Interpreting Composite Endpoints in Cardiovascular Clinical Trials

Concepts and Controversies

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Disclosure Statement

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◆ **Research Grants**
  - Boehringer Ingelheim
  - sanofi aventis
  - Merck
  - Astra Zeneca
  - CSL

◆ **Consultant / Speaker**
  - Merck
  - Bayer

◆ **Data & Safety Monitoring Boards**
  - Eli Lilly
  - Mast Theraputics

Detailed financial disclosure at [http://www.vigour.ualberta.ca](http://www.vigour.ualberta.ca)
Overview

- Challenges for CV clinical trials
- Assessment of current approaches
- A future path & new options
Challenges for Clinical CV Trials

- Rich background evidence-based Rx
- Declining morbidity & mortality
- Shrinking pipeline (vs Oncology for e.g.)
- Increased regulatory complexity
- Uncertain R.O.I. for investigators
- Need for larger samples driving up costs
- 2 billion $ to bring a drug to market 2013
- Industry mergers / consolidation
- Declining R & D investment
Uncertainties in Clinical Trial End Points

- Hard vs soft endpoints
- Patient reported e.g. angina, Funct Class
- MD determined e.g. revasc, LOS vs core lab adjudication e.g. ECG
- Fidelity & alignment with primary question
- Blinded vs. open
- Local vs. core labs e.g. MI definition
What Endpoints Should I Choose for my Clinical Trial?
The future of clinical trials in secondary prevention after acute coronary syndromes

Héctor Bueno1*, Paul W. Armstrong2, Martin J. Buxton3, Nicolas Danchin4, Jacobus Lubsen5, Edmond Roland6, Freek W. Verheugt7, Andrew Zalewski8, Neville Jackson9, Michel Komajda10, and Ph Gabriel Steg11, on behalf of the Cardiovascular Round Table Clinical Trials ThinkTank participants†

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Introduction

Randomized clinical trials (RCTs) are the gold standard for building evidence. However, the strength of evidence in cardiovascular disease guidelines is not keeping pace with the number of emerging recommendations,1 perhaps reflecting the growing difficulties in developing adequately powered RCTs. In the context of secondary prevention after acute coronary syndromes (ACS), the increase in sample size needed to establish benefit, the rising costs, and the growing complexity of the regulatory environment and study logistics are challenging the development of new therapies.

In response to these concerns, the European Society of Cardiology (ESC) convened an ad hoc meeting in May 2009. This paper summarizes the discussions and offers suggestions for improvement (Table 1), which may complement previous proposals.2 [Note: the ideas presented are those of the individual participants (listed in the Appendix) and do not reflect the ideas of the participating bodies].

Basic knowledge

In spite of major advances, our understanding of the pathophysiology of coronary atherosclerosis progression and triggers of recurrent thrombotic events after ACS remains limited. To enhance therapeutic development, a clearer picture of coronary atherothrombosis is required. For that, large collaborative consortia between Pharma and academia focused on pathophysiology, genetic epidemiology, new biomarkers, and other intermediate measurements, as well as clinical research on traditional outcomes are needed to better understand the natural history of coronary artery disease. The identification of new pathways and therapeutic targets, as well as the genetic, phenotypic, or behavioural causes underlying the wide individual variations in responses to therapies, particularly antithrombotic treatments should be prioritized. Traditional and new ways of research will be essential to achieve these objectives (Table 1).

Better ways are also needed to identify patients at high risk for coronary or other vascular recurrences as well as the individual response to treatment perhaps through the emergence of ‘personalized medicine’. Also, more attention should be devoted to the subpopulations whose responses are far from the ‘mean’ responses. The ‘outliers’ are usually diluted in the overall analyses and thus neglected, but may offer keys for interpretation of both atherothrombosis pathophysiology and drug response. Several approaches can be considered, including matching treatments to risk identified by selected phenotypic characteristics (e.g. ACS patients with diabetes, chronic kidney disease, or polyvascular disease), upstream pre-treatment biomarkers (or imaging), on-therapy biomarkers (e.g. response of targets to therapies, pharmacodynamic testing, such as bedside measures of platelet aggregation), or pharmacogenomics, which may help predict response to therapy.

