

# Thrombolysis for Acute Myocardial Infarction

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# Evidence-basis for Thrombolysis as Treatment for Heart Attacks

Primary endpoint: Survival at 30 days

- Nine randomized placebo-controlled trials totaling 58,511 patients
- Overall survival advantage of about 2% (11.5% vs 9.6%) in favor of thrombolysis
- Iatrogenic deaths about 1%

# “Open-artery hypothesis”

## Kim and Braunwald

*Timely opening of the infarct-related artery theoretically explains any survival advantage seen with thrombolysis*

Evidence against the open artery hypothesis:

- Thrombolysis long after irreversible myocardial necrosis seems to help survival
- Survival is not well linked to preserving left ventricular function.
- The "early hazard" – increased mortality in the first 12 hours after thrombolysis

# “The Illusion of Perfusion”

## Inconvenient Angiographic Data

- 85% patency rates of culprit coronary lesions??
  1. Vessels not occluded at baseline
  2. Those that spontaneously achieve patency
  3. Those successfully acted upon by thrombolytic drugs.
- Fewer than 25% of patients have demonstrable improvement in perfusion
- Overall, only 2-3% increase in ejection fraction

# 90 Minute Culprit Artery Patency Rates versus Survival

- Patients who survive –71%
- Patients who die in 24 hours –59%
- Patients who die after 24 hours –  
45%

# Methodological Problems with Meta-analysis of Thrombolysis Trials

- The criterion  $N > 1000$  excluded smaller published studies stopped because of lack of efficacy of treatment
- Unpublished negative studies may have been excluded
- Excess of disabling thrombolysis-caused strokes (4/1000)
- Aspirin not given routinely
- Incomplete double-blinding allowed a placebo effect potentially favoring thrombolysis.

# Aspirin

- Aspirin vs placebo meta-analysis (n = 20,000) reduced death by 29%
- The variable use of aspirin in the 9 thrombolysis trials may have confounded the results and conclusions.
- In the 4 trials in which aspirin was used routinely (n = 21,144), the survival benefit was not statistically significant ( $P = 0.14$ ).

# ISIS-2

(n = 17,187)

- Comparing aspirin, streptokinase (SK), both, and neither
- Aspirin decreased the odds of death by 23%
- SK reduced it by 25%
- Both together by 42%

# Declining Overall Acute MI Hospital Mortality Rates

Deaths from AMI in the control groups

- GISSI (1986) – 13.0%
- ISIS-2 (1988) – 13.2%
- ISAM (1987) – 7.1%
- USNM (1991) – 8.3%
- AMI 30-day hospital mortality rate in the 1980s = 16%
- AMI 30-day hospital mortality rate in the 1990s < 10%

# Complications of Thrombolysis

- CNS Bleeding in meta-analysis of 9 randomized trials: 0.5%
- CNS Bleeding in meta-analysis of randomized studies of thrombolysis vs angioplasty: 1.1%
- Myocardial rupture: 0.5%
- 2100 -3500 deaths / year in USA

# Acute myocardial infarction registries

- Seattle AMI registry (n = 12,331): no reduction in mortality from use of thrombolysis
- Medicare fee-for-service AMI patients (n = 7864)
  - ages 76-86 increased deaths (HR: 1.38, 1.12 – 1.71;  $P = .003$ ).
  - < 76: results confounded by age and other risk factors
- The National Registry of Myocardial Infarction
  - NRMI 1: thrombolysis improves *unadjusted* hospital mortality (13.1% vs 5.9%).
  - NRMI 2: 90% of patients excluded – 41% because they inappropriately received thrombolytics

# Conclusion

- The open-artery hypothesis does not account for survival differences in randomized studies.
- Results of RCTs of thrombolysis in AMI confounded
  1. Lack of uniform use of aspirin
  2. Higher control group AMI mortality than now
  3. Lack of blinding in some studies
- AMI registry statistics do not support the efficacy of thrombolysis in AMI.
- NRMI-2 registry suggests that, of suspected AMI patients receiving thrombolytics, 41% of cases are inappropriate
- 2100-3500 treatment-caused deaths/year in USA