What has EBM done for healthcare?
evidence in heart attack

Carl Heneghan
Centre for Evidence-Based Medicine
www.cebm.net
Historical Evidence in Heart Attack

1967
1st reports in the *Lancet* of the antithrombotic properties of aspirin published

1974
1st Aspirin Trial in the *BMJ* stopped early over concerns of adverse events

1974
*BMJ*: aspirin overview of 145 RCTs

1980
*Lancet* editorial by Richard Peto - reports meta-analysis results of 6 RCTs of aspirin

1980
In hospital mortality 13%

1986
CAST trial initiated

1986
1988
Overview of 31 RCTs of aspirin in the *BMJ*

1988
1990
1995
1996
*Lancet*: reports early Tx with thrombolysis saves lives

1989
Preliminary report of the effect of *Ecainide* and *Fleicanide* published in the *NEJM* of care

1994
4S trial of simvastatin in CHD

1994
BMJ: aspirin overview of 145 RCTs

1996
*Lancet*: reports early Tx with thrombolysis saves lives

1994
1996
Heart Attack evidence

1999
HOPE trial published on ramipril in the NEJM

2000
Lancet: publishes effect of low dose blockers in the elderly

2002
Lancet: HPS study shows benefit of statins independent of baseline level

2003
Lancet: primary PTCA more effective than thrombolysis

2005
Lancet: cholesterol trial list collaboration 90,056 participants in 14 RTCs

2005
Lancet: 2005 COMMIT trial beta blocker should be withheld if the patient is unstable

2005
Lancet: COMMIT trial of early metoprolol in 45,852 participants

2009
Lancet: aspirin is of uncertain net benefit for primary prevention

2009
Paramedic 2 Trial tests effectiveness of adrenaline in cardiac arrest

2010
In hospital mortality 5%

2013
Routine use of Oxygen questioned in a Cochrane review

2015
American College of Physicians guidelines warn against screening asymptomatic individuals

2015
Paramedic 2 Trial tests effectiveness of adrenaline in cardiac arrest
For Debate

A Randomized Controlled Trial of Acetyl Salicylic Acid in the Secondary Prevention of Mortality from Myocardial Infarction


British Medical Journal, 1974, 1, 436-440

Summary

The results of a randomized controlled trial of a single daily dose of acetyl salicylic acid (aspirin) in the prevention of re-infarction in 1,239 men who had had a recent myocardial infarct were statistically inconclusive. Nevertheless, they showed a reduction in total mortality of 12% at six months and 25% at twelve months after admission to the trial. Further trials are urgently required to establish whether or not this effect is real.

Introduction

A definite and prolonged inhibition of platelet aggregation by acetyl salicylic acid (aspirin) has been shown by several workers, and confirmed subsequently. It has repeatedly been suggested that because of this effect aspirin is likely to have a prophylactic effect in thromboembolic conditions, particularly in coronary artery thrombosis. Clinical evidence of such an effect is conflicting and clearly direct evidence of benefit can come only from randomized controlled trials. This paper reports such a trial of aspirin in the preven-
Timeline of historical events in the development of aspirin.

XXXII. An Account of the Success of the Bark of the Willow in the Cure of Agues.

In a Letter to the Right Honourable George Earl of Macclesfield, President of R. S.
from the Rev. Mr. Edmund Stone, of Chipping-Norton in Oxfordshire.

My Lord,

Read June 2d, 1763. Among the many useful discoveries, which this age hath made, there are very few which, better deserve the attention of the public than what I am going to lay before your Lordship.

There is a bark of an English tree, which I have found, by experience, to be a powerful astringent, and very efficacious in curing aguish and intermittent disorders.