Patient selection

Randomized clinical trial populations should reflect the patients who will ultimately receive the study treatment in practice.
Enhancing impact

- ‘Enrichment’ recruit high risk pts (elderly, diabetic, chronic kidney disease)
- Identify/ measure markers that predict individual response e.g. ischemic risk region
- Improve external validity: reduce regional variations care processes / background Rx
- Contemporaneous log similar patients; integrate with registries

Bueno H et al Eur Heart J. 2010
Refining Methods

✦ New creative designs: i.e. ‘intention-to-continue’

✦ New or improved endpoints:
  • # days out of hospital without symptoms
  • Better definition, pre-specify weighing composite outcomes
  • Establish reliable surrogates

✦ Focus on different / unconventional outcomes:
  • Reducing side-effects
  • Quality of life/ return to work
  • Economic evaluation

✦ Collection of all data instead of just first event

✦ Strategies to replace old EBT’s instead of adding new ones
“If a single primary variable cannot be selected from multiple measurements associated with the primary objective, another useful strategy is to integrate or combine the multiple measurements into a single or ‘composite’ variable, using a predefined algorithm.

. . This approach addresses the multiplicity problem without requiring adjustment to the type 1 error.”

Composite Endpoints in Clinical Trials

There's a right way and a wrong way to boost the statistical sensitivity of this type of clinical studies.

By Sarah C.P. Williams | July 1, 2016
“Composite outcome components are often unreasonably combined inconsistently defined and inadequately reported”

Cordoba et al BMJ 2010
Composite Outcomes: Challenges

♦ Declining mortality & rising costs clinical trials places new priority on efficient use of all patient outcomes

♦ Treatment effect may vary amongst components

♦ Not all events are created equal:
  • Traditional time-to-event analysis assigns equal weight to whatever first event within a composite
  • That first event may not be the patient’s only event
  • Yet TTFE method only captures first event

Armstrong et al AHJ 2011
Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction

The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT-3) Investigators

Summary

Background Current fibrinolytic therapies fail to achieve optimum reperfusion in many patients. Low-molecular-weight heparins and platelet glycoprotein IIb/IIIa inhibitors have shown the potential to improve pharmacological reperfusion.

Introduction Tenecteplase—a genetically engineered variant of alteplase—has provided a new standard of fibrinolytic therapy by virtue of its equivalent efficacy with regard to 30-day mortality, its reduced propensity for systemic bleeding complications, and its simple administration as a single dose.

Interpretation The tenecteplase plus enoxaparin or abciximab regimens studied here reduce the frequency of ischaemic complications of an acute myocardial infarction. In light of its ease of administration, tenecteplase plus enoxaparin seems to be an attractive alternative reperfusion regimen that warrants further study.

Findings There were significantly fewer efficacy endpoints in the enoxaparin and abciximab groups than in the unfractionated heparin group: 233/2037 (11.4%) versus 315/2038 (15.4%; relative risk 0.74 [95% CI 0.63-0.87], p=0.0002) for enoxaparin, and 223/2017 (11.1%) versus 315/2038 (15.4%; 0.72 [0.61-0.84], p=0.0001) for abciximab. The same was true for the efficacy plus safety endpoint: 280/2037 (13.7%) versus 347/2036 (17.0%; 0.81 [0.70-0.93], p=0.0037) for enoxaparin, and 287/2016 (14.2%) versus 347/2036 (17.0%; 0.84 [0.72-0.96], p=0.01416) for abciximab.

Interpretation The tenecteplase plus enoxaparin or abciximab regimens studied here reduce the frequency of ischaemic complications of an acute myocardial infarction. In light of its ease of administration, tenecteplase plus enoxaparin seems to be an attractive alternative reperfusion regimen that warrants further study.

Lancet 2001; 358: 605-13
1. There are four events to consider in terms of **efficacy at 30 days**

2. Please allocate **all** twenty points amongst the four efficacy events based on your opinion of their relative severity, starting with death.

<table>
<thead>
<tr>
<th>Event</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>10</td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>5</td>
</tr>
<tr>
<td>CHF</td>
<td>3</td>
</tr>
<tr>
<td>Re-MI</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

n=23 with n=10 external validation  

Armstrong *et al* AHJ 2011
# Weighted Efficacy Composite (applied to ASSENT 3)

<table>
<thead>
<tr>
<th>Rx</th>
<th>Death</th>
<th>Shock</th>
<th>CHF</th>
<th>Re-MI</th>
<th>Traditional (first)</th>
<th>Weighted</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Any event (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UH</td>
<td>2.9/6.0</td>
<td>2.7/3.7</td>
<td>2.5/5.9</td>
<td>4.1/4.3</td>
<td>12.2*</td>
<td>5.8</td>
<td>7.9</td>
</tr>
<tr>
<td>Enox</td>
<td>2.7/5.3</td>
<td>2.8/3.2</td>
<td>2.4/5.6</td>
<td>2.5/2.6</td>
<td>10.4</td>
<td>5.3</td>
<td>7.0</td>
</tr>
<tr>
<td>Abx</td>
<td>3.2/6.6</td>
<td>2.9/3.6</td>
<td>2.3/5.7</td>
<td>2.2/2.2</td>
<td>10.6</td>
<td>5.8</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Armstrong et al AHJ 2011
## Weighted Efficacy Composite

