SURPRISING FINDINGS FROM CLINICAL TRIALS

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Presenters Disclosure Information
◆ Marc A. Pfeffer, M.D., Ph.D.

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Disclosures: Dr. Pfeffer receives honoraria and/or research grants, or serves as a consultant for Amgen, Anthera, Cerenis, Genzyme, Hamilton Health Sciences, Karo Bio, Medtronic, Novartis, Roche, Sanofi-Aventis, Servier and the University of Oxford. The Brigham and Women’s Hospital has patents for the use of inhibitors of the renin-angiotensin system in selected survivors of MI with Novartis Pharmaceuticals AG and Boehringer Ingelheim, GMBH. Dr. Pfeffer is a co-inventor and his shares are irrevocably transferred to charity.

BMJ 2004;328:1519
• “The natural course of pulmonary tuberculosis is in fact so variable and unpredictable that evidence of improvement or cure following the use of a new drug in a few cases cannot be accepted as proof of the effect of that drug.”
• “One hundred and seven patients with acute progressive bilateral pulmonary tuberculosis, unsuitable for collapse therapy, were studied in a clinical trial of streptomycin.”
• “Bed rest accordingly was the treatment given to one group of 52 patients (C), while 55 patients were treated with bed-rest plus streptomycin (S). Patients were assigned to one or the other group by random selection, and only after acceptance as suitable for the trial.”
• “At the end of six months, 7% of S patients and 27% of C patients had died.”

Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up Experience
The Framingham Study
William B. Kannel, MD, Thomas R. Dawber, MD, FACP, Abraham Kagan, MD, FACP, Nicholas Revotskie, MD and Joseph Stokes, III, MD
Framingham, Massachusetts


6-year incidence of coronary heart disease

Effects of Treatment on Morbidity in Hypertension
VA Cooperative Study Group on Antihypertensive Agents
143 men (DBP 115 to 129 mm Hg), mean follow-up ~18 months, 29 events

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n = 70)</th>
<th>HCTZ + Reserpine + Hydralazine HCl group (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (all CV)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Class A events*</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Other treatment failures</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Class B events*</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Total events</td>
<td>27(39%)</td>
<td>2(3%)</td>
</tr>
</tbody>
</table>

Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up Experience

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Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins.

- 44%

All-Cause Death, Non-Fatal MI, or Urgent Revascularization

On Trial Lipid Levels By Study Month
Torchetripa/Atorvastatin Group (Post Run-In)
**Time to Death**

Event Free (%)

- Arozuelo et al deaths = 55
- Torosian et al deaths = 53

Days from Randomization

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**ACCORD BP trial: SBP & Outcomes**

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>Intensive Events (%/yr)</th>
<th>Standard Events (%/yr)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>208 (1.87)</td>
<td>237 (2.09)</td>
<td>0.88 (0.73-1.06)</td>
<td>0.20</td>
</tr>
<tr>
<td>120</td>
<td>150 (1.28)</td>
<td>144 (1.19)</td>
<td>1.07 (0.85-1.35)</td>
<td>0.55</td>
</tr>
<tr>
<td>130</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>140</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Years Post-Randomization

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**Factors Influencing Infarct Size Following Experimental Coronary Artery Occlusions**

By Peter R. Marso, M.D., John E. Kjekshus, M.D., Bernten E. Søraas, M.D., Takeshi Watanami, M.D., James W. Copoll, M.D., John Ross Jr., M.D., and Eugene Brownwald, M.D.

“measures designed for reduction of myocardial oxygen demands and improvement of coronary perfusion, when effected promptly after a patient has been brought to a hospital, might potentially reduce the ultimate size of the infarction.”

