Stroke
  - Encephalopathy
  - Renal Function
- Hypersensitivity

# 6 US CABG Trials

| Study | CABG Population | Number of Patients (Efficacy) Full-Dose Aprotinin | Half-Dose Aprotinin | Placebo |
|---|---|---|---|---|
| D89-004 | Repeat | 53 | 49 | 52 |
| D89-006 | Primary | 74 | NA | 67 |
| | Repeat | 23 | NA | 32 |
| D92-008 | Repeat | 61 | 60 | 65 |
| D91-007 | Primary | 6 | 7 | 5 |
| | Repeat | 6 | 4 | 7 |
| D92-016 | Primary | 160 | 168 | 157 |
| D92-048 | Primary | 401 | NA | 395 |

10,000 KIU test dose, then
FULL DOSE: 2 million KIU loading, 2 million KIU pump prime, 500,000 KIU/h
HALF DOSE: 1 million KIU loading, 1 million KIU pump prime, 250,000 KIU/h

# Trasylol® (aprotinin injection)

## Efficacy in CABG Procedures

# Characteristics of Cardiac Surgery

- Major risks of CABG surgery
  - Bleeding/Blood Transfusion
  - Infection
  - Stroke
  - Renal Failure
  - Re-operation
- Typically, open-heart surgery patients receive 2-6 units PRBCs and 1-10 units platelets*
- 10% to 20% of all blood transfused in the US is used for cardiac surgery

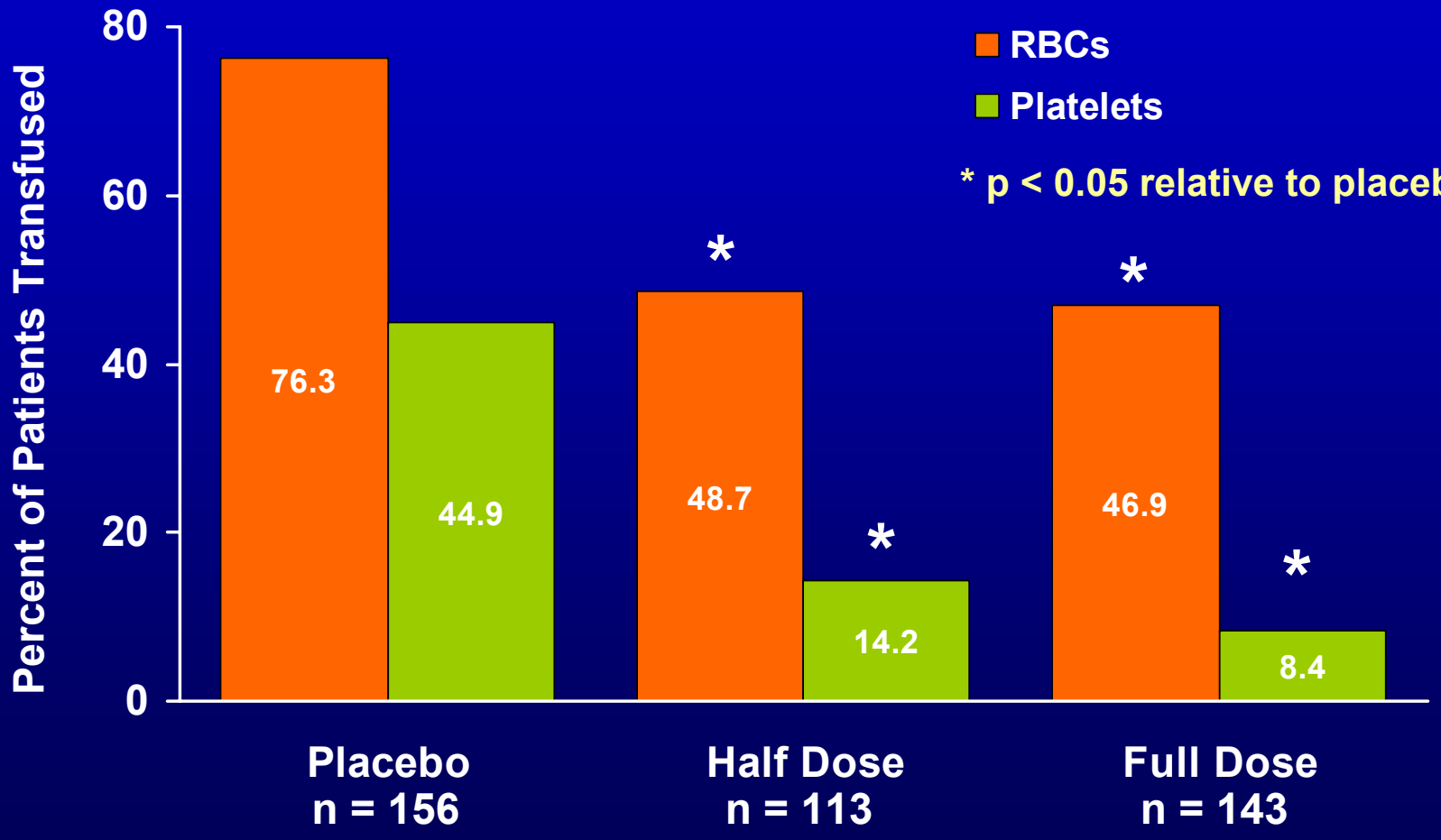
*** Source: American Red Cross**

# Mortality Due to Transfusion

| | Deaths Per Million | |
|---|---|---|
| | Units RBC | Units Platelets |
| Transfusion-related acute lung injury | 10-20 | 10-20 |
| Bacterial contamination | 0.1 | 15-75 (uncultured)<br>4-15 (cultured) |
| Lipid-enveloped viruses | <1.0 | - |
| Transfusion errors | ~1-2 | - |
| Allergic reactions | 5 | 5 |
| Total mortality per million components | 16-27 | 19-100 |

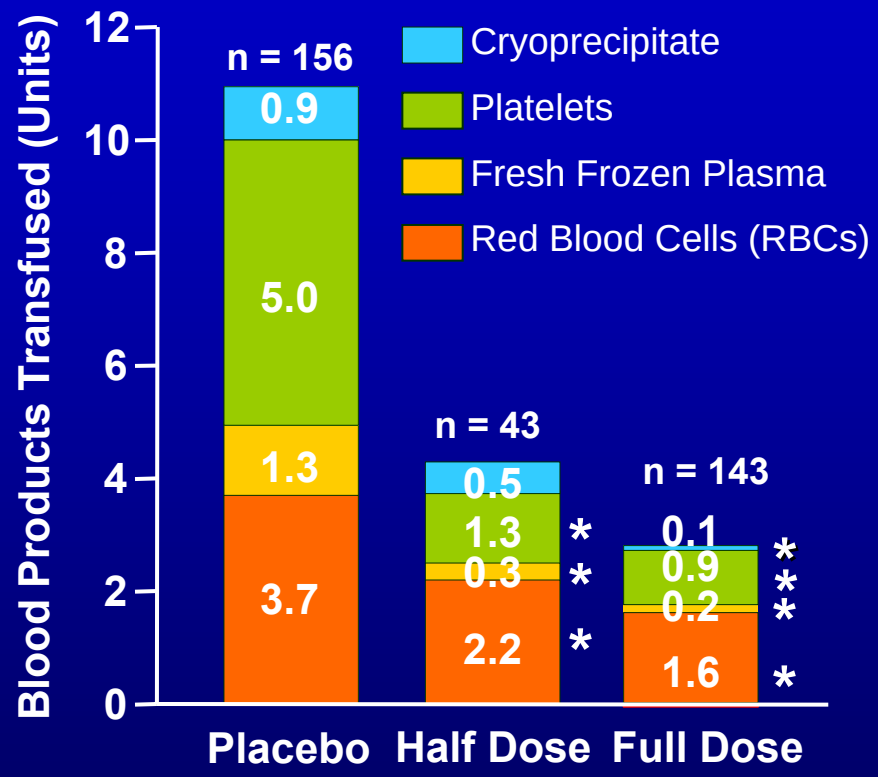
Consensus Panel on the risks of blood transfusion, September 2006:
Lawrence T. Goodnough (chair), Neil Blumberg, Mark Brecher, George Despotis, Victor Ferraris, Steven Kleinman, Paul Ness, Aryeh Shander

# Aprotinin Reduces Transfusion Rate in Repeat CABG




Source: Bayer US CABG Randomized Clinical Trials

# Aprotinin Reduces Number of Units Transfused in Repeat CABG



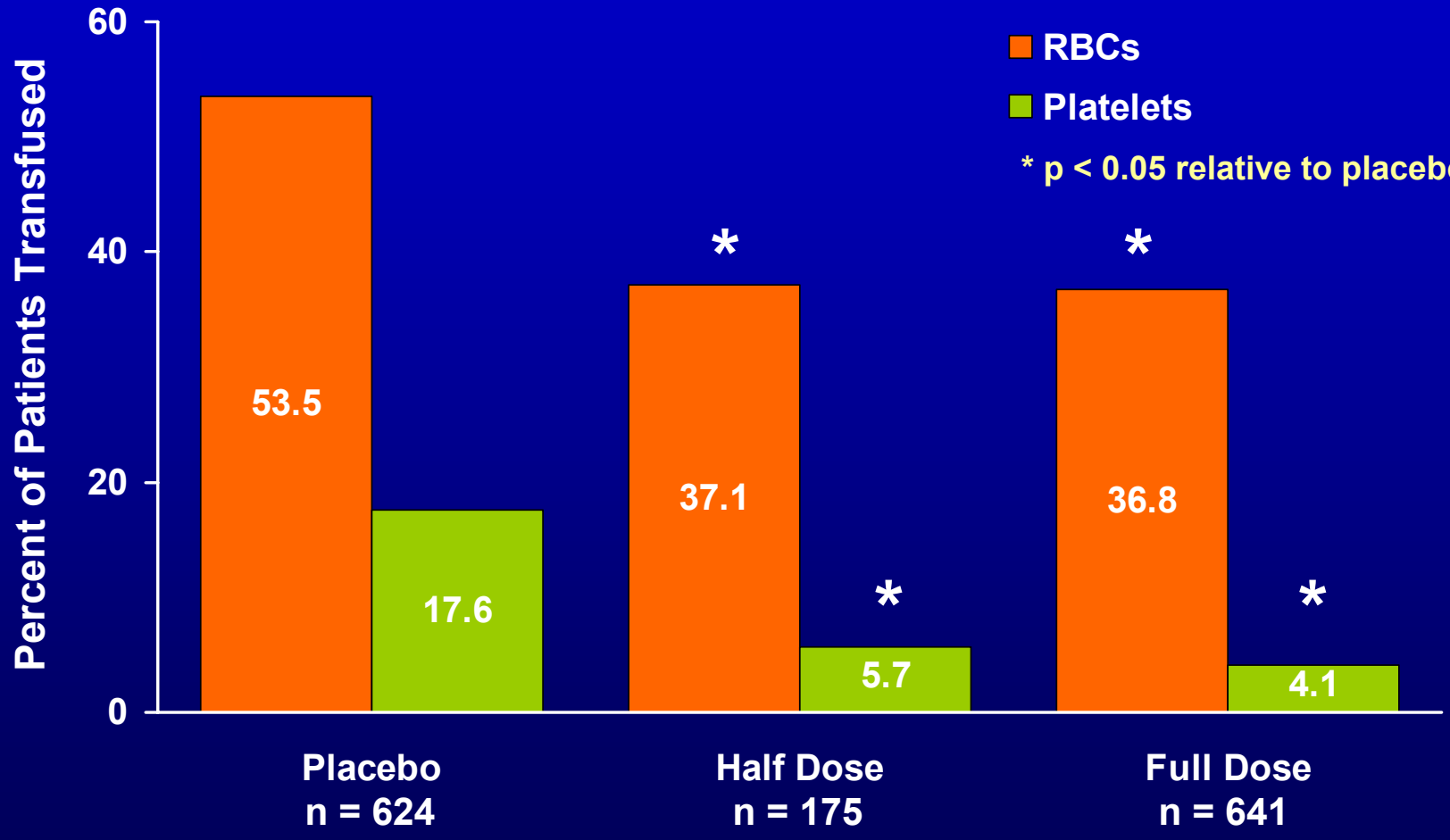

| % Patients receiving ≥ 5 units of RBCs | |
|---|---|
| Placebo | 27.6% |
| Half-dose aprotinin | 12.4%* |
| Full-dose aprotinin | 8.4%* |

| Reoperation for Diffuse Bleeding | |
|---|---|
| Placebo | 1.9% |
| Half-dose aprotinin | 0% |
| Full-dose aprotinin | 0% |

