# Endpoints in Cardiovascular Trials

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**This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.**

# Learning Objectives

- Discuss efficacy endpoints
- Describe frequently used endpoints in cardiovascular trials
- Define and discuss surrogate endpoints and biomarkers
- Describe the basis for traditional approval and accelerated approval

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

# 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials

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**(J Am Coll Cardiol 2018;71:1021-34 + Appendix)**

# Definitions - 1

- Cardiovascular Death
- Non-Cardiovascular Death
- Undetermined Cause of Death
- Myocardial Infarction
- Hospitalization for Unstable Angina

# Definitions - 2

- Stroke
- Interventional Cardiology Definitions
- Peripheral Arterial Revascularization Procedure
- Heart Failure Requiring Hospitalization
- Stent Thrombosis

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ACC/AHA CLINICAL DATA STANDARDS

# 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards)

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*The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the U.S. Food and Drug Administration.

# Efficacy Endpoints

# What is an Efficacy Endpoint?

- A measure designed to reflect the intended effects of a drug

**Guidance for industry *Multiple Endpoints in Clinical Trials* (October 2022)**

# Efficacy Endpoints

- Include
  - assessments of clinical events (mortality, myocardial infarction)
  - symptoms (pain, dyspnea)
  - measures of function (e.g., ability to exercise)
  - surrogate endpoints

# Efficacy Endpoints

- Primary endpoint
- Key secondary endpoint
- Other secondary endpoints
- Exploratory endpoints

**Need to control the Type I error probability**

# Efficacy Endpoints

- Single
- Multiple

# Types of Multiple Endpoints

- Co-Primary Endpoints
- Several Primary Endpoints
- Composite Endpoints
- Multi-Component Endpoints
- Clinically Critical Endpoints Too Infrequent for Use as a Primary Endpoint

# Composite Endpoints

- Often used in cardiovascular trials
  - major adverse cardiovascular events (MACE)
- Use in a trial when
  - more than one clinical outcome is important
  - all outcomes are expected to be affected by treatment
- Defined as the first occurrence of any one of the specified components (time-to-event analysis)

# Clinically Critical Endpoints Too Infrequent for Use as a Primary Endpoint

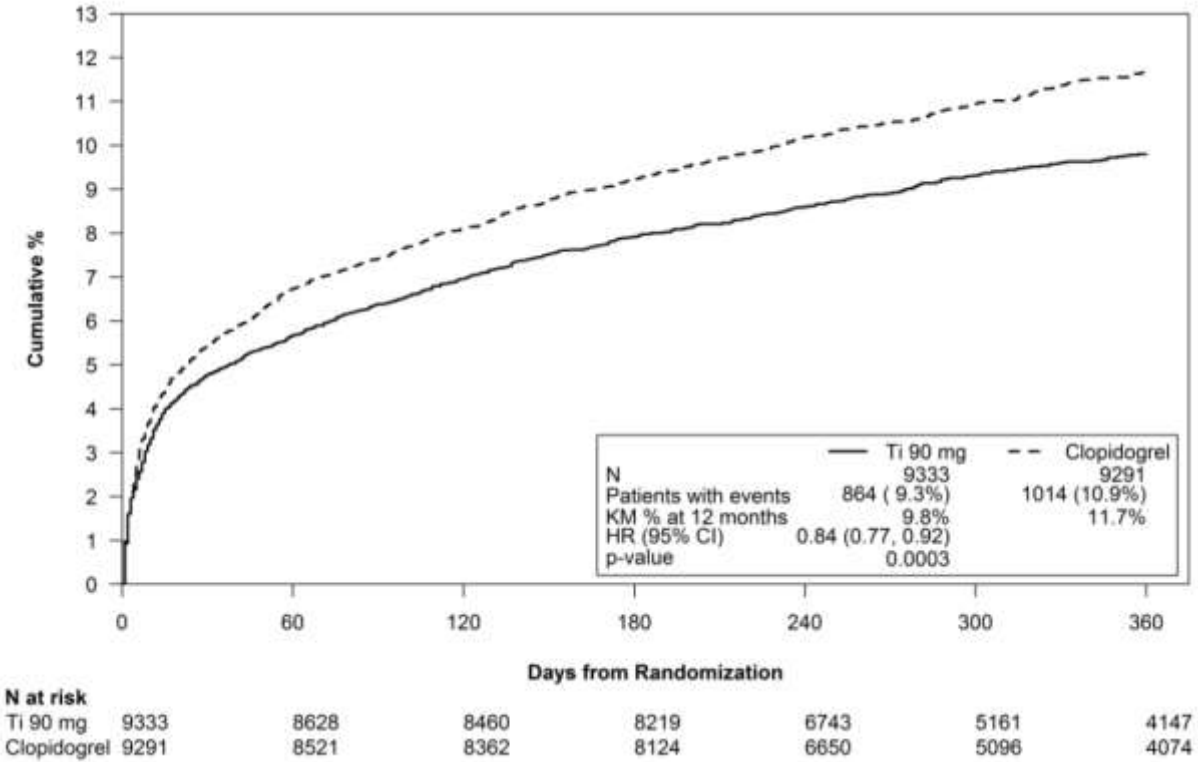
- Examples
  - mortality
  - major morbidity events (e.g., stroke, fracture, pulmonary exacerbation)

