



Primary Endpoint Definition and hot to not miss MACE

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Primary Endpoint Definition

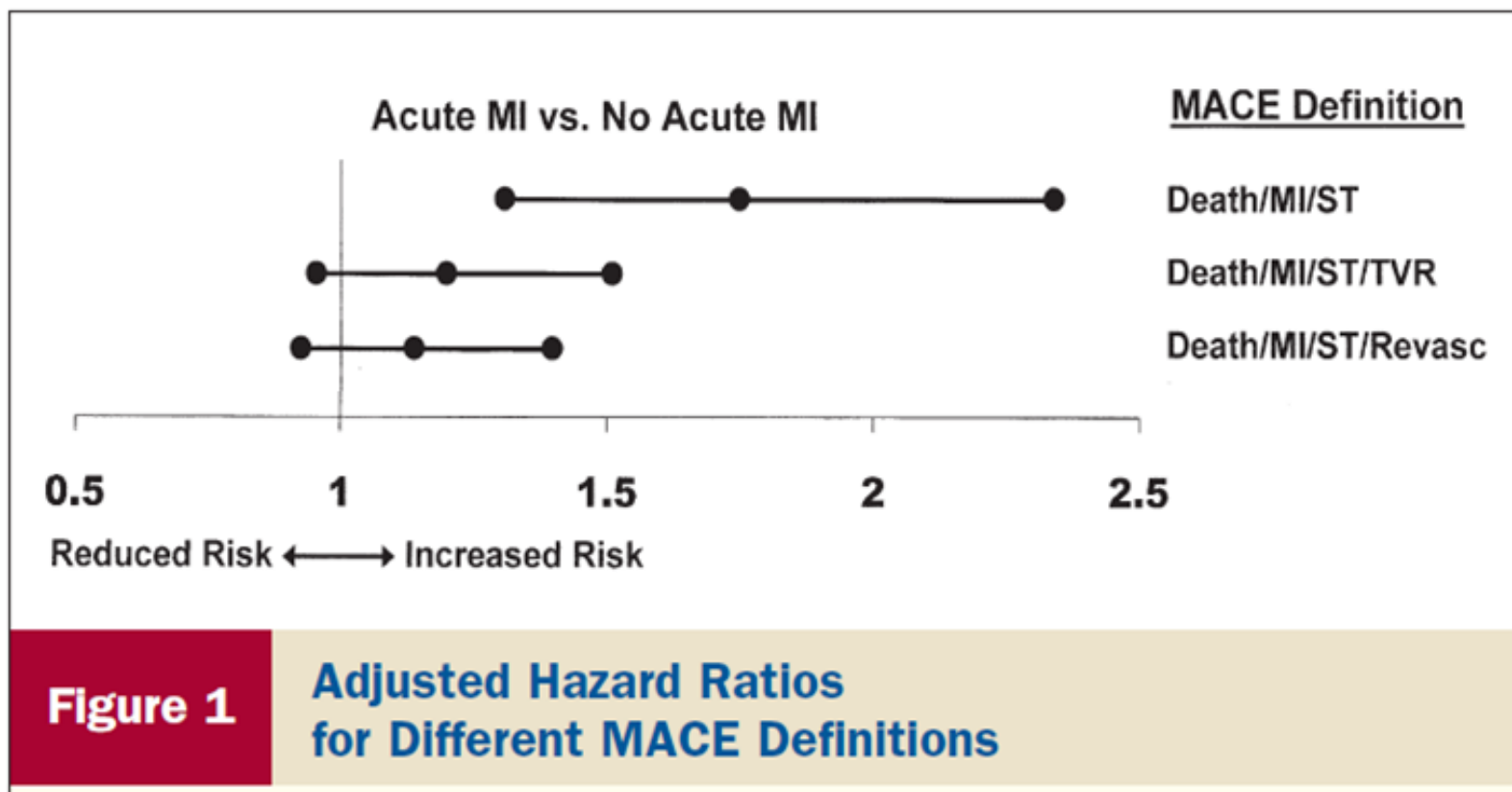
Major Adverse Cardiovascular Events

- » Most commonly used composite endpoint

But

- » No universal definition
- » Substantially different results and conclusions [1]