*p < 0.05 relative to placebo

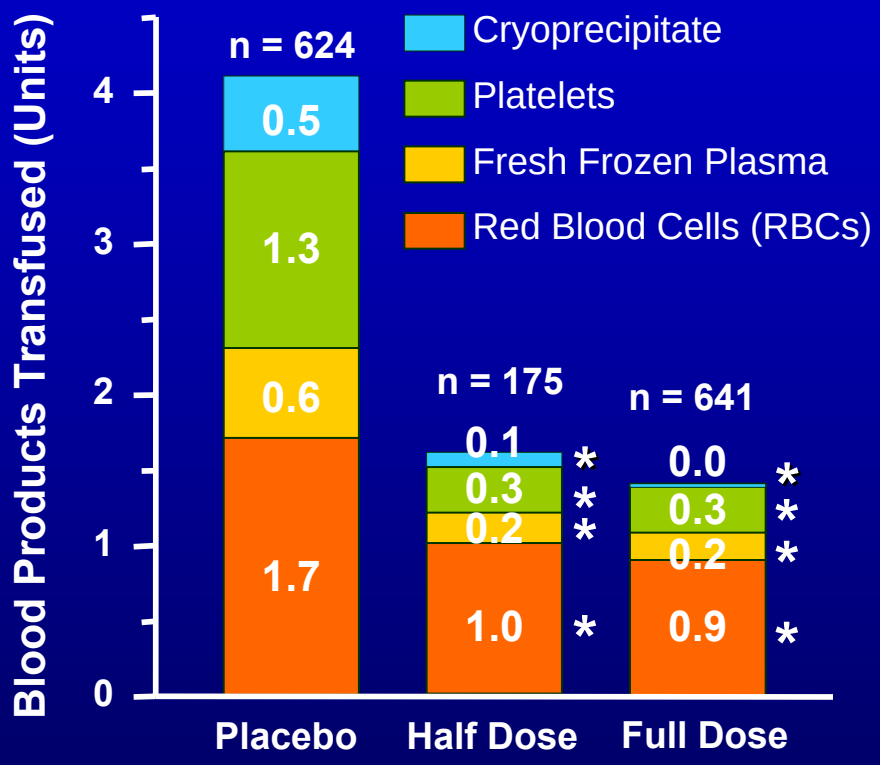
Source: Bayer US CABG Randomized Clinical Trials

# Aprotinin Reduces Transfusion Rate in Primary CABG




Source: Bayer US CABG Randomized Clinical Trials

# Aprotinin Reduces Number of Units Transfused in Primary CABG




| % Patients receiving ≥ 5 units of RBCs | |
|---|---|
| Placebo | 10.1% |
| Half-dose aprotinin | 5.7%* |
| Full-dose aprotinin | 2.8%* |

| Reoperation for Diffuse Bleeding | |
|---|---|
| Placebo | 1.4% |
| Half-dose aprotinin | 0% |
| Full-dose aprotinin | 0%* |

*p < 0.05 relative to placebo

Source: Bayer US CABG Randomized Clinical Trials

# Trasylol® (aprotinin injection)

## Safety in CABG Procedures

# Baseline Characteristics of Global Safety Population

| Demographic Variable | Full-Dose Aprotinin N = 2249 | Placebo N = 2164 |
|---|---|---|
| Mean (± SD) Age (years) | 61.1 ± 9.0 | 61.3 ± 9.0 |
| Male Sex, n (%) | 1993 (88.6) | 1911 (88.3) |
| Race, n (%) | | |
| White | 1579 (70.2) | 1500 (69.3) |
| Black | 40 (1.8) | 29 (1.3) |
| Hispanic | 35 (1.6) | 46 (2.1) |
| Asian or Oriental | 5 (0.2) | 15 (0.7) |
| American Indian | 5 (0.2) | 3 (0.1) |
| Missing/Uncodable | 585 (26.0) | 571 (26.3) |
| Surgical Procedure, n (%) | | |
| Repeat CABG | 276 (12.3) | 255 (11.8) |
| Primary CABG | 1819 (80.9) | 1785 (82.5) |
| Not Categorized | 154 (6.8) | 124 (5.7) |

Source: Bayer Global CABG Randomized Clinical Trial Database

# Key Medical Conditions Similar at Baseline

| Risk Factors | Full-Dose Aprotinin N = 2249 | Placebo N = 2164 |
|---|---|---|
| Diabetes mellitus, n (%) | 394 (17.5) | 422 (19.5) |
| Congestive heart failure, n (%) | 116 (5.2) | 102 (4.7) |
| Prior myocardial infarction, n (%) | 879 (39.1) | 820 (37.9) |
| Cerebrovascular accident, n (%) | 72 (3.2) | 66 (3.0) |
| Hypertension, n (%) | 908 (40.4) | 882 (40.8) |
| Estimated GFR < 60 mL/min, n/N (%) | 435/2046 (21.3) | 404/1953 (20.7) |

Source: Bayer Global CABG Randomized Clinical Trial Database

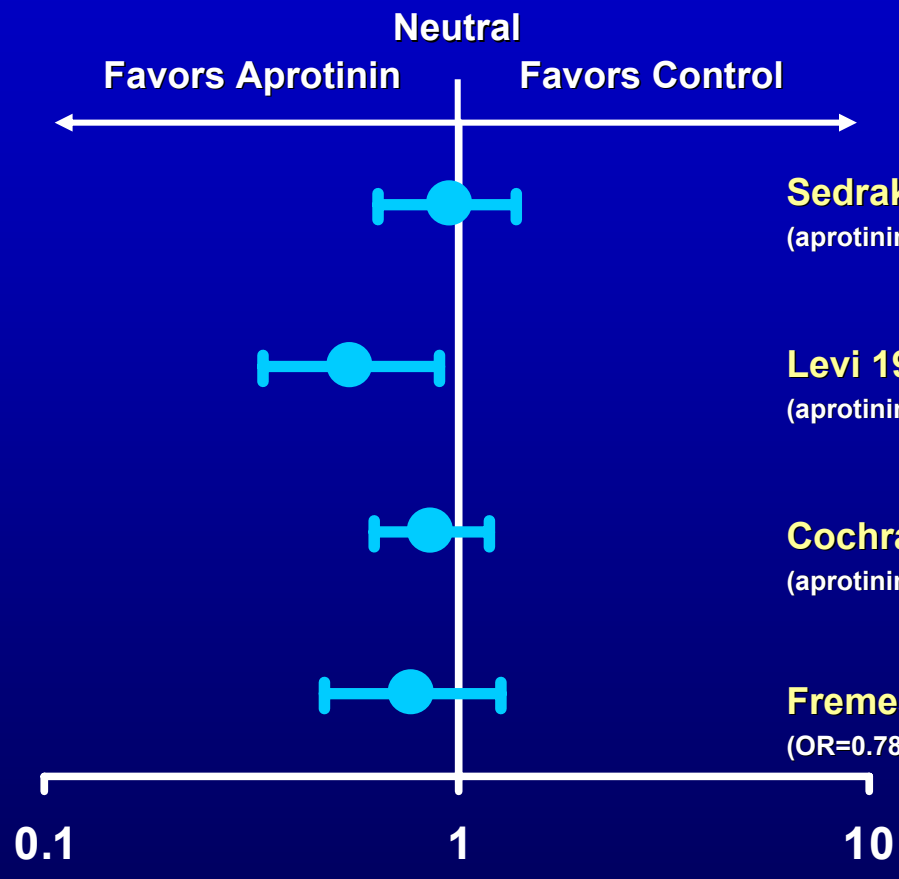
# Overview of Safety Events

| | Full-Dose Aprotinin N = 2249 | | Placebo N = 2164 | |
|---|---|---|---|---|
| | n | % | n | % |
| Any Adverse Event | 1309 | 58.2 | 1327 | 61.3 |
| Any Serious Adverse Event | 298 | 13.3 | 287 | 13.3 |
| Deaths | 65 | 2.9 | 55 | 2.5 |

Includes adverse events reported up to 7 days after study drug. Deaths were reported for the entire course of hospitalization and the follow-up period.

Source: Bayer Global CABG Randomized Clinical Trial Database

# Mortality Risk:
## *Aprotinin vs Control per Meta-Analysis of RCTs*




**Sedrakyan 2004 - CABG (32 trials; 3779 pts)***
(aprotinin 2.5%; control 2.4%; RR=0.96; 95%CI 0.65, 1.40)

**Levi 1999 - cardiac surgery (26 trials; 3212 pts)**
(aprotinin 1.5%; control 2.8%; OR=0.55; 95%CI 0.34, 0.90)

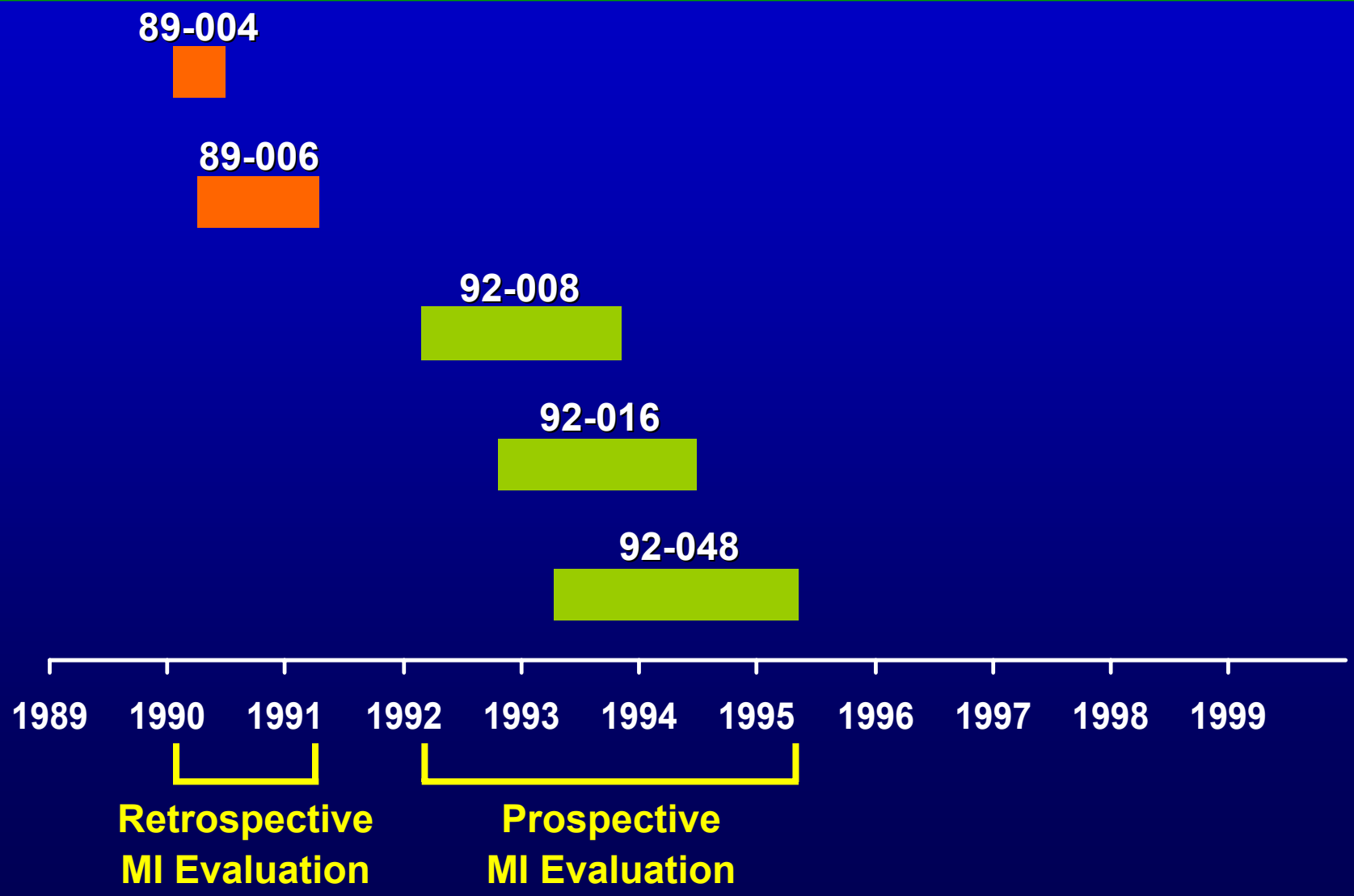
**Cochrane/Henry 1999 - cardiac surgery (28 trials; 4913 pts)***
(aprotinin 3.1%; control 3.5%; RR=0.87; 95% CI 0.63, 1.19)

**Fremes 1994 - open-heart surgery (11 trials; 2350 pts)**
(OR=0.78; 95%CI 0.48, 1.27)

# Trasylol® (aprotinin injection)

## Myocardial Infarction

# Timeline of US Studies



# Incidence of Myocardial Infarction as Determined by Investigator

| Population | Aprotinin n/N | Aprotinin % | Placebo n/N | Placebo % | Odds Ratio (95% CI) |
|---|---|---|---|---|---|
| All CABG[a] | 144/2249 | 6.4 | 118/2164 | 5.5 | 1.18 (0.92, 1.50) |
| Primary CABG | 96/1819 | 5.3 | 95/1785 | 5.3 | 0.99 (0.74, 1.33) |
| Repeat CABG | 41/276 | 14.9 | 22/255 | 8.6 | 1.85 (1.07, 3.20) |