Fuster V, and Sweeney J M Circulation 2011;123:768-778
1967

IMPAIRED PLATELET/CONNECTIVE-TISSUE REACTION IN MAN AFTER ASPIRIN INGESTION

Harvey J Weiss, M.D. Harvard, Louis M Aledort, M.D. Albert Einstein

DOI: http://dx.doi.org/10.1016/S0140-6736(67)91658-3

Please go to ScienceDirect to view the PDF

Abstract

Platelet aggregation was studied by adding a suspension of connective tissue or adenosine diphosphate (A.D.P.) to citrated platelet-rich plasma (P.R.P.). In 10 normal men, aged 25-40 years, ingestion of 3 g. of aspirin per day for 54 hours resulted in significantly less aggregation by washed connective-tissue fragments than after a placebo, owing to impaired release of platelet A.D.P. The aspirin inhibited the release of platelet A.D.P., although the platelets still aggregated normally when this nucleotide was added to P.R.P. The results may explain the increased bleeding tendency after aspirin ingestion, and in addition suggest that the drug may have antithrombotic properties.
The results may explain the increased bleeding tendency after aspirin ingestion, and in addition suggest that the drug may have antithrombotic properties.
For Debate

A Randomized Controlled Trial of Acetyl Salicylic Acid in the Secondary Prevention of Mortality from Myocardial Infarction


British Medical Journal, 1974, 1, 436-440

Summary

The results of a randomized controlled trial of a single daily dose of acetyl salicylic acid (aspirin) in the prevention of reinfarction in 1,239 men who had had a recent myocardial infarct were statistically inconclusive. Nevertheless, they showed a reduction in total mortality of 12% at six months and 25% at twelve months after admission to the trial. Further trials are urgently required to establish whether or not this effect is real.

Introduction

A definite and prolonged inhibition of platelet aggregation by acetyl salicylic acid (aspirin) has been shown by several workers, and confirmed subsequently. It has repeatedly been suggested that because of this effect aspirin is likely to have a prophylactic effect in thromboembolic conditions, particularly in coronary artery thrombosis. Clinical evidence of such an effect is conflicting and clearly direct evidence of benefit can come only from randomized controlled trials. This paper reports such a trial of aspirin in the preven-
Slide that Peter Elwood and Archie Cochrane and prepared and showed at many meetings in the very early 1980s, in the United Kingdom and elsewhere.


<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Reduction (%) in all-cause mortality with aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC I (1974)</td>
<td>1239</td>
<td>26 NS</td>
</tr>
<tr>
<td>CDP (1976)</td>
<td>1529</td>
<td>30 NS</td>
</tr>
<tr>
<td>MRC II (1976)</td>
<td>1725</td>
<td>30 NS</td>
</tr>
<tr>
<td>German (1978)</td>
<td>626</td>
<td>18 NS</td>
</tr>
<tr>
<td>AMIS (1980)</td>
<td>4524</td>
<td>10 NS</td>
</tr>
<tr>
<td>PARIS (1980)</td>
<td>1216</td>
<td>18 NS</td>
</tr>
</tbody>
</table>

All six trials: 10 859 patients

Weighted overall effect of aspirin: 23% reduction, P<0.0001
1988 - 31 trials in patients with a history of TIA, occlusive stroke, unstable angina or prior MI

Secondary prevention of vascular disease by prolonged antiplatelet treatment

Abstract
Thirty one randomised with a history of transient ischaemic attack, unstable angina, or were still in progress reviewed. They included whom had died. Of had no apparent elevation of vascular mortality b (stroke or myocardial infarction) by 50% (4%). This suggested that with good compliance these treatments might reduce vascular mortality by about one sixth, other vascular events by about a

Purpose is inhibition of platelet aggregation. Such overviews have two main purposes. Firstly and most obviously, they include far larger numbers of patients than individual trials do and hence yield results that are far less subject to random error. Secondly, they avoid the substantial systematic bias that may be engendered when dozens of related trials have been conducted and just a few become well known, for trials may tend to become well known partly because their results are unusually promising (or unusually un-promising). The methods used for this overview never compared people at low absolute risk of occlusive disease if antiplatelet treatment produced even a small increase in the incidence of cerebral haemorrhage.