<table>
<thead>
<tr>
<th>Rx</th>
<th>Individual Pt Event Rates</th>
<th>Composite Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First /Any event (%)</td>
<td>Traditional (first)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weighted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>First</td>
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<td>UH</td>
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<tr>
<td></td>
<td>CHF</td>
<td>2.5/5.9</td>
</tr>
<tr>
<td></td>
<td>Re-MI</td>
<td>4.1/4.3</td>
</tr>
</tbody>
</table>

Armstrong et al AHJ 2011
Traditional composite shows disadvantage of UH ($p<0.05$) relative to other Rx

Using all (weighted) events a trend advantage appears for Enox arm ($p=0.18$) based on type & total number of events

Composite components: Death, shock HF, re-MI

Armstrong et al AHJ 2011
Weighted Composite: Implications

♦ This approach adds value to traditional techniques by:
  • Incorporating the *differential severity* of events
  • Including *all events* from a single patient

♦ Better ascertainment *relative value* differing efficacy endpts

♦ Integrating efficacy & safety endpoints provides a more comprehensive Rx assessment i.e. tipping point

♦ Future trial designs should consider this approach

Armstrong *et al* AHJ 2011
Sabermetrics

- Empirical analysis baseball stats
- Batting average ≠ runs scored
- Runs win ball games
- Hence on base % is key: distinguish between hits & assess value i.e. OBS (on base slugging)
- Other stats include weighted on-base average
Lessons from Moneyball

- If you can’t win, shift the game culture
- Break biases / embrace sabermetrics
- Business of baseball is *buying wins and runs*
- Walks are better than strikeouts
- Play smart & get on base
- Not all players or hits are the same
- Use *all of your assets appropriately*
**Table 2. Efficacy Outcomes at 30 Months.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age &lt;75 Years</th>
<th>Overall Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prasugrel (N=3620)</td>
<td>Clopidogrel (N=3623)</td>
</tr>
<tr>
<td>Patients with Event at 30 Mo</td>
<td>no. (%)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Cardiovascular death, myocardial infarction, or stroke</td>
<td>364 (10.1)</td>
<td>(12.2–15.6)</td>
</tr>
</tbody>
</table>
Applying novel methods to assess clinical outcomes: insights from the TRILOGY ACS trial

Jeffrey A. Bakal¹, Matthew T. Roe², E. Magnus Ohman², Shaun G. Goodman¹,³, Keith A.A. Fox⁴, Yinggan Zheng¹, Cynthia M. Westerhout¹, Judith S. Hochman⁵, Yuliya Lokhnygina², Eileen B. Brown⁶, and Paul W. Armstrong¹∗

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Aims
Several methods provide new insights into understanding clinical trial composite endpoints, using both conventional and novel methods. The TRILOGY ACS trial is used as a contemporary example to prospectively compare these methods side by side.
“Let’s Weigh the weights”: MI

- **Mild** = small peri-procedural <5 UNLTrop or <2CKMB
- **Moderate** = spontaneous: 5-30XUNL Trop; 2-10X CKMB
- **Severe** = Large with major ST shift, substantial biomarker rise and LV dysfunction

Bakal et al EHJ 2015
Weighting the weights: Stroke

- **Mild**: TIA with field deficit
- **Moderate**: significant neurologic deficit with recovery in < 3mos
- **Severe**: severe disabling permanent hemiplegia

Bakal et al EHJ 2015
Applying novel methods to assess clinical outcomes: insights from the TRILOGY ACS trial

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Composite Endpoints in Clinical Trials

There's a right way and a wrong way to boost the statistical sensitivity of this type of clinical studies.