Primary Endpoint Definition



[1] Kip KE et al., J Am Coll Cardiol, 2008

MACE

Study Protocol:

- » Nonfatal myocardial infarction
- » Nonfatal stroke
- » Cardiovascular death

Nonfatal Myocardial Infarction

Consensus by ESC/ACCF/AHA/WHF [2]

Classification:

- » Type 1: Spontaneous myocardial infarction
- » Type 2: Secondary to an ischemic imbalance
- » *Type 3: MI resulting in death*
- » Type 4a: MI related to PCI
- » Type 4b: MI related to stent thrombosis
- » Type 5: MI related to CABG

Nonfatal Myocardial Infarction

Clinical definition

Type 1 (and 2):

- » Significant rise of cardiac biomarkers

Plus

- » Symptoms of ischemia *OR*
- » Ischemic ECG-changes *OR*
- » Imaging evidence *OR*
- » Identification of an intracoronary thrombus

Nonfatal Myocardial Infarction

Clinical definition

Type 4a:

- » Significant rise of cardiac biomarkers

Plus

- » Symptoms of ischemia *OR*
- » New ischemic ECG-changes *OR*
- » Angiographic findings *OR*
- » Imaging evidence

Nonfatal Myocardial Infarction

Clinical definition

Type 4b:

- » Significant rise of cardiac biomarkers

Plus

- » Detected by angiography or autopsy

Nonfatal Myocardial Infarction

Clinical definition

Type 5:

- » Significant rise of cardiac biomarkers

Plus

- » New ischemic ECG-changes *OR*

- » Angiographic evidence *OR*

- » Imaging evidence

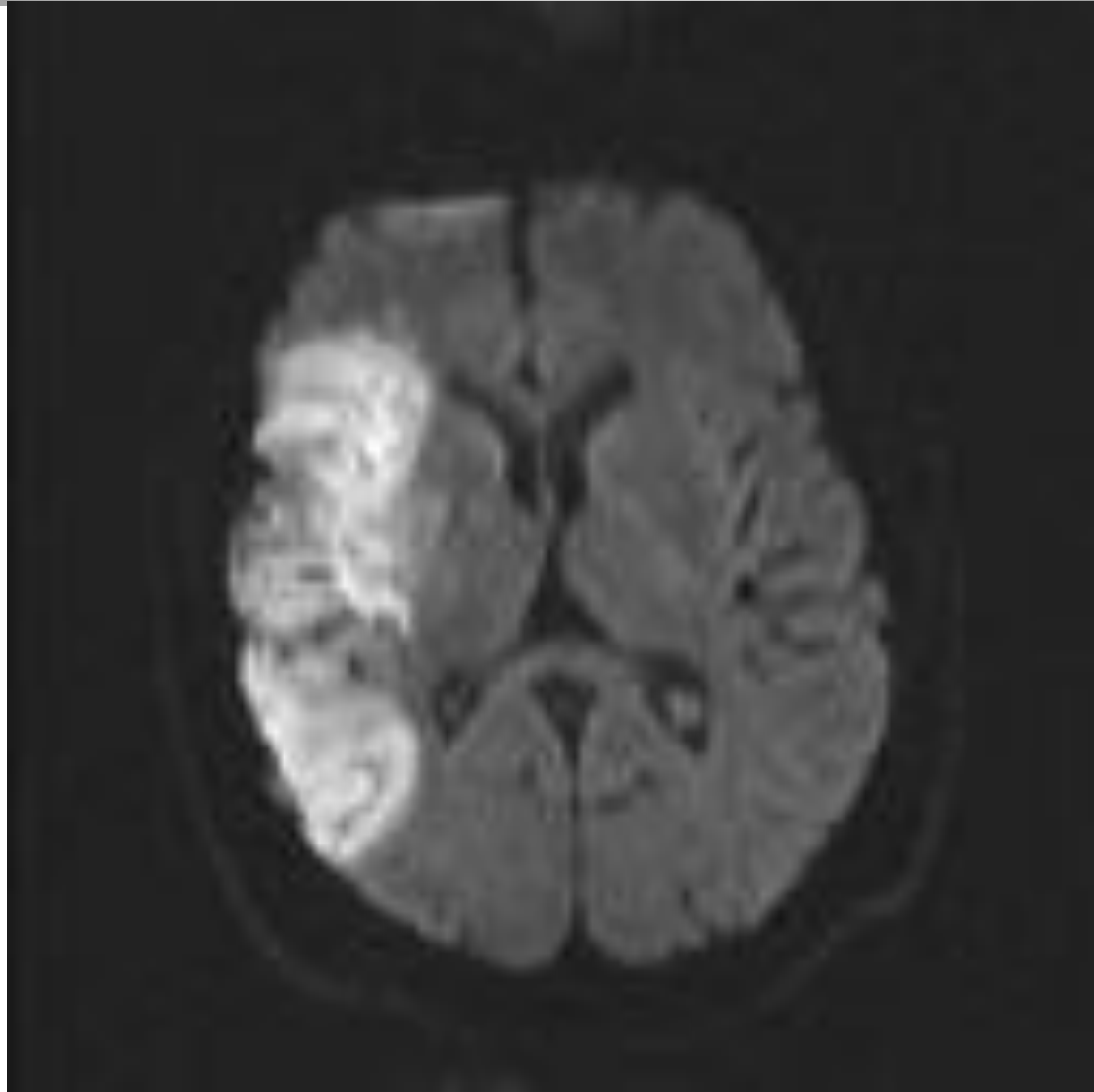
Nonfatal Myocardial Infarction

Suggestions for discussion:

How to handle silent myocardial infarctions?

» How should they be recorded?

Nonfatal Stroke



Nonfatal Stroke

Consensus statement by AHA/ASA [3]

Ischemic stroke

An episode of neurological dysfunction
caused by focal CNS infarction

CNS infarction

brain, spinal cord or retinal cell death
attributable to ischemia

[3] Sacco RL et al., *Stroke*, 2013

Nonfatal Stroke

Clinical definition:

1. Pathological imaging evidence

And/Or

2. Clinical evidence

Nonfatal Stroke

Cerebral hemorrhage

= Stroke, if

- » Nontraumatic
- » Caused by a vascular event
- » Results in injury to the CNS

Nonfatal Stroke

Cerebral hemorrhage

Entities:

- » Intracerebral hemorrhage
- » Subarchnoidal hemorrhage
- » Central venous thrombosis



Nonfatal Stroke

Suggestions for discussion:

How to handle silent CNS infarctions?

- » Should they be recorded?
- » If yes, how?

Cardiovascular Death

“Cardiovascular death is considered as any death with a demonstrable CV cause or any death that is not clearly attributable to a non-CV cause.” [4]

[4] *Wiviott SD et al., Am Heart J, 2006*

Cardiovascular Death

Cardiac Safety Research Consortium [5]:

- » Acute myocardial infarction
- » Sudden cardiac death
- » Death due to heart failure
- » Death due to stroke
- » Death due to cardiovascular procedures
- » Death due to cardiovascular hemorrhages
- » Death due to other cardiovascular causes

[5] Hicks KA et al., <http://www.cardiac-safety.org>, 2012

Cardiovascular Death

Death due to acute myocardial infarction

» ≤ 30 days after a MI

» Related to the immediate consequences,
e.g. progressive heart failure

Cardiovascular Death

Sudden cardiac death

“death following cardiac arrest in a patient with or without known preexisting heart disease, in whom the mode and time of death are unexpected” [6]

[6] Myerburg RJ et al., Philadelphia: Elsevier Saunders, 2014

Cardiovascular Death

Sudden cardiac death

- » Without new or worsening symptoms
- » Onset of new or worsening symptoms
- » Identified arrhythmia
- » Unsuccessful resuscitation from cardiac arrest
- » After successful resuscitation
- » Unwitnessed death

Cardiovascular Death

Death due to heart failure

- » death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology

Cardiovascular Death

Death related to heart failure hospitalization

All criteria should be met:

- » Primary diagnosis of HF
- » In-hospital \geq 24 hours
- » New or worsening symptoms
- » Objective presentation
- » Initiation or intensification of therapy