All adverse events suggestive of myocardial infarction, recorded up to 7 days postoperatively

[a] Includes patients with CABG type not specified

Source: Bayer Global CABG Randomized Clinical Trial Database

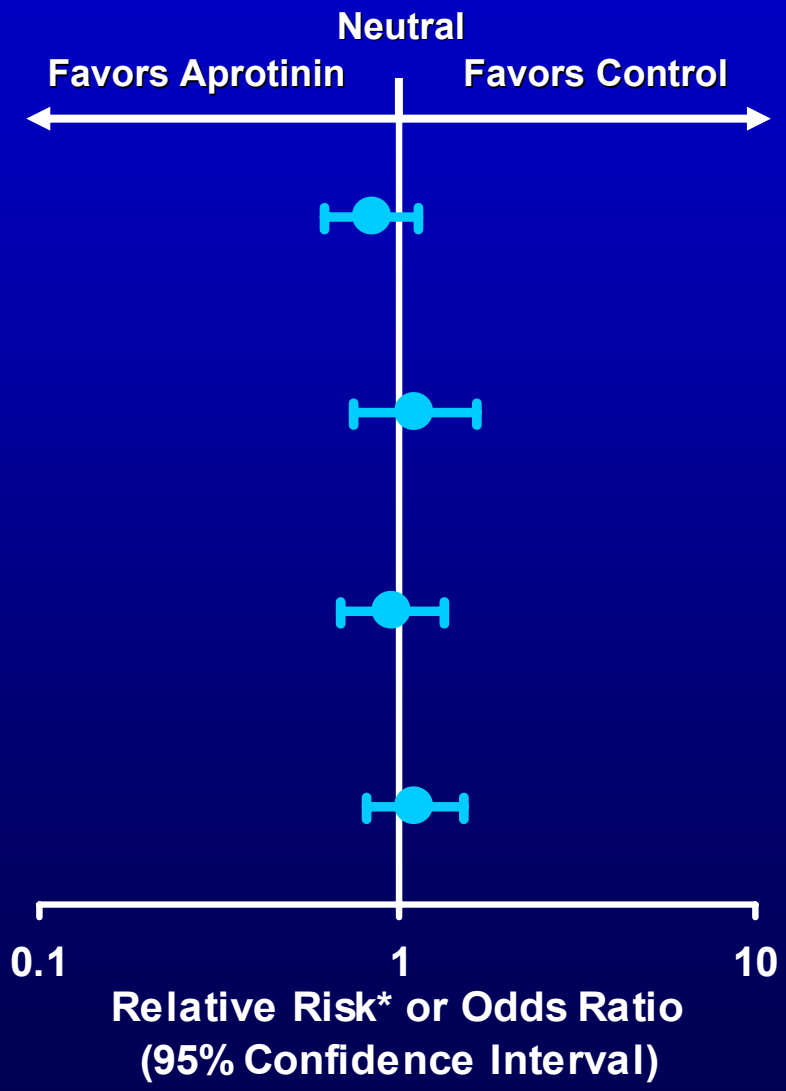
# Incidence of Definite Myocardial Infarction* As Determined By Central, Blinded Evaluator

| | Full-Dose Aprotinin | | Placebo | | Odds Ratio |
|---|---|---|---|---|---|
| | n/N | % | n/N | % | (95% CI) |
| All CABG | 30/646 | 4.6 | 31/661 | 4.7 | 0.96 (0.56, 1.65) |
| Primary CABG | 22/578 | 3.8 | 23/594 | 3.9 | 1.00 (0.53, 1.86) |
| Repeat CABG | 8/68 | 11.8 | 8/67 | 11.9 | 0.88 (0.30, 2.54) |
| Study D92-008 | 8/68 | 11.8 | 8/67 | 11.9 | 0.88 (0.30, 2.54) |
| Study D92-016 | 10/168 | 6.0 | 7/173 | 4.0 | 1.61 (0.58, 4.45) |
| Study D92-048 | 12/410 | 2.9 | 16/421 | 3.8 | 0.75 (0.34, 1.65) |

* Significant new Q wave worsening, persistent new LBBB, or acute necrosis at autopsy

Source: Bayer US CABG Randomized Clinical Trial Database

# Myocardial Infarction Risk:
## *Aprotinin vs Control per Meta-Analyses of RCTs*




**Sedrakyan 2004** - CABG (28 trials; 3555 pts)*
(aprotinin 4.7%; control 5.0%; RR=0.85; 95% CI 0.63, 1.14)

**Levi 1999** - cardiac surgery (18 trials; 1995 pts)
(OR=1.13; 95% CI 0.76, 1.67)

**Cochrane/Henry 1999** - cardiac surgery (20 trials; 2988 pts)*
(aprotinin 5.2%; control 5.2%; RR=0.97; 95% CI 0.69, 1.83)

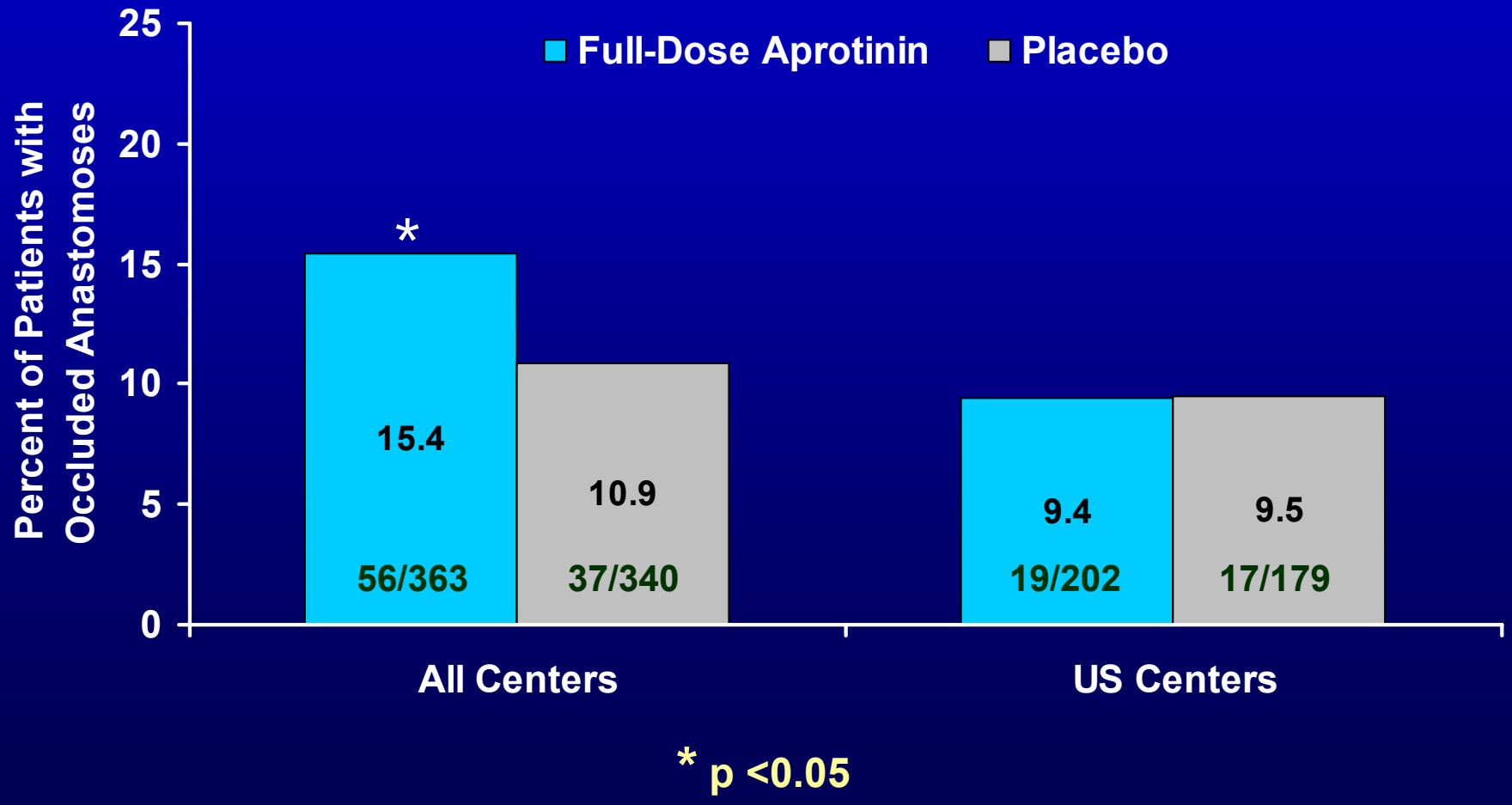
**Laupacis 1997** - cardiac surgery (# trials and pts not provided)
(aprotinin 8%; control 5.6%; OR=1.12; 95% CI 0.82, 1.53)

# Trasylol® (aprotinin injection)

## Graft Patency

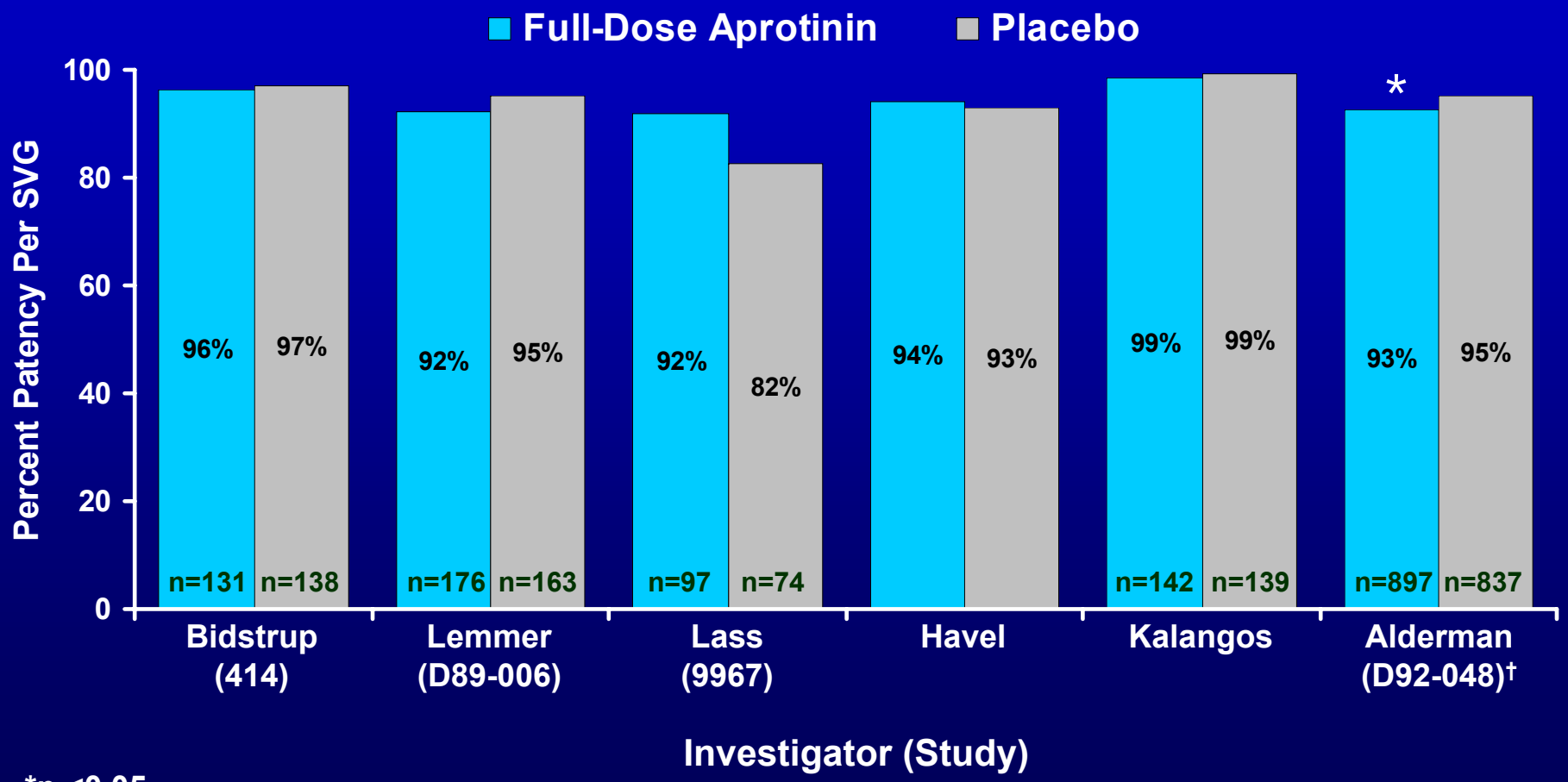
# Study D92-048: Incidence of Graft Closure by Patient

