Improving Clinical Trial Design: Why and How?

PLA/SWLA Chapter Meeting
Grand Wailea Resort, Maui, HI
March 15, 2014

Eliot A. Brinton, MD, FAHA, FNLA
President, American Board of Clinical Lipidology
Director, Atheromterabolic Research
Utah Foundation for Biomedical Research
President, Utah Lipid Center
Salt Lake City
eliot.brinton@utah.edu
Speaker Disclosures

Dr. Brinton has received:

• **Research** funding: Amarin, Health Diagnostic Laboratory, Merck, Roche; Aurora Foundation; NIH

• Honoraria as **consultant/advisor**: Aegerion, Amarin, Arisaph, AstraZeneca, Atherotech, Daiichi-Sankyo, Essentialis, Genzyme, Janssen, Kowa, Merck, Novartis, Regeneron, Sanofi-Aventis, Takeda

• Honoraria as **speaker**: Amarin, Daiichi-Sankyo, Janssen, Kowa, Merck, Takeda
For good or ill, I am not an academically-trained card-carrying clinical trialist. My talk, therefore, can be subtitled:

“Musings on clinical trial design by a clinician, clinical scholar and trialist dilettante”
Talk Outline

• Why does clinical trial design matter?
• Crucial CVD Trials: case studies in RCT design and interpretation
  – WHI
  – HPS2/THRIVE
  – AIM-HIGH
  – ACCORD Lipid
  – JUPITER
  – ENHANCE
  – SHARP
  – IMPROVE-IT
  – CETP-I Trials
  – Clinical Trial evidence in 2013 ACC/AHA Guidelines

• Summary and Conclusions
Why Do Design and Interpretation of Clinical Trials Matter?

- Impact (clinical message) of any clinical trial depends on its:
  - Design,
  - Outcome, and
  - Interpretation
- Interpretation (and implementation) MUST take trial design into account
- “How does this trial apply to my patient?”
- Trials are often misdesigned and misinterpreted
- Misinterpretation can be reduced by careful trial design
Subgroup Analyses in Clinical Trials

Standard Statistical Rules
• No subgroup analyses allowed when 1° endpoint is negative in total study population
• In positive trials, any subgroup results are hypothesis generating only!

But, since RCTs are few and patients are many

My Suggested Amendments
• Subgroup analyses may be considered for clinical application when:
  – Biologically plausible and
  – Consistent between ~comparable trials
HRT and the WHI

• Observational studies show HRT benefits:
  – ↓CHD
  – ↓stroke (low-dose)
  – ↓total mortality, even
  – ↓breast-cancer mortality

• RCTs of HRT (WHI E+P, WHI E only, HERS) all showed net harm (CVD, etc.)

• Standard interpretation: HRT is “a classic example” that RCTs are always right and observational data can’t be trusted
HRT and the WHI

• Observational studies show HRT **benefits**:  
  – ↓CHD  
  – ↓stroke (low-dose)  
  – ↓total mortality, even  
  – ↓breast-cancer mortality

• RCTs of HRT (WHI E+P, WHI E only, HERS) all showed net **harm** (CVD, etc.)

• Standard interpretation: **HRT is “a classic example”** that RCTs are always right and observational data can’t be trusted

• *Alternative approach: careful review of discrepancies may →different conclusion!*
HRT and the WHI (cont.)

• Traditional explanation: observational data are misleading due to “healthy-user” bias
• Alternative explanation: RCT data are misleading due to effects of age at HRT start
• Observational studies: HRT started <60 y/o
  • WHI found:
    – HRT harmful when started >60 y/o*
    – HRT beneficial when started <60 y/o*
    – Most WHI subjects >60 y/o, so WHI showed net harm
  However
• Since ~99% of HRT starts are <60 y/o
  \[\text{WHI (as a whole) is irrelevant to clinical practice!}\]
  Only the <60 y/o subgroup is relevant but since “subgroup analyses are no good” → “Catch 22”