Cardiovascular Death

Death due to stroke

- » Direct consequence *OR*
- » Complication of stroke

Cardiovascular Death

Death due to cardiovascular procedures
» Caused by immediate complications

Cardiovascular Death

Death due to cardiovascular hemorrhage

- » Non-stroke intracranial hemorrhage
- » Non-procedural or non-traumatic vascular rupture
- » Hemorrhage causing cardiac tamponade

Cardiovascular Death

Death due to other cardiovascular causes

» other specific, known cause, e.g. pulmonary embolism, peripheral artery disease

Cardiovascular Death

Suggestions for discussion:

How to handle comorbidities?

Example:

- » ♂, 54 y
- » no stenosis in CT, but NSCLC
- » Chemotherapy → Heart Failure → Death

Cardiovascular Death: Own Contribution

National death registries

- » Every Clinical Site
- » Does a national death registry exist?
- » Information to discharge.eu@charite.de

Summary

We are pioneers

Table 1 RCTs of BMS Versus DES With MACE as an Outcome

Reference Year (Ref. #) Journal	Trial Name	Composite Name	Death	Cardiac Death	MI	Q-Wave MI	ST	TLR	TVR	CABG (Emergent)	CABG	Stroke
Morice et al. 2002 (11) <i>N Engl J Med</i>	RAVEL	MACE, P	✓		✓				✓		✓	
Grube et al. 2003 (12) <i>Circulation</i>	TAXUS-I	MACE, P	✓			✓	✓		✓			
Colombo et al. 2003 (13) <i>Circulation</i>	TAXUS-II	MACE, S		✓	✓				✓			
Moses et al. 2003 (14) <i>N Engl J Med</i>	SIRIUS	MACE P & S	✓ S	✓ P	✓ P		✓ S	✓ S	✓ P			
Schofer et al. 2003 (10) <i>Lancet</i>	E-SIRIUS	MACE, S	✓		✓			✓		✓		
Ardissino et al. 2004 (15) <i>JAMA</i>	SES-SMART	MACE and CVA, S		✓	✓			✓			✓	✓
Gershlick et al. 2004 (16) <i>Circulation</i>	ELUTES	MACE, S	✓		✓		✓	✓				
Grube et al. 2004 (17) <i>J Am Coll Cardiol</i>	SCORE	MACE, S		✓	✓			✓				
Grube et al. 2004 (18) <i>Circulation</i>	FUTURE I	MACE, P	✓		✓			✓ within 30 days			✓ TVR	

[1] Kip KE et al., *J Am Coll Cardiol*, 2008

Summary: Implications

- Implementation of the consensus definitions
 - Establishment of an accurate documentation
 - » eCRF
 - Contact National Death Registries
-
- Every myocardial infarction
 - Every stroke
 - Every death should be documented entity-specific and sent to Coordination Center

References

- [1] Kip, K.E., et al., *The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention*. J Am Coll Cardiol, 2008. **51**(7): p. 701-7.
- [2] Thygesen, K., et al., *Third universal definition of myocardial infarction*. J Am Coll Cardiol, 2012. **60**(16): p. 1581-98.
- [3] Sacco, R.L., et al., *An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association*. Stroke, 2013. **44**(7): p. 2064-89.
- [4] Wiviott, S.D., et al., *Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38)*. Am Heart J, 2006. 152(4): p. 627-35.
- [5] Hicks, K.A. *Standardized Definitions for Cardiovascular Outcomes Trials: Draft Recommendations - Draft Definitions for Testing November 9- 2012 with MI Preamble CLEAN.pdf*. 2014; Available from: <https://www.cardiac-safety.org/think-tanks/ecrf-forms-for-posting/Draft%20Definitions%20for%20Testing%20November%209-%202012%20with%20MI%20Preamble%20CLEAN.pdf>.
- [6] Myerburg, R.J., Castellanos, A., *Sudden Cardiac Death* in Zipes, D.P., *Cardiac electrophysiology from cell to bedside*. 6th ed. 2014, Philadelphia: Elsevier Saunders. 1365 S.