703 patients with assessable saphenous vein grafts




* p <0.05

# Graft Patency Results Per SVG




*p <0.05

†Per anastomosis

# Trasylol® (aprotinin injection)

## Congestive Heart Failure

# Incidence of Congestive Heart Failure

| Patient Population | Full-Dose Aprotinin n/N | Full-Dose Aprotinin % | Placebo n/N | Placebo % | Odds Ratio (95% CI) |
|---|---|---|---|---|---|
| All CABG | 141/2249 | 6.3 | 127/2164 | 5.9 | 1.08 (0.84, 1.38) |
| Primary CABG | 81/1819 | 4.5 | 82/1785 | 4.6 | 0.97 (0.71, 1.33) |
| Repeat CABG | 39/276 | 14.1 | 28/255 | 11.0 | 1.33 (0.79, 2.24) |

Includes adverse events recorded up to 7 days postoperatively

Source: Bayer Global CABG Randomized Clinical Trial Database

# Cardiac Safety Summary

- Aprotinin was not associated with an increased incidence of myocardial infarction
- In 5 of 6 studies, aprotinin was not associated with an increased risk of graft closure. In the sixth study, there was an increased risk of graft closure overall, but not at US sites
- Aprotinin was not associated with an increased incidence of congestive heart failure

# Trasylol® (aprotinin injection)

## Cerebrovascular Events

# Incidence of Stroke

| Patient Population | Full-Dose Aprotinin n/N | Full-Dose Aprotinin % | Placebo n/N | Placebo % | Odds Ratio (95% CI) |
|---|---|---|---|---|---|
| All CABG | 25/2249 | 1.1 | 34/2164 | 1.6 | 0.80 (0.53, 1.21) |
| Primary CABG | 20/1819 | 1.1 | 24/1785 | 1.3 | 0.82 (0.45, 1.48) |
| Repeat CABG | 2/276 | 0.7 | 8/255 | 3.1 | 0.23 (0.05, 1.07) |

Includes adverse events recorded up to 7 days postoperatively

Source: Bayer Global CABG Randomized Clinical Trial Database

# Incidence of Encephalopathy

| Patient Population | Full-Dose Aprotinin n/N | Full-Dose Aprotinin % | Placebo n/N | Placebo % | Odds Ratio (95% CI) |
|---|---|---|---|---|---|
| All CABG | 5/2249 | 0.2 | 6/2164 | 0.3 | 0.94 (0.55, 1.60) |
| Primary CABG | 3/1819 | 0.2 | 3/1785 | 0.2 | 0.98 (0.20, 4.87) |
| Repeat CABG | 0/276 | 0.0 | 3/255 | 1.2 | 0.13 (0.01, 2.54) |

Includes adverse events recorded up to 7 days postoperatively

Source: Bayer Global CABG Randomized Clinical Trial Database

# Cerebrovascular Safety Summary

- Aprotinin was not associated with an increased incidence of either stroke or encephalopathy

# Trasylol® (aprotinin injection)

## Renal Function

# Incidence of Serum Creatinine Elevations or Dialysis

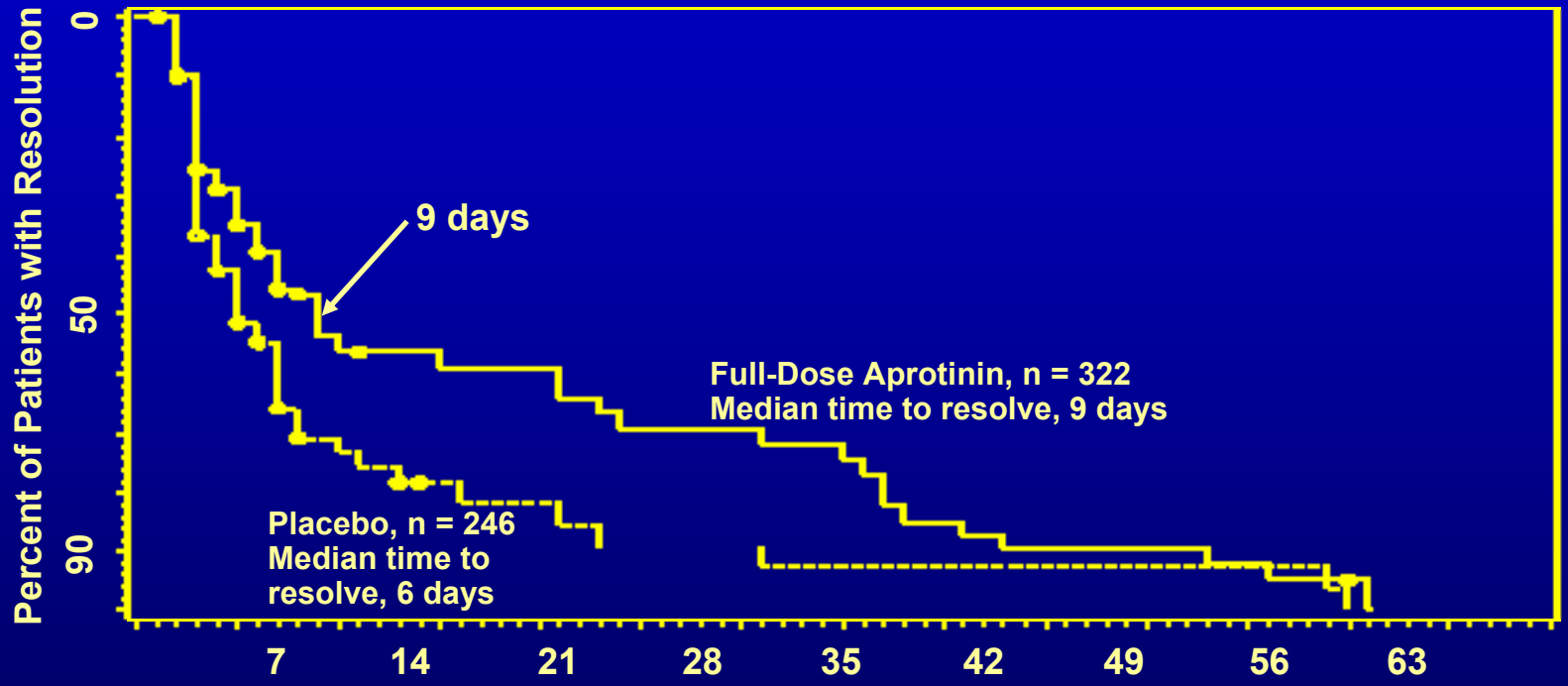
| | Full-Dose Aprotinin | | Placebo | | Odds Ratio |
|---|---|---|---|---|---|
| | n/N | % | n/N | % | (95% CI) |
| **Serum Creatinine Elevation** | | | | | |
| >0.5 mg/dL over baseline | 185/2047 | 9.0 | 129/1957 | 6.6 | 1.41 (1.12, 1.79) |
| >2.0 mg/dL over baseline | 23/2047 | 1.1 | 16/1957 | 0.8 | 1.16 (0.73, 1.85) |
| Dialysis† | 6/2249 | 0.3 | 7/2164 | 0.3 | 0.82 (0.54, 1.56) |

† Dialysis performed or recommended

Source: Bayer Global CABG Randomized Clinical Trial Database

# Estimated Time to Return to Within 20% of Baseline Creatinine for Patients With Treatment-Emergent Increases Above Upper Limit of Normal

## Kaplan-Meier Estimates for Median Time to Resolution in Days




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Aprotinin | 332 | 133 | 31 | 28 | 26 | 23 | 5 | 4 | 2 |
| Placebo | 246 | 65 | 9 | 6 | 5 | 4 | 2 | 2 | 2 |

Number of Patients Remaining

Source: Bayer Global CABG Randomized Clinical Trial Database

# Incidence of Serum Creatinine Elevations or Dialysis Based on Dose

| | Full-Dose Aprotinin | | Half-Dose Aprotinin | | Placebo | |
|---|---|---|---|---|---|---|
| | n/N | % | n/N | % | n/N | % |
| **Serum Creatinine Elevations** | | | | | | |
| >0.5 mg/dL over baseline | 37/335 | 11.0 | 26/333 | 7.8 | 27/342 | 7.9 |
| >2 mg/dL over baseline | 6/335 | 1.8 | 4/333 | 1.2 | 4/342 | 1.2 |
| **Dialysis** | 1/361 | 0.3 | 3/366 | 0.8 | 3/365 | 0.8 |

Source: Bayer Global CABG Randomized Clinical Trial Database (Dose Response Studies)

# Serum Creatinine Elevations >0.5 mg/dL Based on Possible Risk Factors for Renal Dysfunction

| Risk Factor | Full-Dose Aprotinin n/N | Full-Dose Aprotinin % | Placebo n/N | Placebo % | Odds Ratio (95% CI) |
|---|---|---|---|---|---|
| Overall | 185/2047 | 9.0 | 129/1957 | 6.6 | 1.41 (1.12, 1.79) |
| Peri-op aminoglycoside use | 43/184 | 23.4 | 22/198 | 11.1 | 2.63 (1.49, 4.65) |
| Baseline estimated GFR <60 mL/min* | 77/435 | 17.7 | 43/404 | 10.6 | 1.60 (1.11, 2.31) |
| Presence of diabetes mellitus | 47/369 | 12.7 | 36/386 | 9.3 | 1.32 (0.87, 2.02) |
| Pre-op ACE inhibitor use | 40/347 | 11.5 | 36/323 | 11.1 | 1.05 (0.67, 1.65) |

* Calculated using the Cockcroft-Gault formula
ACE = angiotensin-converting enzyme; GFR = glomerular filtration rate

Source: Bayer Global CABG Randomized Clinical Trial Database

# Renal Safety Summary

Increased incidence of serum creatinine elevations >0.5 mg/dL with full-dose aprotinin in CABG surgery

- Not seen with half-dose aprotinin
- No clinically relevant difference in the rates of serum creatinine elevations >2.0 mg/dL
- Elevations were typically transient
- No difference in the rates of dialysis
- Increased incidence with peri-operative aminoglycosides but not with pre-operative ACE inhibitors
- Increased incidence in patients with baseline renal dysfunction (estimated GFR <60 mL/min)

# Trasylol® (aprotinin injection)

## Hypersensitivity

# Hypersensitivity

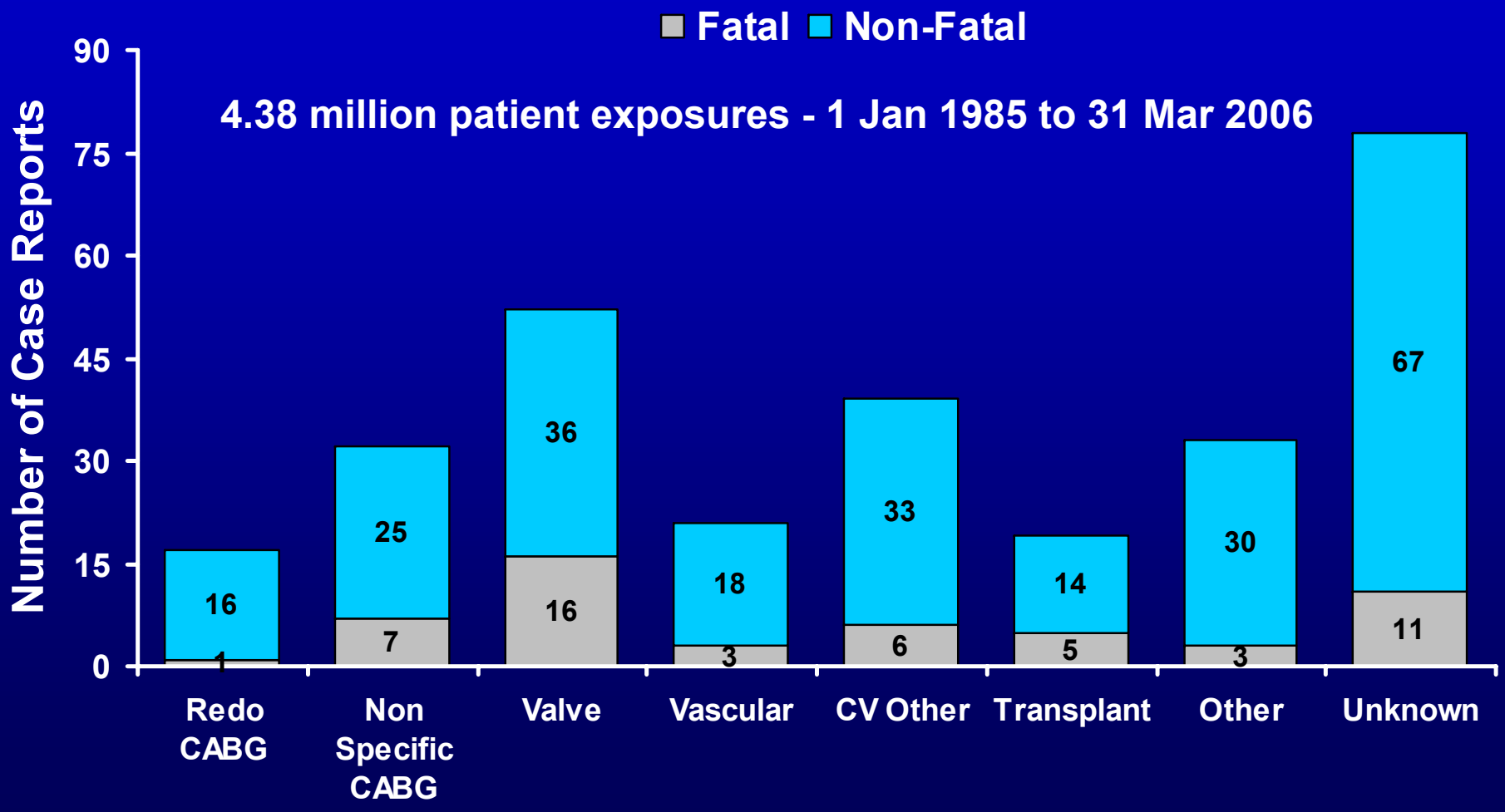
- Hypersensitivity is a recognized adverse event associated with aprotinin and is highlighted in a boxed warning in the Trasylol Package Insert
- Risk of hypersensitivity/anaphylaxis* is related to exposure history
  - < 0.1% for no prior exposure
  - 2.7% for any re-exposure
    - 5.0% for re-exposure within 6 months
    - 0.9% for re-exposure greater than 6 months