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**Cumulative Number of Vascular Deaths**

- Placebo alone: 568/4300 (13.2%)
- Aspirin alone: 461/4295 (10.7%)
- Streptokinase alone: 448/4300 (10.6%)
- Streptokinase plus aspirin: 343/4292 (8.0%)

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**THE LANCET**

Saturday 13 August 1988

Cumulative Number of Vascular Deaths

- STEMI – NSTEMI
- NSTEMI <6hrs

Days From Randomization

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**Time = Myocytes: A major educational initiative**

EMS on-scene

- thrombolysis in 10/111 min
- goal: 10 min

Time interval 111 min

STEMI – NSTEMI

- on-scene
- on-scene

Goals

- Time = Myocytes
- A major educational initiative

Anisman E. et al. JACC 2004, Circulation 2004
Effect of captopril on survival following MI (rat)

Survival And Ventricular Enlargement Trial

Evolution of Guidelines for Acute Myocardial Infarction

419 recommendations:
- 59 (14%) based on level of evidence A
- 166 (40%) based on level of evidence B
- 194 (46%) based on level of evidence C

ACC Staff, Sidney Smith Personal Communication
Mortality and morbidity in patients receiving encainide, flecainide, or placebo.
The Cardiac Arrhythmia Suppression Trial

- Post-MI patients with > 6 PVCs/hour and ≤ 15 beats of NSVT and LVEF ≤ 55%.
- If PVCs suppressed, then randomized to effective drug or placebo.
- Randomized to Flecainide, Encainide, or Moricizine in Open-Label Fashion.

The Cardiac Arrhythmia Suppression Trial
Death or RSD

Risk of CV mortality associated with LV ejection fraction post-MI

PROFILE – Survival with Flosequinan

Positive Inotropic Drugs and HF
BETA-BLOCKER HF TRIALS

US carvedilol programme 1996

CIBIS-2 1998

MERIT-HF 1999

COPERNICUS 2001

ESRD - USRDS: Higher Hematocrit is Associated with Lower Risk of Death

Li & Collins, Kid Int 2004, 65:626-633

55,879 incident HD patients in the US between Jan 98 – Dec 1999
Follow-up 2.5 yrs (hospitalization) and 3.0 yrs (mortality)

Normal Hematocrit Dialysis Trial


~Hb 10

~Hb 13

N=618

Hb 11 g/dL a CMS Performance Measure

Steinbrook, Lancet 2006;368:2191.

Incremental Risk of CKD and Anemia on Mortality in Subjects With Diabetes

ARIC, Cardiovascular Health Study, Framingham Heart Studies, n = 3015 subjects with DM


Hemoglobin Levels

Darbepoetin alfa

Placebo

Hb Median: 12.5 IQR [12.0 – 12.8]
Median dose: 175 μg IQR [104 – 208]
Mean: 225 μg ± 208

Hb Median: 10.6 IQR [9.9 – 11.3]
Median dose: 0 μg IQR [0 – 1]
Mean: 5 μg ± 11
Cardiovascular Composite: Death, MI, Myocardial Ischemia, HF, Stroke

Primary Composite and Component Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Darbepoetin alfa N = 2012</th>
<th>Placebo N = 2026</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Composite</td>
<td>632 (31.4)</td>
<td>602 (29.7)</td>
<td>1.05 (0.94-1.17)</td>
<td>0.41</td>
</tr>
<tr>
<td>Death</td>
<td>412 (20.5)</td>
<td>395 (19.5)</td>
<td>1.05 (0.92-1.21)</td>
<td>0.48</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>205 (10.2)</td>
<td>229 (11.3)</td>
<td>0.89 (0.74-1.08)</td>
<td>0.24</td>
</tr>
<tr>
<td>MI</td>
<td>124 (6.2)</td>
<td>129 (6.4)</td>
<td>0.96 (0.75-1.22)</td>
<td>0.73</td>
</tr>
<tr>
<td>Stroke</td>
<td>101 (5.0)</td>
<td>53 (2.6)</td>
<td>1.92 (1.38-2.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial Ischemia</td>
<td>41 (2.0)</td>
<td>49 (2.4)</td>
<td>0.84 (0.65-1.27)</td>
<td>0.40</td>
</tr>
<tr>
<td>Renal Composite</td>
<td>652 (32.4)</td>
<td>618 (30.5)</td>
<td>1.06 (0.95-1.19)</td>
<td>0.29</td>
</tr>
<tr>
<td>ESRD</td>
<td>338 (16.8)</td>
<td>330 (16.3)</td>
<td>1.02 (0.87-1.18)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Case