Introduction
1988 - 31 trials in patients with a history of TIA, occlusive stroke, unstable angina or prior MI

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESPS</td>
<td>Aspirin + dipyridamole</td>
</tr>
<tr>
<td>UK - TIA</td>
<td>Aspirin</td>
</tr>
<tr>
<td>AICL-A</td>
<td>Aspirin + dipyridamole, aspirin</td>
</tr>
<tr>
<td>CCSG</td>
<td>Aspirin, sulphinpyrazone, both</td>
</tr>
<tr>
<td>Sweden</td>
<td>Aspirin</td>
</tr>
<tr>
<td>McMaster</td>
<td>Suloctidil</td>
</tr>
<tr>
<td>Toulouse</td>
<td>Aspirin + dipyridamole, aspirin</td>
</tr>
<tr>
<td>AIITA</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Toronto</td>
<td>Sulphinpyrazone</td>
</tr>
<tr>
<td>DCS</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Stoke</td>
<td>Dipyridamole</td>
</tr>
<tr>
<td>Tennessee</td>
<td>Sulphinpyrazone</td>
</tr>
<tr>
<td>German TIA</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

All cerebrovascular trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIS</td>
<td>Aspirin</td>
</tr>
<tr>
<td>PARIS - II</td>
<td>Aspirin + dipyridamole</td>
</tr>
<tr>
<td>PARIS - I</td>
<td>Aspirin + dipyridamole, aspirin</td>
</tr>
<tr>
<td>Cardiff - II</td>
<td>Aspirin</td>
</tr>
<tr>
<td>ART</td>
<td>Sulphinpyrazone</td>
</tr>
<tr>
<td>CDP - A</td>
<td>Aspirin</td>
</tr>
<tr>
<td>GDR</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Cardiff - I</td>
<td>Aspirin</td>
</tr>
<tr>
<td>ARIS</td>
<td>Sulphinpyrazone</td>
</tr>
<tr>
<td>GAMIS</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

All myocardial infarction trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA</td>
<td>Aspirin</td>
</tr>
<tr>
<td>McMaster</td>
<td>Aspirin, sulphinpyrazone, both</td>
</tr>
</tbody>
</table>

All unstable angina trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>All available trials</td>
<td></td>
</tr>
</tbody>
</table>

FIG 3—Odds ratios (active treatment:control) for first stroke, myocardial infarction, or vascular death during scheduled treatment period in completed antiplatelet trials. ■ = Trial results and 99% confidence intervals (area of ■ proportional to amount of information contributed). ◇ = Overview results and 95% confidence intervals. Dashed vertical line represents odds ratio of 0.75 suggested by overview of all trial results. Solid vertical line represents odds ratio of unity (no treatment effect).
1994 Overview of 145 randomised trials of "prolonged" antiplatelet therapy versus control.

Proportional effects on vascular events (myocardial infarction, stroke, or vascular death) in 11 randomised trials of prolonged antiplatelet therapy (for one month or more) versus control in patients with prior myocardial infarction.

Antiplatelet Trialists' Collaboration BMJ 1994;308:81-106
Aspirin in the primary prevention of vascular disease: collaborative data from randomised clinical trials of antithrombotic therapy (ATT)

† Members listed at end of text
In the early 1980s newly introduced antiarrhythmics were found to be highly successful at suppressing arrhythmias. Not until a RCT was performed was it realized that, although these drugs suppressed arrhythmias, they actually increased mortality. The **CAST** trial revealed excess mortality of 56/1000. At least a decade before the initiation of CAST, it was recognized that myocardial infarction patients with frequent and complex ventricular premature depolarizations (VPDs) detected on ambulatory ECG monitoring had an increased risk of subsequent arrhythmic death as compared with patients without these arrhythmias. Like most noninvasive markers of increased risk, VPDs lack
Preliminary Report: Effect of Encainide and Flecainide on Mortality in a Randomized Trial of Arrhythmia Suppression after Myocardial Infarction

We conclude that neither encainide nor flecainide should be used in the treatment of patients with asymptomatic or minimally symptomatic ventricular arrhythmia after myocardial infarction, even though these drugs may be effective initially in suppressing ventricular arrhythmia. Whether these results apply to other patients who might be candidates for antiarrhythmic therapy is unknown.
Accumulating the evidence: Thrombolysis

Antman & Lau. JAMA 1992; 268: 240-8
Accumulating the evidence: Thrombolysis

• By 1980s - 23 small RCTs completed, (6000 patients)
  – bleeding could be a side-effect (sometimes fatal)
  – trials too small to answer the question: does thrombolysis save lives in patients with heart attacks?
  – Benefit might be about 20 lives saved per 1000 patients treated

