Experiences with interim trial monitoring, particularly with early stopped trials

Robert J Glynn, ScD

Divisions of Preventive Medicine and Pharmacoepidemiology & Pharmacoeconomics, Brigham & Women’s Hospital
Disclosure

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Outline

• Discuss stopping decisions and impact of stopping on interpretation of three early stopped trials coordinated by the Division of Preventive Medicine:
  • 1. Aspirin component of the Physicians’ Health Study, stopped in 1987
  • 2. Prevention of Recurrent Venous Thromboembolism Trial (PREVENT), stopped in 2002
  • 3. Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), stopped in 2008
Physicians’ Health Study

- **Large, simple trial**: randomized, double-blind, placebo-controlled.

- Testing the effects of *low-dose aspirin* – 325 mg every other day (and beta carotene) in the **primary prevention** of CVD and cancer.

- Among **22,071 U.S. male physicians**, aged 40-84 at baseline. Funded by US **NIH**; pills and packaging provided by **industry**.

- First large scale RCT to look at question of **efficacy** of low-dose aspirin in **primary prevention** of first myocardial infarction.
# Aspirin and CVD: Summary of Evidence

<table>
<thead>
<tr>
<th></th>
<th>MI</th>
<th>Stroke</th>
<th>Vascular Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary prevention</td>
<td>Conclusive</td>
<td>Conclusive</td>
<td>Conclusive</td>
</tr>
<tr>
<td></td>
<td>benefit</td>
<td>benefit</td>
<td>benefit</td>
</tr>
<tr>
<td>Treatment of evolving MI</td>
<td>Conclusive</td>
<td>Conclusive</td>
<td>Conclusive</td>
</tr>
<tr>
<td></td>
<td>benefit</td>
<td>benefit</td>
<td>benefit</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
Physicians' Health Study:
2x2 Factorial Design

22,071 U.S. Male Physicians aged 40-84

Aspirin
11,037

Aspirin Placebo
11,034

Beta Carotene
5,517

Beta Carotene Placebo
5,520

Beta Carotene
5,519

Beta Carotene Placebo
5,515
### Endpoints in The Physicians' Health Study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Aspirin Group</th>
<th>Placebo Group</th>
<th>RR</th>
<th>95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total MI</td>
<td>139</td>
<td>239</td>
<td>0.56</td>
<td>(0.45-0.70)</td>
</tr>
<tr>
<td>Total Stroke</td>
<td>119</td>
<td>98</td>
<td>1.22</td>
<td>(0.93-1.60)</td>
</tr>
<tr>
<td>MI, Stroke or CV Death</td>
<td>307</td>
<td>370</td>
<td>0.82</td>
<td>(0.70-0.96)</td>
</tr>
<tr>
<td>CV Death</td>
<td>81</td>
<td>83</td>
<td>0.96</td>
<td>(0.60-1.54)</td>
</tr>
<tr>
<td>Total Death</td>
<td>217</td>
<td>227</td>
<td>0.96</td>
<td>(0.80-1.14)</td>
</tr>
</tbody>
</table>

DOUBLE CHEESEBURGER, LARGE FRIES, JUMBO COFFEE...OH, AND AN ASPIRIN—GOTTA TAKE CARE OF THE TICKER, Y'KNOW.
Stopping decision for aspirin arm of PHS

- Trial stopped early by its DSMB on 12/18/1987 after a mean treatment time of 5.0 years
- Reasons for stopping: futility for the primary endpoint of CV mortality; extreme benefit for secondary endpoint of MI; and aspirin used by >85% of subjects after MI
- Trial targeted a 20% reduction in CV mortality
- But observed standardized CV mortality ratio (vs US white males) was between 0.1 and 0.15*
- Even among physicians, those willing and able to complete a run-in phase have substantially lower CV death risk, adjusted for measured comorbidities†

*Data monitoring board of the PHS; Ann Epidemiol 1991; †HD Sesso et al; Controlled Clin Trials 2002
PREVENT: Background and Rationale

• Standard therapy for idiopathic VTE typically includes 5 to 10 days of heparin followed by 3 to 12 months of oral anticoagulation with full dose warfarin, adjusting the target INR between 2.0 and 3.0.