- 66 year old female with type 2 DM, HTN (20yrs), quit smoking 15 years ago, BMI 28.6
- Feels generally well but relates difficulty caring for her 3 yr old granddaughter
- Meds: simvastatin, lisinopril, amlodipine, furosemide, ASA, metformin, alendronate, vit D, HRT d/c in 2003,

2004: Give ESA 2006: Give ESA

- BP: 130/70, HR: 65 Exam benign
- Labs.: HbA1c: 6.9%, LDL: 85 mg/dL, Hb: 10.4g/dL Creatinine: 1.4 mg/dL, eGFR: 39 mL/min/1.73 m2, UACR 400mg/g

2009: NO TREAT

Biomarkers & Surrogates

- Ventricular arrhythmias post MI
- LV ejection fraction in HF
- Plasma NE in HF
- Hemoglobin in CKD
- Endothelial function with HRT
- HbA1C in diabetes
- LDL
- HDL
- Blood pressure

WHI Estrogen+Progestin Trial Findings, July 2002

(N=16,608; mean age 63 yrs; mean follow-up 5.2 yrs)

Risks

- Coronary Heart Disease 29%
- Stroke 43%
- Pulmonary Embolism 11.9%
- Breast Cancer 26%

Benefits

- Hip Fracture 34%
- Colorectal Cancer 34%

Threshold Level

STOPPED Early, Clear Harm

2004: Give ESA
2006: Give ESA
to a lower target

Hip Fracture 34%
Colorectal Cancer 34%

STOPPED 3.3 years early

Writing Group for the Women’s Health Initiative. JAMA 2002;288:321-333

Table 1: Primary and Secondary Clinical End Points and End Points Through Day 180

Victims of nesiritide in patients with Acute Decompensated Heart Failure

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nesiritide (N = 150)</th>
<th>Placebo (N = 150)</th>
<th>p-value (95% CI)</th>
<th>F Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular arrhythmias post MI</td>
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<tr>
<td>LV ejection fraction in HF</td>
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<tr>
<td>Plasma NE in HF</td>
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<td>Hemoglobin in CKD</td>
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<td>Endothelial function with HRT</td>
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<td>HbA1C in diabetes</td>
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<tr>
<td>LDL</td>
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<tr>
<td>HDL</td>
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<tr>
<td>Blood pressure</td>
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The unexpected

PRAISE
Prospective Randomized Amlodipine Survival Evaluation

Prospective Randomized Amlodipine Survival Evaluation
Non-Ischemic Subgroup

Death

Placebo: 66/212 vs amlodipine 37/209
RR = 45% (95% CI: 21 – 61), p<0.001

PRAISE 2
Prospective Randomized Amlodipine Survival Evaluation 2

- 1652 pts HF (EF <30%) nonischemic cardiomyopathy
- amlodipine vs. placebo
- Follow-up ~ 48 months
- Endpoint
  - All cause mortality

Clinical (Outcomes) Trials, Why do them?

To provide the foundation for evidence-based medicine (safety as well as efficacy)

To continue to improve the practice of medicine

What are the alternatives?
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Education

Implementation

Public Health Improved

RCT

Epidemiology → Hypothesis → Pathophysiology

Societies, Regulators, Payers, Practitioners

Guidelines

The Cycle of Clinical Therapeutics

Adapted from Califf R et al. JACC 2002.

Superior doctors prevent the disease.
Mediocre doctors treat the disease before evident.
Inferior doctors treat the full blown disease.

- Huang Dee: Nai-Ching (2600 B.C. 1st Chinese Medical Text.)