* **Trasylol Package Insert, 2003: Dietrich W et al. Antigenicity of Trasylol in 387 Patients with Re-exposure – Retrospective analysis. PH-25504, 1996 (Bayer Pharmaceuticals Corporation, Data on File)**

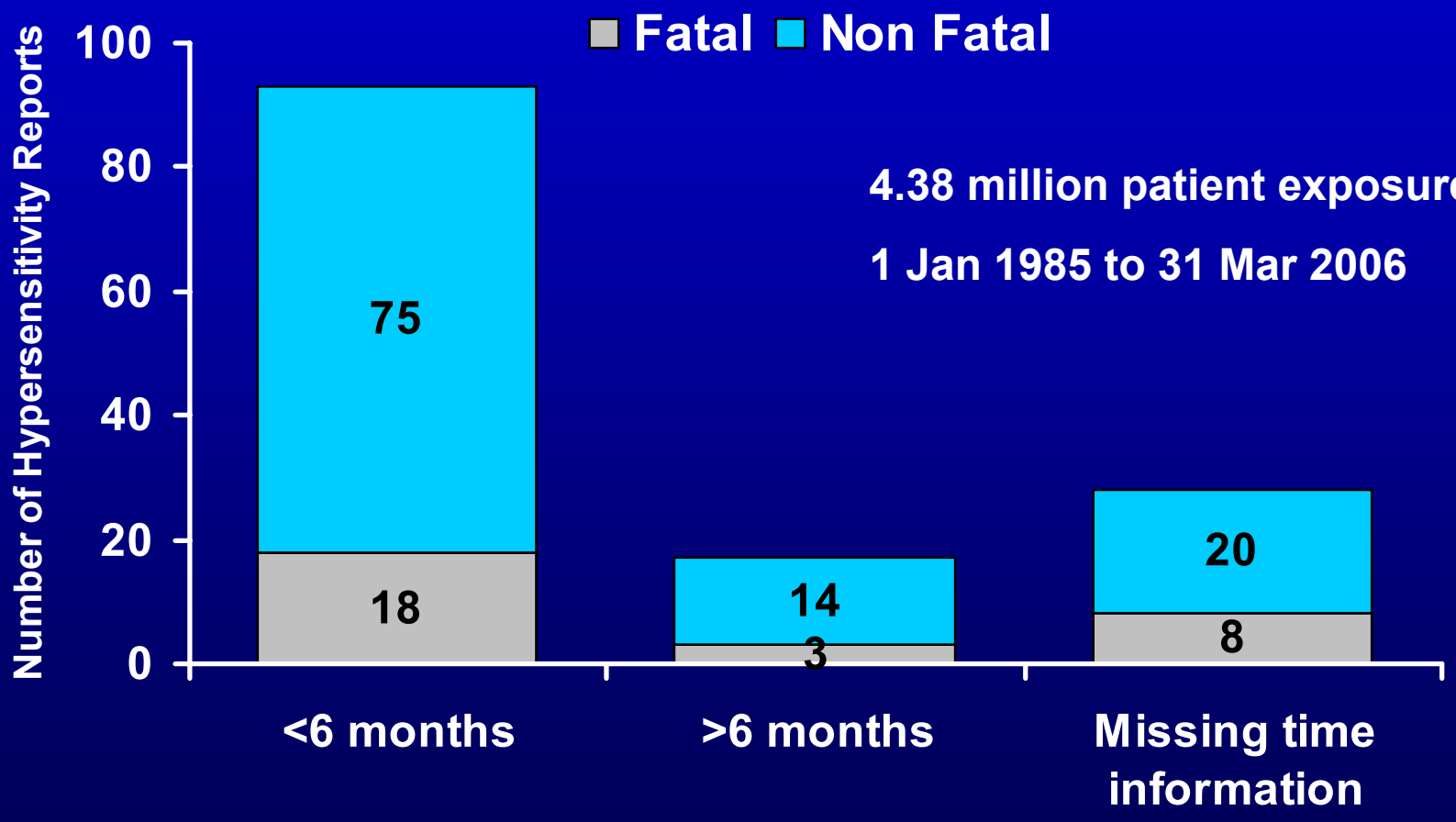
# Hypersensitivity: Spontaneous Reports

- Estimated cumulative 4.38 million patient exposures - 1 Jan 1985 to 31 Mar 2006
- Independent review of 311 hypersensitivity cases
  - 291 cases of hypersensitivity were assessed as possibly associated with Trasylol
  - Of the 291(91 US) reports
    - 239 (76 US reports) were non-fatal
    - 52 (15 US reports) were fatal

# Bayer Global Spontaneous Data: Hypersensitivity Reports by Indication



# Hypersensitivity Reactions in Patients with Documented Prior Exposure to Aprotinin*




*Total includes 29 Fatal and 109 Non-fatal global reports with documented re-exposure

# Assessing Risk of Hypersensitivity: Test Dose

## Hypersensitivity Reports Possibly Associated with Trasylol

| | Fatal (N=52) | Non-fatal (N=239) |
|---|---|---|
| Test Dose Documented | 27 | 115 |
| Reaction after Test Dose | 19* | 63 |

* One patient had a reaction to test dose and was administered loading dose

- Administration: 1mL of Trasylol IV at least 10 minutes prior to loading dose
- Data from spontaneous reports do not permit an assessment of how many reactions with therapeutic dose were avoided by use of the test dose

# Actions to Minimize Risk of Hypersensitivity (1)

- Prescriber Education – Key Messages
  - Use only for CABG patients at increased risk for blood loss and blood transfusions
  - Increased risk following re-exposure within 6 months (boxed warning)
  - Obtain complete medical history
  - Other products may contain aprotinin
  - Correct use of test dose
  - Be prepared to treat a potential reaction

# Actions to Minimize Risk of Hypersensitivity (2)

- Aprotinin-specific IgG assay
  - Lab assay – near term
  - Point of care assay – development ongoing
- Labeling concept submitted to the FDA
  - Contraindicate Trasylol in patients with detectable aprotinin-specific IgG

# Summary

- Aprotinin provides important clinical benefits for CABG patients
- Labeling concepts proposed to FDA to reflect results of updated analyses
- Aprotinin-specific IgG assay proposed to further reduce risk of hypersensitivity
- Bayer is convinced that the benefits of aprotinin outweigh risks

# Trasylol® (aprotinin injection) Risk-Benefit Assessment

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Director of Cardiothoracic Anesthesiology
Deputy Chairman for Research
Emory University School of Medicine

# Risk-Benefit Overview

- Categories of Risk Considered
  - Hypersensitivity
  - Renal function
  - Other safety considerations raised in recent observational studies
- Beneficial Effects of Aprotinin
- Risk-Benefit Assessment

# Hypersensitivity in Cardiac Surgery

- Test doses of most agents with potential for anaphylaxis are administered in the operating room
- The hallmark of perioperative anaphylaxis is hypotension
- Mortality is rare when patients are intubated, extensively monitored, and clinicians are expert at resuscitation
- In 23 cases of anaphylaxis reported during cardiac surgery, most reactions occurred before the start of cardiopulmonary bypass (CPB)*
  - Rapid placement onto CPB facilitated a good outcome
  - All but one operation proceeded as planned
  - No intraoperative or postoperative deaths were recorded

***Ford SA, Kam PC, Baldo BA, Fisher MM. Anaphylactic or anaphylactoid reactions in patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth 2001;15(6):684-8**

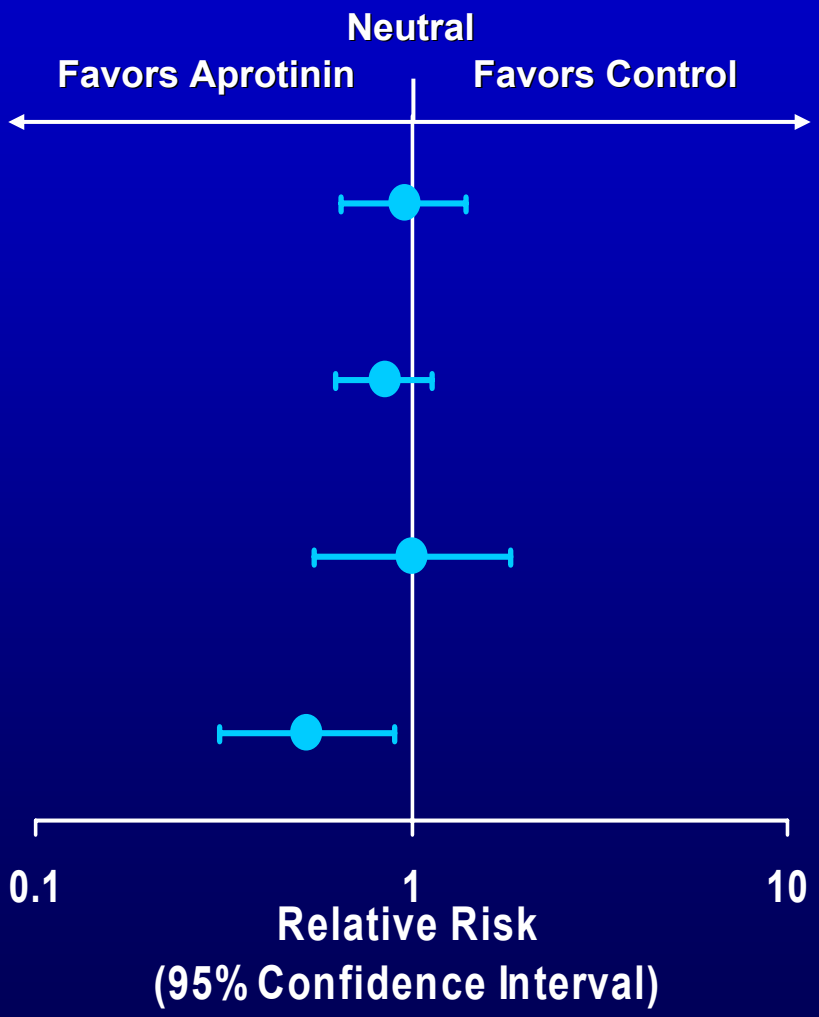
# Agents Causing Hypersensitivity Reactions in the Operating Room

- Antibiotics (e.g., vancomycin)
- Blood
- Latex
- Neuromuscular blocking agents
- Proteins (e.g., aprotinin, protamine)
- Others

# Hypersensitivity and Aprotinin

- Hypersensitivity (including fatal anaphylaxis) with aprotinin is known
  - Particularly with re-exposure within 6 months
  - Reflected in label with boxed warning
  - Standard emergency treatments should be available including when the test dose is administered
- Aprotinin-specific IgG test expected to reduce risk
  - Compensates for uncertain history of prior exposure
  - May obviate need for test dose