*Rossouw, JE. JAMA 2007;297;:1465-77.
Similar findings in DOPS subj <60 y/o: Schierbeck LL BMJ 2012 epub 9Oct
WHI Interpretation and Misinterpretation

Correct Interpretations:
• HRT is generally harmful when started (for the 1\textsuperscript{st} time) \textit{AFTER} age 60(!)
• HRT $\rightarrow$ breast cancer (if \textit{w/} MPA)

Misinterpretation:
• “HRT \textit{always} $\rightarrow$ breast cancer” (but ↓w/ E-only)
• “HRT generally dangerous” (\textit{but global benefit} seen when started < 60 y/o=clinically relevant)
• Adverse effects if \textit{started} >60 y/o => adverse effects when \textit{continued} >60 y/o? (≠biol. plaus.)
• “Stop HRT ASAP”, but
  – ↑\textit{benefit} w/ longer \textit{use in WHI},
  – ↓\textit{benefit} w/ stopping (in obs studies),
  – \textit{effects of stopping never studied} in RCT!
HPS2/THRIVE

• Study design
  – Population: 2° prevention, N=25,673
  – Rx: ERN+Laropiprant/simva vs simva only
  – Endpoints: CVD events

• Results
  – Lipid benefit ~ as expected, but
  – No ↓CVD, and
  – ↑AE’s

• Quick Conclusions:
  – “Findings are consistent with previous niacin trials”, and
  – “[W]e now know that [niacin’s] adverse side effects outweigh the benefits when used with current treatments.” (emphasis added)

HPS2/THRIVE: Baseline Lipids

- LDL-C 63 mg/dL on statin
- HDL-C 44 (no selection)
- TG 125 (no selection)

HPS2/THRIVE: Baseline Lipids

- LDL-C 63 mg/dL on statin
- HDL-C 44 (no selection)
- TG 125 (no selection)

No need for niacin!

HPS2/THRIVE: Baseline Lipids

- LDL-C 63 mg/dL on statin
- HDL-C 44 (no selection)
- TG 125 (no selection)

No benefit from niacin!

HPS2/THRIVE

- **Study design**
  - Population: 2º prevention, N=25,673
  - Rx: ERN+Laropiprant/simva vs simva only
  - Endpoints: CVD events

- **Results**
  - Lipid benefit ~ as expected, but
  - No ↓ CVD, and
  - ↑ AE’s

**Thoughtful conclusions**—niacin may be good
- *If LDL-C ≥ 58 mg/dL?*
- *If HTG/low HDL-C? (not yet tested properly)*
- *In Caucasians? (↓ CVD vs ↑ in Chinese)*
- *In long-term? (HR curves diverg. 2-4y; ~CDP)*
- *W/O laropiprant? (↑ hemor stroke & infection)*
AIM-HIGH

• “Test of HDL-raising hypothesis”¹ (vs test of niacin??)
• How to test/prove a lipid hypothesis?
  – Probably can’t be done by one trial
  – Probably can’t be done by one drug
  – Best done in retrospect from many studies with several classes of agents, for example
  – Best evidence for LDL hypothesis is from statin PLUS non-statin trials!
• AIM-HIGH “failure”—possible reasons:
  – Low-dose niacin in “placebo” arm,²
  – Excess statins/nonstatins in “placebo” arm²
  – Lack of focus on low HDL-C + HTG pts³

¹. AIM-HIGH Investigators, Amer Heart J 2011;161;471-7.
ACCORD-Lipid

Design
- Pop: DM2, TG <750/400, LDL-C 60-180, HDL-C <55/50; N=5518
- Rx: Fenofibrate 145 mg/d vs pbo on bkg statin
- Endpoints: CVD