**Include the event in a composite endpoint (primary endpoint) and as a planned secondary endpoint**

# PLATO

| | BRILINTA* N=9333 | Clopidogrel N=9291 | Hazard Ratio (95% CI) | *p*-value |
|---|---|---|---|---|
| | Events / 1000 patient years | Events / 1000 patient years | | |
| Composite of CV death, MI, or stroke | 111 | 131 | 0.84 (0.77, 0.92) | 0.0003 |
| CV death | 32 | 43 | 0.74 | |
| Non-fatal MI | 64 | 76 | 0.84 | |
| Non-fatal stroke | 15 | 12 | 1.24 | |
| Secondary endpoints† | | | | |
| CV death | 45 | 57 | 0.79 (0.69, 0.91) | 0.0013 |
| MI‡ | 65 | 76 | 0.84 (0.75, 0.95) | 0.0045 |
| Stroke‡ | 16 | 14 | 1.17 (0.91, 1.52) | 0.22 |
| All-cause mortality | 51 | 65 | 0.78 (0.69, 0.89) | 0.0003 |

# PLATO – Time to First Occurrence of CV death, MI, or stroke



# Clinical Considerations

- Endpoint selection
- Population
- Timing of the endpoint / study duration

# Event Analyses - 1

- Time to Event Analyses
  - Cardiovascular trials
    - MACE
  - Oncology trials
    - Progression free survival
    - Overall survival

# Event Analyses - 2

- Change from baseline
  - blood pressure
  - depression scores
  - HbA1c
  - 6 minute walk distance (6MWD)
- Clinically meaningful change
  - patient focused drug development

# Attributes of a Quality Clinical Trial

- Excellent follow-up
  - minimize loss to follow-up
  - no missing data
- Withdrawal of consent and follow-up options
  - follow-up visits
  - telephone contacts
  - medical records checks

# Examples of Endpoints in Cardiovascular Trials

| Population | Primary Endpoint |
| --- | --- |
| Acute Coronary Syndrome | Major Adverse Cardiovascular Events (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) |
| Heart Failure | Cardiovascular death, hospitalization for heart failure or urgent heart failure visit |
| Nonvalvular Atrial Fibrillation | Stroke and systemic embolism |

| Population | Primary Endpoint |
| --- | --- |
| Pulmonary Hypertension | • Time to first adjudicated clinical worsening (morbidity or mortality) event<br>  ○ Death (all causes)<br>  ○ Hospitalization due to worsening pulmonary arterial hypertension (PAH)<br>  ○ Initiation of an inhaled or infused prostacyclin or epoprostenol sodium for the treatment of worsening PAH<br>  ○ Disease progression<br>  ○ Unsatisfactory long-term clinical response<br>• 6-Minute Walk Test (6MWT) |
| | |

# Surrogate Endpoints

# What is a Surrogate Endpoint?

"A surrogate endpoint, or 'marker,' is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy."