• However, after cessation of full dose anticoagulation, recurrent VTE is a major clinical problem with rates between 6 and 9 percent annually.

PREVENT: Primary Objectives

- To determine whether long-term, low-intensity warfarin (INR 1.5 - 2.0) will prevent recurrent venous thrombosis among patients who have completed standard outpatient anticoagulation with full dose-warfarin, yet remain at risk for recurrent thrombotic events.

- To determine whether long-term, low-intensity warfarin will result in a net clinical benefit in terms of recurrent venous thrombosis, major bleeding episodes, and all cause mortality.

PREVENT: Study Design

Index Events

Completion of standard full intensity warfarin therapy

28 day run in and low-intensity warfarin titration

Randomization

Follow-up period with double blind INR assessment every 2 months

Warfarin (INR 1.5-2.0)

Placebo

Study Duration (years)

-2 -1 0 1 2 3 4

PREVENT: Recruitment and Follow-up

- The PREVENT trial was designed to enroll 750 patients for an average follow-up of 4 years.
- However, the trial was terminated early by its Independent Data and Safety Monitoring Board after 508 patients were randomized due to the emergence of a statistically extreme benefit of low-intensity warfarin in the absence of any substantial evidence of harm.
- Mean duration of follow-up was 2.1 years with a maximum of 4.3 years.
- The median INR was 1.0 in placebo group and 1.7 in the low-intensity warfarin group with a dose range between 0.5 to 10 mg po daily (median dose 4 mg).

## PREVENT: Major Study Endpoints by Treatment Group

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Low-Intensity Warfarin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrent VTE</strong></td>
<td>N=37</td>
<td>N=14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate *</td>
<td>7.2</td>
<td>2.6</td>
<td>0.36 (0.19, 0.67)</td>
<td>0.0007</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major **</td>
<td>N=2</td>
<td>N=5</td>
<td>2.53 (0.49, 13.03)</td>
<td>0.25</td>
</tr>
<tr>
<td>Minor</td>
<td>N=34</td>
<td>N=60</td>
<td>1.92 (1.26, 2.93)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>N=8</td>
<td>1.4</td>
<td>0.50 (0.15, 1.68)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>N=9</td>
<td>1.6</td>
<td>0.45 (0.14, 1.47)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td>N=2</td>
<td>0.4</td>
<td>1.54 (0.26, 9.24)</td>
<td>0.63</td>
</tr>
<tr>
<td>**Composite Endpoint *****</td>
<td>N=41</td>
<td>N=22</td>
<td>0.52 (0.31, 0.87)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

* Rates are given as events per 100 person years. ** Major bleeding was defined as those resulting in hospitalization, transfusion of packed red blood cells, or hemorrhagic stroke. *** The pre-specified composite endpoint includes first VTE, major bleed, or death.

Stopping decision for PREVENT

- Boundary was crossed at estimated 43% information time, reported in the Oct. 30, 2002 DSMB meeting
- DSMB requested additional analyses to clarify: the sensitivity of the findings to losses to follow-up; the relationship of demographic factors with risk of recurrence; the relationship of recurrent VTE with death in the trial; and the effect of treatment at different times after randomization.
- On December 4, 2002, upon receipt of the additional analyses, the DSMB concluded that PREVENT should be terminated because of strong evidence of efficacy and boundary crossing for the primary outcome.
PREVENT: monitoring boundaries by study time

Observed logrank Z-value and critical values by information time
Based on a Lan–DeMets procedure with an O'Brien and Fleming spending function

Graph showing observed logrank Z-values and critical values as a function of information fraction.
The primary objective was to investigate whether long-term treatment with rosuvastatin 20 mg decreases the rate of first major cardiovascular events compared with placebo in patients with low to normal LDL-C but at increased cardiovascular risk as identified by elevated CRP levels.