• Doctors not convinced: treatment not used
Accumulating the evidence: Thrombolysis

- 2 Mega-trials, (ISIS-2 and GISSI), showing thrombolysis reduced risk of death after MI by about a fifth: clotbusters save lives
Publication of large-scale MI trials followed by increased use in UK Trent region

(Ketley and Woods *Lancet* 1993: 342: 891-4)
For every 1000 patients treated 65 more will be alive at 1 month if treatment is administered in the first hour – the ‘golden hour’ – after symptom onset, compared with not giving thrombolysis

- **37 Lives** are saved for every 1000 patients treated in the 1–2 hour interval
- 26 lives are saved for every 1000 patients treated in the 2–3 hour interval
- 29 lives are saved for every 1000 patients treated in the 3–6 hour interval
- **20 lives** are saved for every 1000 patients treated in the 7–12 hour interval
Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour

Eric Boersma, MSc, Arthur CP Maass, MD, Prof Jaap W Deckers, MD, Prof Maarten
Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials

Findings Primary PTCA was better than thrombolytic therapy at reducing overall short-term death (7% [n=270] vs 9% [360]; p=0.0002), death excluding the SHOCK trial data (5% [199] vs 7% [276]; p=0.0003), non-fatal reinfarction (3% [80] vs 7% [222]; p<0.0001), stroke (1% [30] vs 2% [64]; p=0.0004), and the combined endpoint of death, non-fatal reinfarction, and stroke (8% [253] vs 14% [442]; p<0.0001). The results seen with primary PTCA remained better than those seen with thrombolytic therapy during long-term follow-up, and were independent of both the type of thrombolytic agent used, and whether or not the patient was transferred for primary PTCA.

Interpretation Primary PTCA is more effective than thrombolytic therapy for the treatment of ST-segment elevation AMI.

Lancet 2003; 361: 13–20
cholesterol lowering
## Statin Trials: Chronology

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Year</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>4S</td>
<td>2002</td>
<td>PROSPER</td>
</tr>
<tr>
<td>1995</td>
<td>WOSCOPS</td>
<td>2002</td>
<td>ALLHAT-LLA</td>
</tr>
<tr>
<td>1996</td>
<td>CARE</td>
<td>2002</td>
<td>ASCOT-LLA</td>
</tr>
<tr>
<td>1998</td>
<td>AFCAPS/TEXCAPS</td>
<td>2004</td>
<td>PROVE-IT</td>
</tr>
<tr>
<td>1998</td>
<td>LIPID</td>
<td>2004</td>
<td>A to Z</td>
</tr>
<tr>
<td>2001</td>
<td>MIRAACL</td>
<td>2005</td>
<td>TNT</td>
</tr>
<tr>
<td>2002</td>
<td>HPS</td>
<td>2005</td>
<td>IDEAL</td>
</tr>
</tbody>
</table>

Primary prevention

Acute Coronary Syndromes

Chronic Coronary Heart Disease
Scandinavian Simvastatin Survival Study (4S)

Mortality (%)

Placebo
11.5

Simvastatin
8.2

30% RRR

P<0.001

Lancet 1994;344:1383–1389
Primary Endpoint: 4S trial

Lancet, Vol 344, November 19, 1994
Heart Protection Study (HPS)- Simvastatin trial

20,536 patients with CAD, other occlusive arterial disease, or DM randomized to simvastatin (40 mg) or placebo for 5.5 years.

<table>
<thead>
<tr>
<th>Baseline LDL-C (mg/dL)</th>
<th>Statin (n = 10,269)</th>
<th>Placebo (n = 10,267)</th>
<th>Event Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>282 (16.4%)</td>
<td>358 (21.0%)</td>
<td>Statin Better 0.76 (0.72–0.81) P&lt;0.0001</td>
</tr>
<tr>
<td>100–129</td>
<td>668 (18.9%)</td>
<td>871 (24.7%)</td>
<td>Statin Worse 1.00</td>
</tr>
<tr>
<td>≥130</td>
<td>1083 (21.6%)</td>
<td>1356 (26.9%)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td></td>
</tr>
</tbody>
</table>

3832 (8·5%) deaths among the 45 054 participants allocated a statin compared with 4354 (9·7%) among the 45 002 controls.