**New drug, antibiotic and biological drug product regulations: accelerated approval. Proposed Rule. 57 Federal Register 13234-13242 (1992).**

# Validated Surrogate Endpoints

- Blood pressure
- HbA1c
- LDL cholesterol

# Accelerated Approval (Subpart H)

- Based on an effect on a surrogate endpoint or an intermediate clinical endpoint “that is reasonably likely to predict a drug’s clinical benefit.”
- Conditions
  - serious or life-threatening illness
  - meaningful advantage over available therapies
  - post-approval studies are required to verify and describe the drug’s clinical benefit
  - expedited withdrawal

# Pitfalls of Surrogate Endpoints*

- The surrogate may not be valid
- The drug may have unexpected unfavorable effects leading to a net unfavorable outcome
- Many times, it is unclear what magnitude of change in the surrogate endpoint is required to achieve a particular magnitude of clinical benefit
- Balancing risk and benefit is unclear

# Surrogate Endpoints*

**Reliance on a surrogate is usually an alternative to a large outcome trial (not performed until phase 4)**

*Temple, R. Are surrogate markers adequate to assess cardiovascular disease drugs? *JAMA*.1999;282(8):789-795.

# What is Required to Validate a Surrogate Endpoint?

- Understand the pathophysiology
- Identify a marker (several drugs working by different mechanisms)
- Validate the marker
- Demonstrate the marker's association with clinical outcome

# Hypertension as a Surrogate Endpoint

| | Hypertension |
|---|---|
| Pathophysiologic Concept | X |
| Clinical Endpoint | X |
| Epidemiological Data | Elevated blood pressure increases adverse outcomes (stroke, myocardial infarction, heart failure, renal failure) |
| Intervention | Decreasing blood pressure results in decreased adverse outcomes (e.g., diuretics, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, etc.) |
| Assessment | Physical Examination |

# Biomarkers

# BEST* Definition of Biomarker

- "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is **not** an assessment of how a patient feels, functions, or survives."

***The Biomarkers, EndpointS, and other Tools (BEST) Resource Glossary**

**(FDA-NIH Biomarker Working Group)**

# Sacubitril and Valsartan

- **Pediatric Indication** for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.

# Basis for Traditional Approval and Accelerated Approval

# Traditional Approval

- Based on
  - clinical endpoints that reflect patient benefits (i.e., how patients feel, function, or survive)

    **OR**

  - validated surrogate endpoints (i.e., those that have been shown to predict a specific clinical benefit)

# Accelerated Approval

- Based on a demonstrated effect on a
  - surrogate endpoint that is reasonably likely to predict a clinical benefit but where there are not sufficient data to show that it is a validated surrogate endpoint

    **OR**

  - Intermediate clinical endpoint that is reasonably likely to predict an effect on irreversible morbidity or mortality (IMM) or other clinical benefit

# Summary - 1

- An efficacy endpoint is a measure designed to reflect the intended effects of a drug.
- Efficacy endpoints include
  - assessments of clinical events
  - symptoms
  - measures of function
  - surrogate endpoints

# Summary - 2

- A surrogate endpoint is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy.”
- Accelerated Approval is based on an effect on a surrogate endpoint or an intermediate clinical endpoint “that is reasonably likely to predict a drug’s clinical benefit.”

# Summary - 3

- A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.
- A biomarker is **not** an assessment of how a patient feels, functions, or survives.

# Resources - 1

- Guidance for Industry *Multiple Endpoints in Clinical Trials* (October 2022)
- Draft Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)
- Guidance for Industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014)

# Resources - 2

- Draft Guidance for Industry *Treatment for Heart Failure: Endpoints for Drug Development* (June 2019)
- Guidance for Industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016)
- Drugs @FDA

# Challenge Question #1

**Validated surrogate endpoints include all of the following except:**

A. LDL cholesterol

B. Blood pressure

C. Vulnerable plaque

D. HbA1c

# Challenge Question #2

**Which of the following statements is FALSE?**

**A surrogate endpoint is**

A. a laboratory measurement or physical sign

B. used in therapeutic trials as a substitute for a clinically meaningful endpoint

C. a direct measure of how a patient feels, functions, or survives

D. not expected to predict the effect of the therapy

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# Questions?

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