Results and Interpretation
- No ↓CVD in overall study population, but
- ↓CVD in HTG/low HDL-C (pre-specified)
- “Fenofibrate no good” (→ subgroup “Catch 22”)
- Why were most pts w/o HTG/low HDL-C? (“Didn’t want to burden ACCORD subj. recruit.”)
- Does fenofibrate →↓CVD in patients w/ a lipid indication? —seems likely but no proof yet!
- VA-FIT needed (test CVD eff. feno in TG >200)

Ginsberg, HN. NEJM 2010 epub March 14.
JUPITER

Design
• Pop: 1\textsuperscript{o} prev, hsCRP >2.0, LDL-C<130, ↑CVD risk by age (>50/>60); N=17,802
• Rx: Rosuva 20mg/d vs pbo, 1.9 y median f/u
• Endpoint: major CVD events
• Results: ↓CVD (HR 0.56)

Good was accomplished:
• 1\textsuperscript{st} large test of rosuvastatin CVD effects
• New statin indication (medium-risk 1\textsuperscript{o} prev)

But results tended to be misinterpreted:
• “hsCRP → ~50% ↓CVD” (but rosuva Rx→ bene)
• “hsCRP ID’s pts needing statins” (nl CRP excl.)
• “hsCRP measures Rx benefit” (only vs LDL-C)

Ridker, PM. NEJM 2008;359:2195-207.
ENHANCE

• Study design
  – Population: HeFH, lots of prior Rx, N=720
  – Rx: Simva monoRx vs Simva + ezet
  – Endpoint: CIMT serially over 2 years

• Results and interpretation
  – Nice stepwise lipid effect, but
  – No CIMT difference between study arms, so
  – “Ezetimibe has no CVD benefit”, but
  – No CIMT benefit w/ simva monoRx, and
  – CIMT ≠ CVD events (“surrogate endpt.”)
  – Trial is of limited clinical utility

SHARP

Study design
• Pop: renal insuff. (creat >1.7/1.5), N=9270
• Rx: Eze/simva vs pbo (no simva-only arm!)
• Endpoints: CVD events

Results and interpretation
• Lipid benefit ~ as expected
• CVD benefit (mainly in pre-dialysis pts)
• Ezet/simva works in CKD, but how much benefit is from **statin vs added ezet**. ???
• ∴ Trial is of **limited clinical utility**

IMPROVE-IT

• **Best** uses of ezetimibe:
  – LDL-C/Non-HDL-C goal non-attainment with statin monotherapy
  – Statin intolerance
  – Statin phobia

• **Marginal** use of ezetimibe:
  – Patients with extremely well controlled LDL-C/Non-HDL-C on statin monotherapy

IMPROVE-IT

**Best** uses of ezetimibe:
- LDL-C/Non-HDL-C goal non-attainment with statin monotherapy
- Statin intolerance
- Statin phobia

**Marginal** use of ezetimibe:
- Patients with extremely well controlled LDL-C/Non-HDL-C on statin monotherapy

*IMPROVE-IT study population*

Is an LDL-C of ~52 mg/dL better than ~66? Do I care to know?

CETP-I: Torcetrapib

Overall Design and Results
Rx: Atorva + torcet vs atorva alone
Lipid Δ: HDL-C ↑53-72%; LDL-C ↓19-25%
BP Δ: ↑2.8-5.4 mmHg

Specific Trial Results
• ILLUSTRATE (IVUS)
  – Neutral (% vol) to favorable (abs vol)
• RADIANCE 1 & 2 (CIMT)
  – Neutral (max) to adverse (mean)
• ILLUMINATE
  – ↑25% CVD, ↑58% tot mort

Quick conclusions:
• “HDL-raising is worthless”, and/or
• “CETP-I produces dysfunctional HDL”

ILLUMINATE; Barter, PJ. NEJM 2007;357:2109-22.
CETP-I: Torcetrapib

**Overall Design and Results**

Rx: Atorva + torcet vs atorva alone  
Lipid $\Delta$: HDL-C $\uparrow$ 53-72%; LDL-C $\downarrow$ 19-25%  
BP $\Delta$: $\uparrow$ 2.8-5.4 mmHg