Represents a 12% proportional reduction in all-cause mortality per mmol/L LDL cholesterol reduction (RR 0·88, 95% CI 0·84–0·91; p<0·0001)
Beta-blockers
Conclusions: β Blockers are effective in long term secondary prevention after myocardial infarction, but they are underused in such cases and lead to avoidable mortality and morbidity.

Papers

β Blockade after myocardial infarction: systematic review and meta

2005 COMMIT trial: beta blocker should be withheld if the patient is unstable.

**Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial**

COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group

† Collaborators and participating hospitals listed at end of reference 21

**INTERPRETATION:** The use of early beta-blocker therapy in acute MI reduces the risks of reinfarction and ventricular fibrillation, but increases the risk of cardiogenic shock, especially during the first day or so after admission. Consequently, it might generally be prudent to consider starting beta-blocker therapy in hospital only when the haemodynamic condition after MI has stabilised.
Beta-Blocker Therapy should not be withheld from AMI Patients with COPD

Beta blocker after MI is effective in patients with chronic lung disease. In an analysis of 201,752 patients with an acute myocardial infarction (MI), those with chronic obstructive pulmonary disease (COPD) who received a beta blocker had a significant increase in survival at two years compared to patients with COPD who did not receive this therapy (83.2 versus 72.2 percent). (Data from Gottlieb, SS, McCarter, RJ, Vogel, RA. N Engl J Med 1998; 339:489.)
ACE-inhibitors
Primary Outcome - Ramipril vs Placebo

RR=0.78 (0.70-0.86)  P=0.000002

Nov. 20, 1999
Clopidogrel

COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke

Days since randomisation (up to 28 days)

<table>
<thead>
<tr>
<th>Event</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + ASA</td>
<td>2311</td>
</tr>
<tr>
<td>Clopidogrel + ASA</td>
<td>2125</td>
</tr>
</tbody>
</table>

9% (SE 3) relative risk reduction (2P = 0.002)
COMMIT: Effects of CLOPIDOGREL on Death, Re-MI or Stroke

Placebo + ASA: 2311 events (10.1%)
Clopidogrel + ASA: 2125 events (9.3%)

9% (SE3) relative risk reduction (2P=0.002)
Oxygen May Not Help Heart Attack Victims
Study ties treatment to greater heart damage, but more research urged

By Dennis Thompson
HealthDay Reporter

WEDNESDAY, Nov. 19, 2014 (HealthDay News) -- Strapping an oxygen mask to someone suffering a heart attack might make their heart attack worse, new research suggests.

Heart attack victims treated with oxygen endured 25 to 30 percent more heart damage than patients not given oxygen, said lead investigator Dr. Dion Stub, an interventional cardiologist at St. Paul's Hospital in Vancouver, Canada.

"This study backs up previous research that shows oxygen should be treated as a drug, and prescribed appropriately," said Stub, who's also a researcher at the Baker IDI Heart and Diabetes Institute in Melbourne, Australia. "If a heart attack patient's oxygen levels are normal, you should not give them oxygen."
The PARAMEDIC2 trial is looking at whether adrenaline is helpful or harmful in the treatment of a cardiac arrest that occurs outside a hospital.

Answering this question will help to improve the treatment of people who have a cardiac arrest.
Prevention of Overdiagnosis

In 2015, the American College of Physicians (ACP) released guidelines on screening for coronary heart disease, including the following\[1\]:

- There is no evidence that cardiac screening improves patient outcomes in asymptomatic, low-risk adults.

- Potential harms of cardiac screening include false-positive results causing patients to undergo potentially unnecessary tests and procedures.

- Among adults at low risk, prevalence of coronary heart disease is low, and cardiac screening is of low predictive value. Therefore, cardiac screening is of low yield, and the probability that positive findings will influence therapeutic decision making is low.
Consider the consequence of a health system without evidence.

What would the treatment of heart attack look like in an evidence void?
Consider the consequence of a health system without evidence.

What would the treatment of heart attack look like in an evidence void?

Thank you for listening