By Sarah C.P. Williams | July 1, 2016
Computing Methods for Composite Clinical Endpoints in Unprotected Left Main Coronary Artery Revascularization
A Post Hoc Analysis of the DELTA Registry

Davide Capodanno, MD, PaD, Giuseppe Gargiuolo, MD, Sergio Buccheri, MD, Alaide Chieffo, MD, Emanuele Meliga, MD, Azem Latib, MD, Seung-Jung Park, MD, Yoshinobu Onuma, MD, Piera Capranzano, MD, Marco Valgimigli, MD, Inga Narbute, MD, Raj R. Makkar, MD, Igor F. Palacios, MD, Young-Hak Kim, MD, Pewel E. Buszman, MD, Tarun Chakravarty, MD, Imad Sheiban, MD, Roxana Mehran, MD, Christoph Naber, MD, Ronan Margery, MD, Arvind Agnihotri, MD, Sebastiano Marra, MD, Martin B. Leon, MD, Jeffrey W. Moses, MD, Jean Fajadet, MD, Thierry Lefèvre, MD, Marie-Claude Morice, MD, Andrejs Erglis, MD, Ottavio Alfieri, MD, Patrick W. Serruys, MD, Antonio Colombo, MD, Corrado Tamburino, MD, on behalf of the DELTA Investigators

ABSTRACT

OBJECTIVES The study sought to investigate the impact of different computing methods for composite endpoints other than time-to-event (TTE) statistics in a large, multicenter registry of unprotected left main coronary artery (ULMCA) disease.

BACKGROUND TTE statistics for composite outcome measures used in ULMCA studies consider only the first event, and all the contributory outcomes are handled as if of equal importance.

METHODS The TTE, Andersen-Gill, win ratio (WR), competing risk, and weighted composite endpoint (WCE) computing methods were applied to ULMCA patients revascularized by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) at 14 international centers.

RESULTS At a median follow-up of 1,295 days (interquartile range: 928 to 1,713 days), all analyses showed no difference in combinations of death, myocardial infarction, and cerebrovascular accident between PCI and CABG. When target vessel revascularization was incorporated in the composite endpoint, the TTE (p = 0.03), Andersen-Gill (p = 0.04), WR (p = 0.025), and competing risk (p < 0.001) computing methods showed CABG to be significantly superior to PCI in the analysis of 1,204 propensity-matched patients, whereas incorporating the clinical relevance of the component endpoints using WCE resulted in marked attenuation of the treatment effect of CABG, with loss of significance for the difference between revascularization strategies (p = 0.10).

CONCLUSIONS In a large study of ULMCA revascularization, incorporating the clinical relevance of the individual outcomes resulted in sensibly different findings as compared with the conventional TTE approach. In particular, using the WCE computing method, PCI and CABG were no longer significantly different with respect to the composite of death, myocardial infarction, cerebrovascular accident, or target vessel revascularization at a median of 3 years.

(J Am Coll Cardiol Intv 2016;9:2280-8) © 2016 by the American College of Cardiology Foundation.
Analysis Methods for Composite Endpoint Evaluation

- Used TTFE as reference to assess 4 different strategies
  - Anderson-Gill,
  - Win-ratio (WR),
  - Competing risk
  - Weighted composite endpoint (WCE)

Capadanno et al JINT 2016
Analysis of Composite Endpoints: TTFE

- Traditional analysis compares the time to first event using standard survival analysis.
Andersen-Gill: Recurrent (All) Events

Sample Patients

A

B

C

Observation Time

X

Used

Re-MI

CHF

LTFU

Death

Death
Win-Ratio

*A Priori* Ranking: Death, CHF, re-MI

No. of Wins versus Losses

*Step 1: Evaluate pairs on Death*

Matched or Unmatched Patients

*Step 2: Evaluate pairs on CHF*

Observation Time
**Weighted Composite Endpoint**

*A Priori* Weighting: Death (1.0), CHF (0.3), re-MI (0.2)
Event Survival Curves in Propensity Matched Cohort (n=602)

A. Death/MI/CVA Time to Event

B. MACCE Time to Event

C. Death/MI/CVA WCE

D. MACCE WCE

Log-rank p-value = 0.906

Log-rank p-value = 0.003

Log-rank p-value = 0.798

Log-rank p-value = 0.102

Capodanno et al. JCIN 2016
Analysis Methods for Composite Endpoint Evaluation

- Anderson-Gill, WR, or Competing Risk methods did not differ from TTE analysis
- Repeat revasc was major contributor to CABG superiority vs PCI
- “Incorporating the clinical relevance of individual outcomes......resulted in a more sensible deviation” from results obtained with conventional TTE analysis
Overview Clinical Trial Endpoints

- Challenges for CV clinical trials
- Assessment of current approaches
- A future path & new options
Overview Clinical Trial Endpoints

- Future Challenges for CV clinical trials
- Assessment of current approaches
- A future path & new options
The best way to predict the future is to invent it

Alan Kay