# CABG Meta-analysis of RCTs: Other Safety Considerations




**Mortality (32 trials; 3779 pts)**
(aprotinin 2.5%; control 2.4%; RR=0.96; 95% CI 0.65, 1.40)

**Myocardial Infarction (28 trials; 3555 pts)**
(aprotinin 4.7%; control 5.0%; RR=0.85; 95% CI 0.63, 1.14)

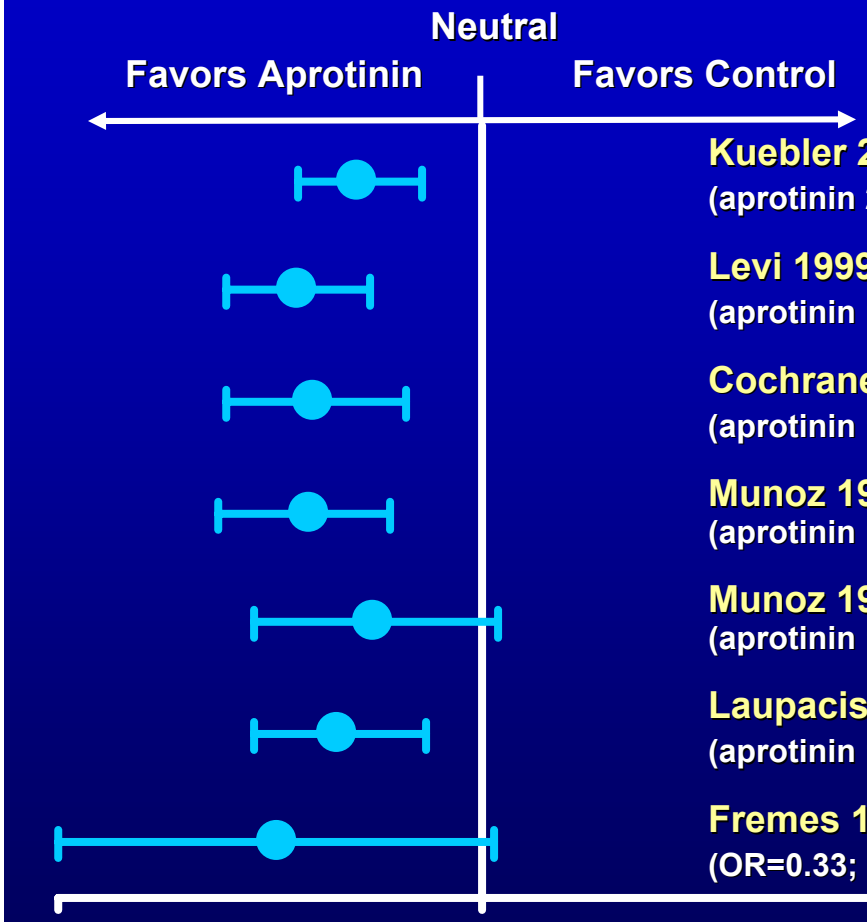
**Renal Failure (17 trials; 3003 pts)**
(aprotinin 1.5%; control 1.3%; RR=1.01; 95% CI 0.55, 1.83)

**Stroke (18 trials; 2976 pts)**
(aprotinin 1.1%; control 2.2%; RR=0.53; 95% CI 0.31, 0.90)

Sedrakyan A et al. J Thorac Cardiovasc Surg 2004; 128:442-8

# Benefits of Aprotinin

# Aprotinin Limits Re-operation in Meta-analyses of RCTs




**Kuebler 2000** - CABG (33 trials; 3626 pts)*
(aprotinin 2.9%; control 5.9%; RR=0.51; 95% CI 0.37, 0.72)

**Levi 1999** - cardiac surgery (26 trials; 3644 pts)
(aprotinin 1.9%; control 5.1%; OR=0.37; 95% CI 0.25, 0.55)

**Cochrane/Henry 1999** - cardiac surgery (29 trials; 2900 pts)*
(aprotinin 1.7%; control 5.1%; RR=0.40; 95% CI 0.25, 0.66)

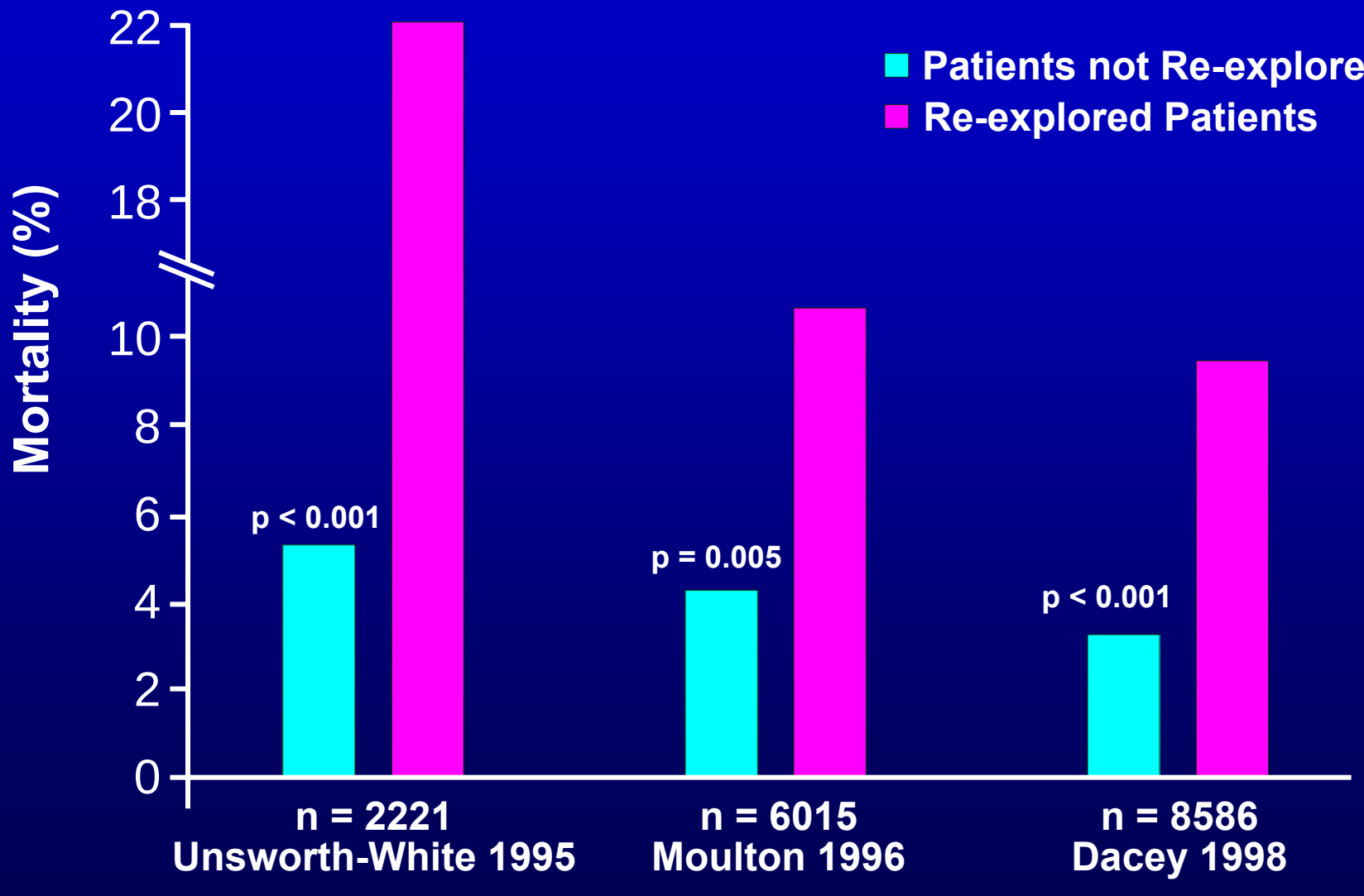
**Munoz 1999 Higher Dose** - cardiac surgery (# trials not provided; 2154 pts)
(aprotinin 1.1%; control 4.2%; OR=0.39; 95% CI 0.24, 0.61)

**Munoz 1999 Lower Dose** - cardiac surgery (# trials not provided; 1042 pts)
(aprotinin 1.7%; control 3.7%; OR=0.54; 95% CI 0.22, 1.33)

**Laupacis 1997** - cardiac surgery (# trials and pts not provided)
(aprotinin 1.8%; control 5.2%; OR=0.46; 95% CI 0.29, 0.73)

**Fremes 1994** - open heart surgery (12 trials; 620 pts)
(OR=0.33; 95% CI 0.10, 1.06)

# Effect of Re-exploration on Mortality

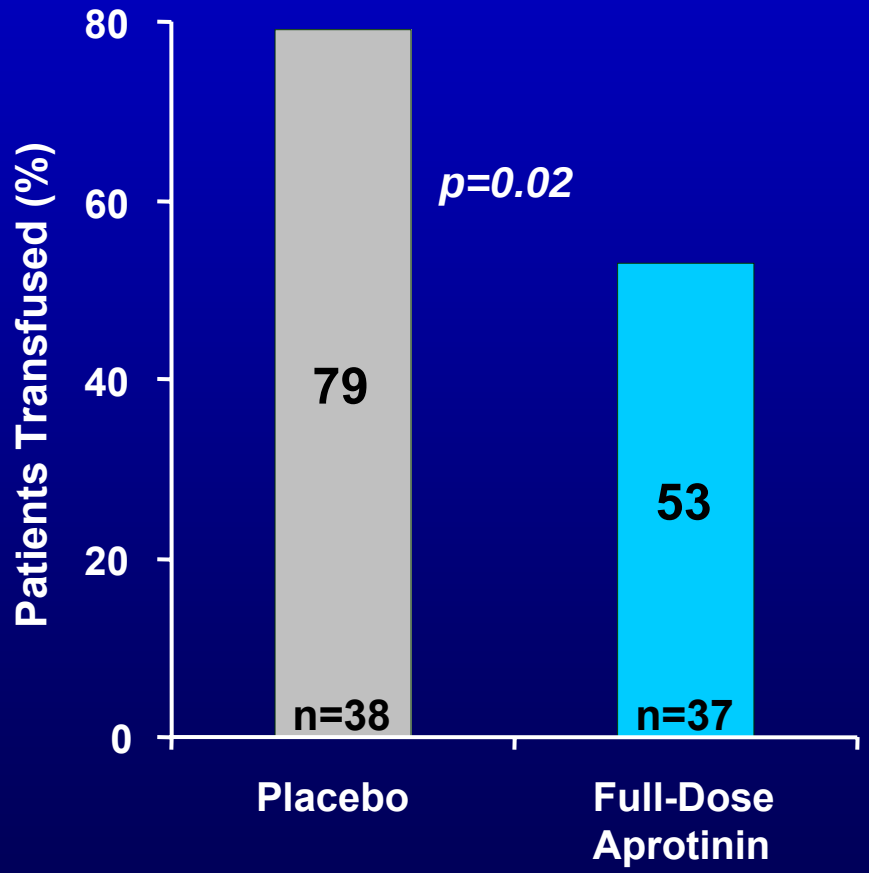


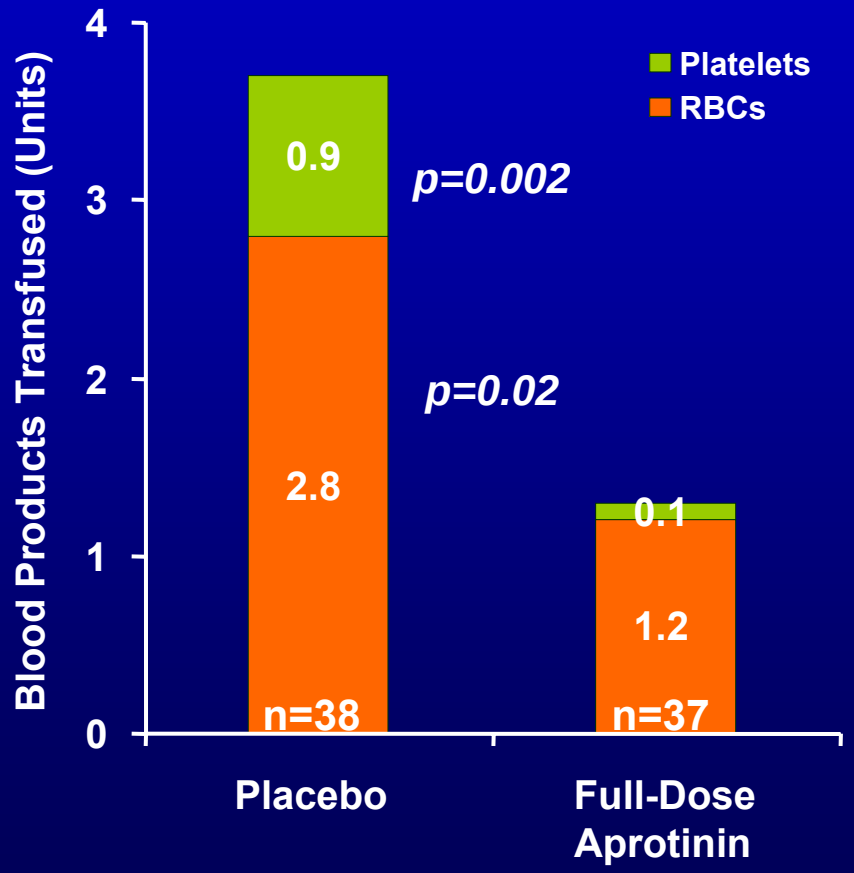
# Clopidogrel in Cardiac Surgery

- Clopidogrel significantly increases:
  - Blood loss
  - Need for transfusion of blood and blood products
  - Re-operation for bleeding
  - ICU and hospital stay
- Class 1 recommendation (ACC/AHA and STS) to stop clopidogrel at least 5 days before CABG surgery
  - However, patients requiring emergent surgery may still present on clopidogrel