Ridker PM. *Circulation* 2003; **108**: 2292–2297
JUPITER

Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP

No Prior CVD or DM
Men ≥50, Women ≥60
LDL <130 mg/dL
hsCRP ≥2 mg/L

4-week run-in

Rosuvastatin 20 mg (N=8901)

Placebo (N=8901)

MI Stroke Unstable Angina CVD Death CABG/PTCA

Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

JUPITER (Ridker et al. NEJM 2008)

Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

Number Needed to Treat (NNT<sub>5</sub>) = 25

Placebo 251 / 8901
Rosuvastatin 142 / 8901

109 Fewer Events
Stopping decision for JUPITER

- At the first formal efficacy evaluation (Sept. 2007 with 42% of expected information accrued), the O'Brien-Fleming stopping boundary determined by means of the Lan-DeMets approach was crossed.
- DSMB determined that the evidentiary criteria specified in its charter* were not yet met and voted to continue the trial.
- At its next meeting in March 2008, the committee considered the incremental evidence, durability of effects, side effects, and impact on total mortality in its decision to recommend stopping the trial.

*Proof beyond reasonable doubt that for all, or specific types of patients, rosuvastatin is clearly indicated or contra-indicated which might reasonably be expected to influence management decisions for study subjects.
Criticisms of early stopped trials

- Incremental data on longer-term safety and efficacy, both overall and within defined subgroups, can sharpen the assessment of the risk to benefit ratio of a treatment.
- Stopping a trial early on the basis of an apparently large treatment benefit can over-estimate that benefit.*
- Some have concluded that stopping a trial early for benefit is ethically questionable†
- Others argue that trialists have an ethical responsibility to end an experiment when the main question is answered,
- And that stopping on the basis of principled and conservative guidelines yields valid treatment effects‡

Popular perspectives on stopping JUPITER

• “An independent safety-monitoring board ended the study early, saying that it was unethical to continue once it was clear that statins provided a benefit not available to the subjects on the placebo.”

• “Critics argue that shortening the trial, which was funded by a drug company, exaggerated the potential benefits and underestimated long-term harm, but the researchers strongly disagree.”

J Groopman, New Yorker, 2015
JUPITER: monitoring boundaries
JUPITER results for primary endpoint at interim analyses and final report

<table>
<thead>
<tr>
<th>Analysis date</th>
<th>Rosuvastatin</th>
<th>Placebo</th>
<th>Nominal relative rate (95% CI)†</th>
<th>Monitoring-adjusted relative rate (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 7, 2007</td>
<td>Events 81</td>
<td>Rate 0.58</td>
<td>Events 138</td>
<td>Rate 0.99</td>
</tr>
<tr>
<td>March 29, 2008</td>
<td>Events 119</td>
<td>Rate 0.63</td>
<td>Events 209</td>
<td>Rate 1.11</td>
</tr>
<tr>
<td>Increment</td>
<td>Events 38</td>
<td>Rate 0.77</td>
<td>Events 71</td>
<td>Rate 1.36</td>
</tr>
<tr>
<td>November 20, 2008</td>
<td>Events 142</td>
<td>Rate 0.77</td>
<td>Events 251</td>
<td>Rate 1.36</td>
</tr>
</tbody>
</table>

*Rates are per 100 person-years
†Nominal confidence intervals make no adjustments for sequential testing
‡Adjusted for sequential monitoring by the method of Kim & DeMets
Summary

- Perspectives on monitoring and stopping trials for efficacy have changed over time, yet decisions to stop are complex and require multiple considerations.
- Specification of criteria in a DSMB Charter, with consideration of analytic guidelines is critical.
- Decisions to stop remain controversial, particularly in industry-funded trials.
- Evaluation of potential bias due to early termination is important.