**Specific Trial Results**

- **ILLUSTRATE (IVUS)**
  - Neutral (% vol) to favorable (abs vol)
- **RADIANCE 1 & 2 (CIMT)**
  - Neutral (max) to adverse (mean)
- **ILLUMINATE**
  - $\uparrow$ 25% CVD, $\uparrow$ 58% tot mort
  - Harm inverse to $\Delta$ HDL-C (HDL still protective)
  - Harm worse w/ $\downarrow$ K+, etc. (hyperlaldosteronism)

**Thoughtful conclusions:**

- Athero endpoints can mislead
- HDL *not* dysfunctional w/ CETP-I
- Off-target harms $>$ lipid benefits
CETP-I: Dalcetrapib w/o ↓CVD (dal-OUTCOMES)

Why no ↓CVD?
- Favorable Δ 30% ↑HDL-C (inverse v CVD)
- Adverse Δ’s
  - ↑BP 0.6 mmHg;
  - ↑hsCRP 0.2 mg/L (both p<0.0001)

Off-target harm ≈ Lipid benefit?

Possible hyperaldo & ↑inflam with anacetrapib?
Few/no data for evacetrapib.

Schwartz, GG. NEJM, epub Nov. 5, 2013
**Why Have CETP-Inhibitors Failed to ↓CVD (so far)?**

<table>
<thead>
<tr>
<th>CETP-I Agent</th>
<th>↑HDL-C</th>
<th>HDL-C →↓CVD</th>
<th>↓LDL-C</th>
<th>↓Lp(a)</th>
<th>↑Aldost. (↑BP etc.)</th>
<th>↑CRP</th>
<th>△ CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torcetrapib¹</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
<td>?</td>
<td>++++</td>
<td>0?</td>
<td>Adverse</td>
</tr>
<tr>
<td>Dalcetrapib²</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>?</td>
<td>++</td>
<td>0⁶ to +++?</td>
<td>Neutral</td>
</tr>
<tr>
<td>Anacetrapib³</td>
<td>++++</td>
<td>?</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Evacetrapib⁴</td>
<td>++++</td>
<td>?</td>
<td>++</td>
<td>?</td>
<td>-⁵</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

(Also possible beneficial CVD effect of ↓glucose w/ torcetrapib & anacetrapib.)

**Balance of benefits & harms w/ anacetrapib & evacetrapib (net CVD effect) is unknown (subject of ongoing RCTs)**

5. Cao, G. *JLR* 2011 52(12)2169-76.
New/Ongoing Trials With Clinically Relevant Design

**REDUCE-IT**
- Testing CVD effects of omega-3 (pure EPA) in pts with ~TG 200-500 mg/dL

**VA-FIT**
- Testing CVD effects of fenofibrate in patients with ~TG 200-500 mg/dL

*First studies ever to test TG-lowering meds in high TG subjects!!?!!*
Trial Design/Interpretation Issues in 2013 ACC/AHA Cholesterol Guidelines

- NHLBI decision (~5 y ago)
  - Focus only on highest quality data (multi RCTs, RCT-meta-analyses)
  - Exclude ~all other evidence, on which all other guidelines (ATP I-III, IAS, ESC, Canadian) are/have been based (+ single RCTs, biological & observational data, expert opinion)

- Δ evidence rules → Δ guidelines (no real change in data)

- No RCTs re: LDL-C goals → no goals
  Not from RCTs proving goals are no good!

Stone, NJ. Circulation 2013 epub 12 November
Clinical Trial Design and Interpretation: Bottom Line

- In trial design, ask clinically relevant questions, using care to:
  - Select clinically relevant patients
  - Compare to relevant control treatment
    - Degree of Rx (don’t over treat controls)
    - Type of Rx (use relevant comparators)
- In trial interpretation, avoid:
  - Over-reliance on overall results in heterogeneous study populations
- Absence of proof ≠ proof of absence