# Aprotinin Decreases Transfusion in Clopidogrel-Pretreated Patients

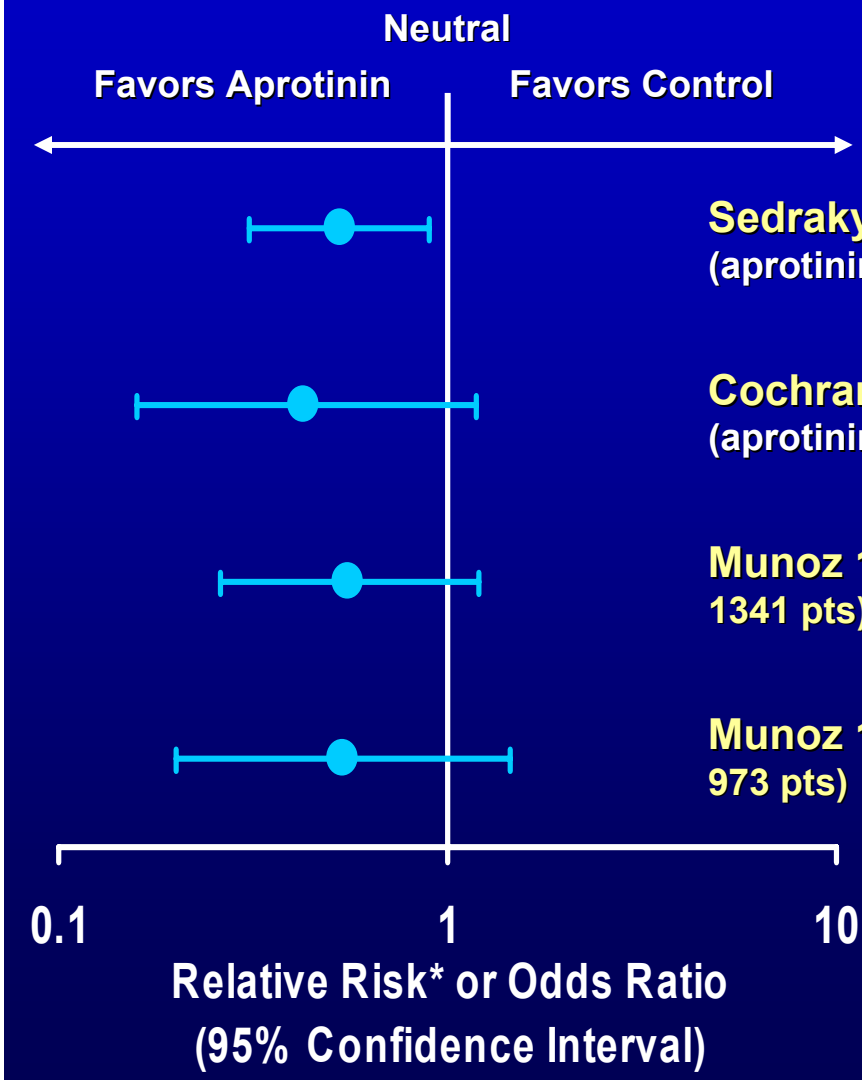
Prospective, double-blind trial in patients with unstable angina having urgent or acute isolated CABG




van der Linden. Circulation 2005;112:I-276-80

# Stroke
## *Aprotinin vs Control per Meta-Analyses*




**Sedrakyan 2004** - CABG (18 trials; 2976 pts)*
(aprotinin 1.1%; control 2.2%; RR=0.53; 95% CI 0.31, 0.90)

**Cochrane/Henry 1999** - cardiac surgery (8 trials; 978 pts)*
(aprotinin 1%; control 2.6%; RR=0.43; 95% CI 0.16, 1.19)

**Munoz 1999 Higher Dose** - cardiac surgery (# trials not provided; 1341 pts) (aprotinin 0.6%; control 1.7%; OR=0.56; 95% CI 0.26, 1.21)

**Munoz 1999 Lower Dose** - cardiac surgery (# trials not provided; 973 pts) (aprotinin 0.4%; control 1.4%; OR=0.54; 95% CI 0.20, 1.45)

# Beneficial Effects of Aprotinin Based on Randomized Clinical Trials

- Reduces blood loss and transfusion in CABG surgery
  - Also effective in aspirin/clopidogrel pre-treated patients (2005 STS Guidelines for anti-platelet therapy)
  - Recommended in STS Guidelines for reducing blood transfusion (Class I)
- Limits re-operation
  - Re-operation is known to have significant adverse clinical consequences
  - Recommended in STS Guidelines to limit re-operation (Class II)
- May reduce stroke

# Aprotinin: Risk-Benefit Conclusions

- Hypersensitivity reactions and creatinine elevations are known safety events
  - Bayer is pursuing additional measures to reduce the risk of these events
- Beyond reducing blood loss and transfusion, aprotinin reduces re-exploration and may reduce stroke
- Aprotinin is an important therapeutic option for the CABG surgery patient, with a favorable risk-benefit profile

# FDA Cardiology and Renal Drugs Advisory Committee

September 21, 2006

TRASYLOL® (aprotinin injection)

Risk-Benefit Review

Bayer Pharmaceuticals Corporation

# Q&A Slides Shown

# Aprotinin: Hemostatic not Prothrombotic

- Thrombin generation
  - Inhibits initiation
  - Inhibits amplification
- Platelet effects
  - Inhibits pathological impact of CPB
  - Allows normal hemostatic platelet function
- Inhibits free plasmin
  - Inhibits pathological but not physiological fibrinolysis
- Overall, maintains normal hemostatic balance

# Incidence of Arterial or Venous Thrombotic Events as Reported by Investigator

| | Full-Dose Aprotinin N=2249 | | Placebo N=2164 | | |
|---|---|---|---|---|---|
| Event | n | % | n | % | Odds Ratio (95% CI) |
| Any Arterial or Venous Thrombotic Event | 178 | 7.9 | 165 | 7.6 | 1.05 (0.84, 1.31) |
| Any Arterial Event | 174 | 7.7 | 161 | 7.4 | 1.05 (0.84, 1.31) |
| Any Venous Event | 5 | 0.2 | 4 | 0.2 | 1.00 (0.58, 1.74) |

Source: Bayer Global CABG Clinical Trial Database

# Definition of Myocardial Infarction (Minnesota Code Classification System)

- Definite MI
  - New Q wave worsening (2-step worsening), persistent new LBBB, or acute necrosis at autopsy
- Probable MI
  - Abnormal postop cardiac enzyme profile: CK-MB >120 U/L, or abnormal profile with Q-wave worsening (1-step worsening)
- Possible MI
  - Abnormal cardiac enzyme profile (persistent CK-MB >100 U/L)
- No MI
  - Absence of any criteria

Cardiac enzymes considered non-diagnostic for MI when all CK-MB values <100 U/L

# Myocardial Infarction Diagnosis (Core ECG Lab, St Louis)

**Based on a blinded review using the Minnesota Code Classification System**

- All ECGs (pre-op and post-op days 3, 5, and 7 or discharge)
- All CK, CK-MB, SGOT, LDH (pre-op ICU, 6, 12, 18, 24 hours post-op; days 3, 5, and 7 or discharge)
- Case report forms
- Clinical summary
- Any other applicable information (e.g., operative notes, discharge summaries, autopsy reports)

# Incidence of Serum Creatinine Elevations Based on Pre-Operative ACE Inhibitor Use

**Treatment-Emergent Serum Creatinine Elevations >0.5 mg/dL Over Baseline**

| Pre-Operative ACE Inhibitor Use | Full-Dose Aprotinin n/N | % | Placebo n/N | % | Odds Ratio (95% CI) |
|---|---|---|---|---|---|
| Overall | 185/2047 | 9.0 | 129/1957 | 6.6 | 1.41 (1.12, 1.79) |
| No | 145/1700 | 8.5 | 93/1634 | 5.7 | 1.54 (1.18, 2.00) |
| Yes | 40/347 | 11.5 | 36/323 | 11.1 | 1.05 (0.67, 1.65) |

The treatment interaction based on ACE inhibitor use was not significant (homogeneity test; p = 0.16)
ACE = angiotensin-converting enzyme

Source: Bayer Global CABG Clinical Trial Database

# Practice Guidelines: Aprotinin Limits Bleeding in Patients on Aspirin

- STS Practice Guidelines (2005)
  - Cite Level A and B evidence that aprotinin limits bleeding in aspirin-treated patients requiring CABG surgery
  - State that aprotinin has a good safety profile in this patient population
  - Provide Class IIa recommendation for the use of aprotinin in aspirin-treated CABG patients who fall into high risk categories
  - Caution that these recommendations cannot be extrapolated to lysine analogues (Class II b with level B and C evidence)

# 2006 STS Draft Practice Guidelines on Blood Conservation

- Full-dose aprotinin significantly reduces blood transfusions (class I recommendation based on Level A evidence)
- Half-dose aprotinin reduces the number of patients needing blood transfusions (class IIb recommendation based on Level B evidence)
- Full-dose aprotinin reduces reoperations (class IIa recommendation based on Level A and B evidence)

# Pre-operative evaluation of aprotinin-specific IgG

| | Aprotinin exposures, n | | | Re-exposures | Predictive value |
|---|---|---|---|---|---|
| | Total | IgG-pos. | Anaphylaxis | [%] | No reaction |
| Dietrich, 2001 | 121 | 18 | 3 | 100 | 100 (97.4-100) |
| Scheule, 2000 | 448 | 15 | 1 | 45.6 | 100 (99.3-100) |
| Cumulative | 569 | 33 | 4 | 55.4 | 100 (99.3-100) |

**Dietrich:** Re-exposed patients
**Scheule:** 244 patients with no known exposure, 194 with possible exposure, and 10 with documented prior exposure

All 4 patients with anaphylaxis were positive for aprotinin-specific IgG

**Beierlein et al (2005) Ann Thorac Surg 79: 741-748**

# Prevalence of Detectable IgG in Patients with Prior Exposure (Dietrich 2001)

| Interval since Exposure | Number of Patients | Number with positive IgG | % positive IgG |
|---|---|---|---|
| Less than 6 mo | 29 | 12 | 41.3 % |
| 6 month to 1 year | 12 | 5 | 41.7 % |
| > 1 year* | 80 | 1 | 1.2 % |

Dietrich et al (2001) Anesthesiology 95:64-71

# Renal Findings and Aprotinin Use During Total Hip Replacement Surgery

| | High dose aprotinin* | | Placebo | |
|---|---|---|---|---|
| | n/N | % | n/N | % |
| **Pooled data** | | | | |
| >upper limit of normal | 12/269 | 4.5 | 17/257 | 6.6 |
| >0.5 mg/dL over baseline | 4/280 | 1.4 | 9/271 | 3.3 |
| >0.5 mg/dL over baseline and a value >2.0 mg/dL | 2/280 | 0.7 | 4/271 | 1.5 |
| >2.0 mg/dL over baseline | 1/280 | 0.4 | 0/271 | 0.0 |

* High dose = 2 x $10^6$ KIU loading dose followed by 500,000 KIU/hr infusion during surgery

Source: Bayer medical research reports

# Changing Patient Characteristics

| Isolated CABG Patients | | | |
|---|---|---|---|
| Variable | 1995-1999 | 2000-2003 | Percent Change |
| Number of Records | 793,299 | 546,586 | |
| Age(Years) | 64.6 | 65.0 | 0.6% |
| Weight(kg) | 83.5 | 85.9 | 2.8% |
| Diabetes | 32.0% | 34.9% | 9.1% |
| Peripheral Vascular Dz | 15.5% | 15.7% | 1.6% |
| Cerebral Vascular Dz | 10.9% | 13.0% | 20.1% |
| Previous Other Cardiac (PCI) | 16.8% | 39.6% | 135.6% |
| Blood Products | 41.5% | 44.1% | 6.4% |
| Total Hours Ventilated | 13.3 | 15.3 | 14.9% |
| Readmisson <=30 Days | 7.6% | 8.9% | 16.9% |
| Gender (Male) | 72.1% | 72.3% | 0.2% |
| Ejection Fraction | 50.6 | 50.8 | 0.4% |
| Post Operative Length of Stay | 6.6 | 6.3 | -4.2% |
| Operative Mortality | 3.3% | 2.6% | -22.0% |
| Mortality - % Cardiac Cause | 67.5% | 54.4% | -19.4% |
| Multivariate Predicted Risk of: | | | |
| Mortality | 2.8% | 3.0% | 5.5% |
| Deep Sternal Wound Infection | 0.6% | 0.7% | 17.1% |
| Reoperation | 4.9% | 5.3% | 6.9% |
| Permanent Stroke | 1.6% | 1.7% | 9.2% |
| Prolonged Ventilation | 5.4% | 6.0% | 10.7% |
| Renal Failure | 3.3% | 3.8% | 14.7% |
| Morbidity or Mortality | 12.6% | 13.6% | 7.5% |

Worsening

Improving

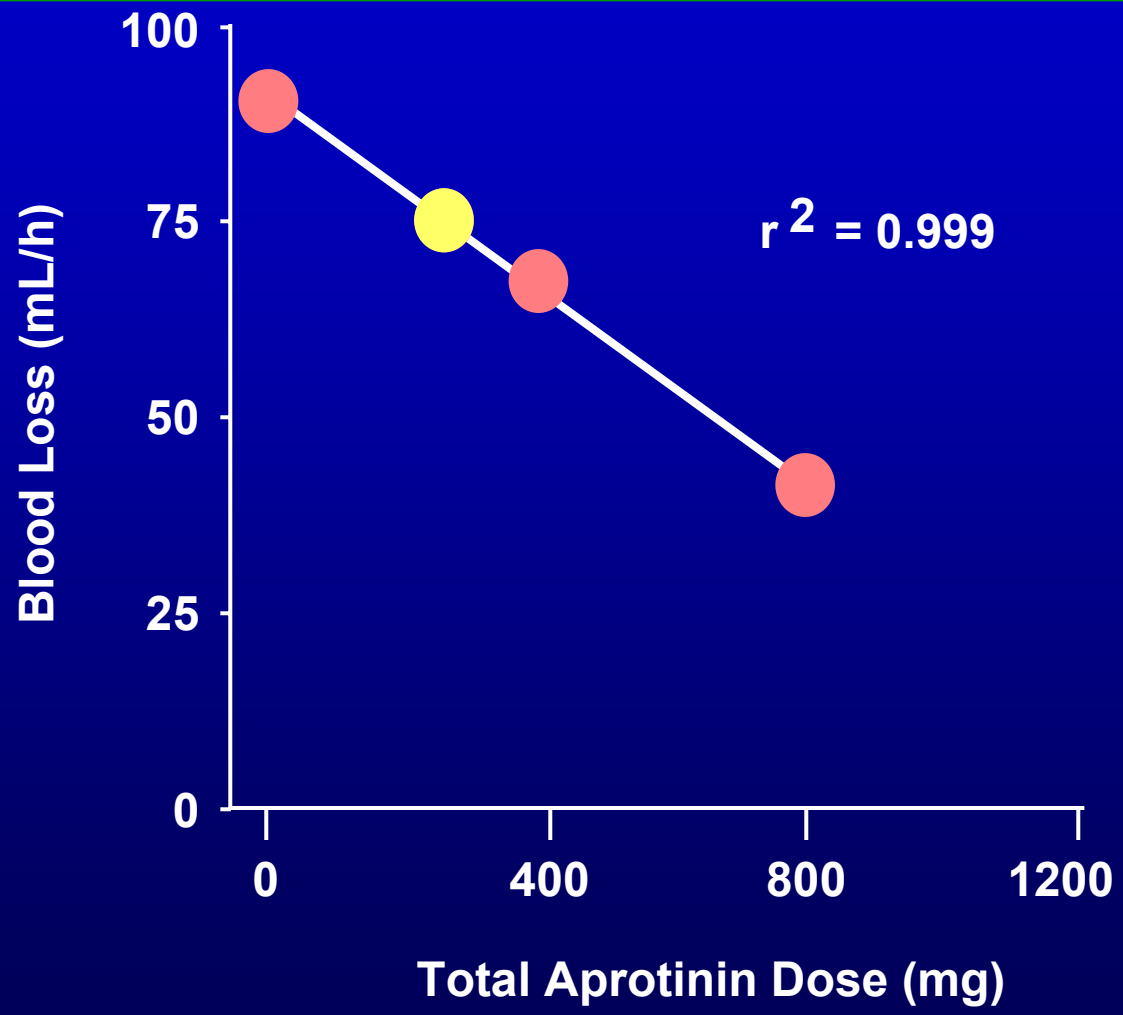
Worsening

# Dose-Dependent Properties of Aprotinin

| | Aprotinin Dose | |
|---|---|---|
| | **Half Dose** (Plasmin-inhibiting dose) | **Full Dose** (Kallikrein-inhibiting dose) |
| Inhibits free plasmin | √ | √ |
| Reduces blood loss (thoracic drainage) | √ | √ |
| Reduces transfusion requirements | √ | √ |
| Inhibits CPB-induced platelet activation | | √ |
| Inhibits direct and mediator-induced granulocyte activation | | √ |
| Inhibits kallikrein-kinin system | | √ |
| Modulates CPB-induced systemic inflammatory response | | √ |

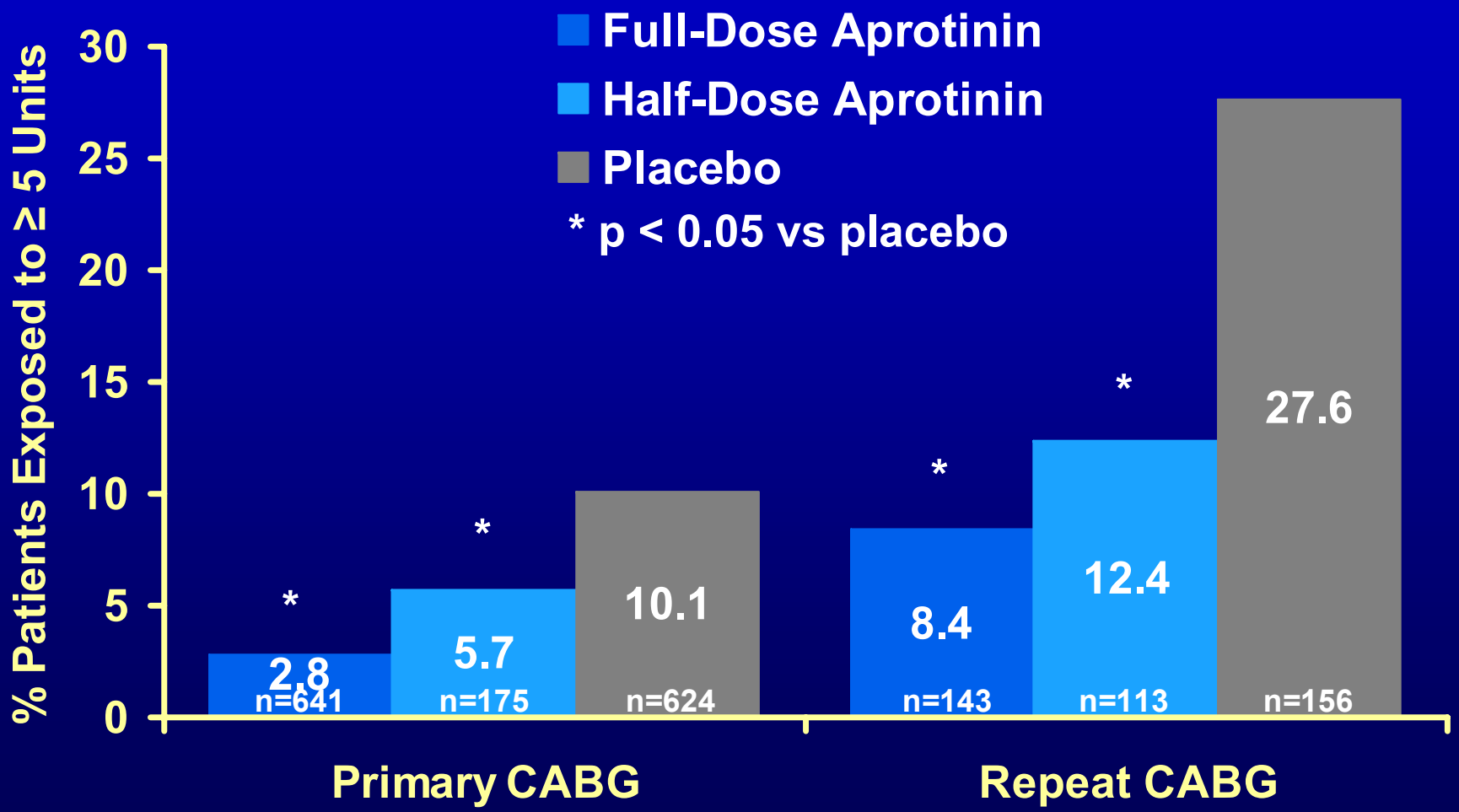
Pharmacologic properties do not necessarily imply clinical efficacy and all are not reflected in the US package insert.

# Aprotinin Dose vs Hourly Blood Loss



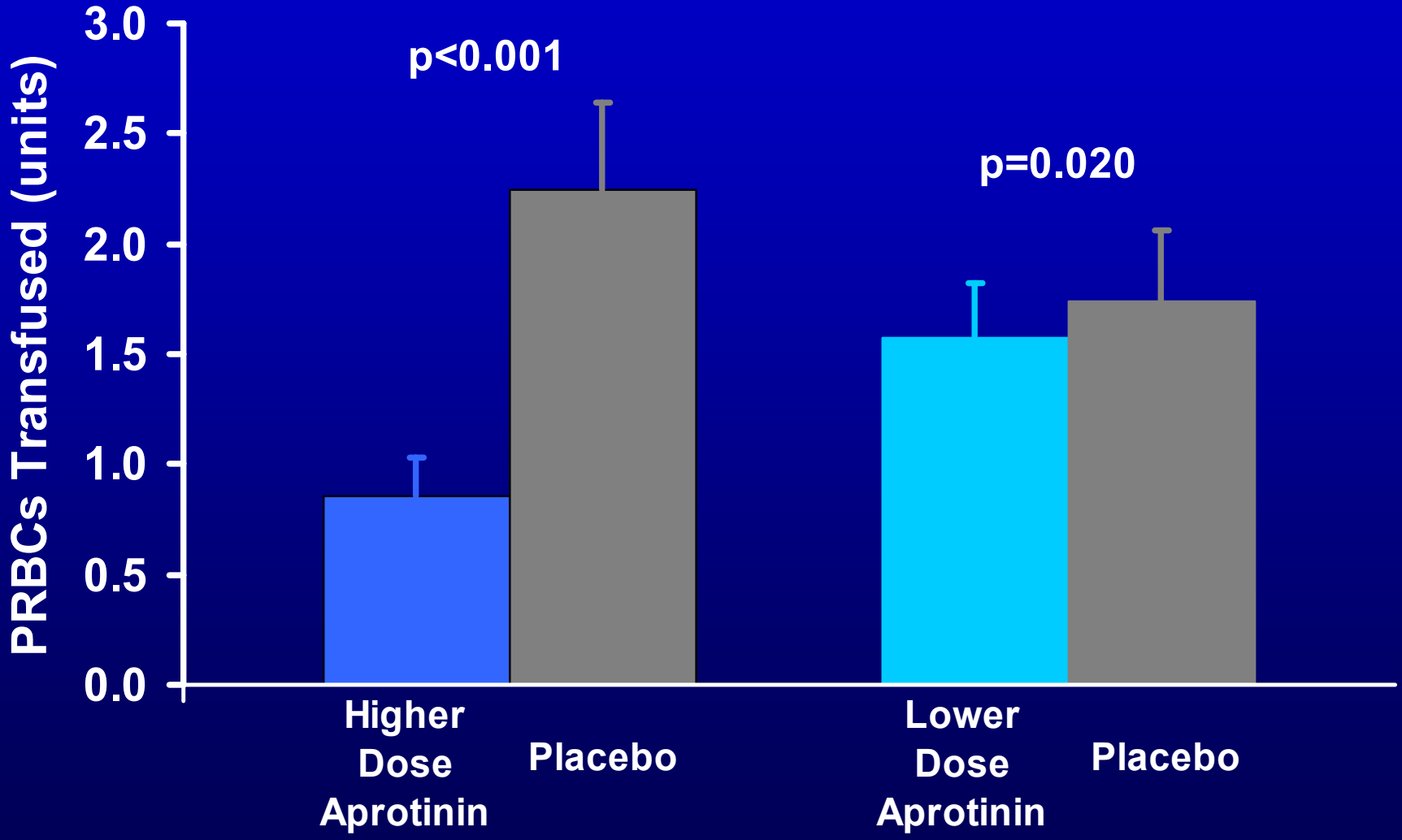

Royston Ann Thorac Surg 1998

# Patient Exposure to ≥ 5 Units of Blood and/or Blood Products
## (Bayer US Clinical Trials)



# Meta-Analysis of Aprotinin by Dose

***Dose-Dependent Reduction of Amount of RBCs Transfused***




Munoz JJ. Circulation 1999;99:81-89