Poster Board / Publication No.: A-433

Impact of Variance in Definition for Major Adverse Cardiovascular Event (MACE): A Real-World Evidence Analysis

Scan for poster + more

Jared Kamauu, BFA,[1] Aimee Harrison, MFA,[1] Scott L. DuVall, PhD,[2] Michael Buck, PhD,[1] Craig Parker, MD, MS,[1] Aaron Kamauu, MD, MS, MPH[1]

[1]Navidence Inc., USA; [2]PurpleLab Healthcare Analytics , USA

DISCLOSURES: JK, MB, CP, and AK are employees of Navidence. AH was an employee of Navidence during this work. SLD is an employee of PurpleLab. The authors report no financial or non-financial relationships relevant to this work.

So What?

Substantial variation in MACE patient populations across commonly used definitions demonstrates that definitional heterogeneity has tangible clinical implications — even significant differences in outcome rates, like in this study where rates increased from the baseline to as high as 30% to 50%.

BACKGROUND

Context

Major adverse cardiovascular event (MACE) is one of the most widely used composite endpoints in cardiovascular research. A 2021 systematic review identified substantial heterogeneity in MACE definitions across observational studies using real-world data (RWD).[1] The most common components used to define MACE were stroke and acute myocardial infarction (AMI).

50
reference sources defined MACE using stroke

45
reference sources defined MACE using AMI

Most common MACE component conditions identified in a 2021 systematic review of RWD studies — more than double the next most common components.[1]

The Gap / Problem

The most common compound MACE definitions were AMI or stroke; AMI or stroke or cardiovascular (CV) death; AMI or stroke or all-cause death; stroke or acute coronary syndrome; and AMI or stroke or heart failure.[1] This review pointed to a lack of standardization for MACE definitions across real-world evidence (RWE) studies — yet the practical consequence of choosing one definition over another has not been quantified.

Pharmacoepidemiologic Relevance

When MACE definitions differ across studies, event rates are not directly comparable, limiting the ability of regulators, payers, clinicians, and researchers to interpret, replicate, or pool cardiovascular outcomes evidence.

OBJECTIVES

Primary Objective

To quantify differences in patient MACE episodes based on three common MACE definitions using real-world data.

MACE Definitions Evaluated

- **Definition 1 —** AMI or stroke
- **Definition 2 —** traditional 3-point: AMI or stroke or cardiovascular (CV) death
- **Definition 3 —** AMI or stroke or all-cause death

Components included in each definition

	AMI	Stroke	CV death	All-cause death
Definition 1	■	■		
Definition 2	■	■	■	
Definition 3	■	■		■

Shaded = component included. Definition 1 is a subset of Definition 2, which is a subset of Definition 3.

LIMITATIONS

- Cardiovascular and all-cause death are captured differently in a national claims database than in a single-center hospital dataset.
- Look-back periods differed by data source, so counts should not be compared directly between PurpleLab and MIMIC.
- MIMIC-IV reflects a single hospital system; findings from that source may not generalize to other care settings or populations.

METHODS

Study Design & Data Source

Retrospective analysis of two independent real-world data sources: PurpleLab® CLEAR Claims, a large U.S. administrative claims database, and MIMIC-IV, a hospital electronic health record dataset.[2] The three MACE definitions were applied to a 5-year and a 2-year look-back period, respectively.

Study Population

Adult populations in each data source. Outcomes were reviewed for 195,375,869 adult patients in PurpleLab data and 45,266 adult patients in MIMIC data. The same source population was used for all three definitions within each data source, so differences in patient counts reflect the definition applied rather than the underlying cohort.

Exposures & Outcome Measures

Three prevalent MACE definitions were evaluated: (1) AMI or stroke; (2) traditional 3-point MACE — AMI or stroke or cardiovascular (CV) death; and (3) AMI or stroke or all-cause death. Definition 1 is a subset of definition 2, which is a subset of definition 3. The same computable operational definitions (CODefs™) and code lists were used across all three definitions.

Statistical Analysis

We compared the number of patients with a documented MACE episode across each definition, within each data source, and expressed the change as the relative increase over the narrower definition.

Study & Analysis Flow

Source populations
Adult patients in PurpleLab® CLEAR Claims (5-year look-back) and MIMIC-IV hospital data (2-year look-back)

↓

Identical CODefs™ & code lists
Acute myocardial infarction, stroke, cardiovascular death, all-cause death

↓

Three nested MACE definitions
Def 1: AMI or stroke | Def 2: + CV death | Def 3: + all-cause death

↓

Compare patient counts
Number of patients with a documented MACE episode under each definition

Figure 1. Identical computable operational definitions and code lists were applied to both data sources; only the composite definition varied.

Computable Operational Definitions (CODefs™)

Study elements — exposures, outcomes, and covariates — were defined using Navidence CODefs™: rigorous, data source-agnostic algorithms that ensure precision and reproducibility across real-world data sources.

navidence.com

RESULTS

195,375,869
Adult Patients, PurpleLab® CLEAR Claims

45,266
Adult Patients, MIMIC-IV Hospital Data

~1.3×
More MACE Patients When CV Death Added

MACE Patients by Definition

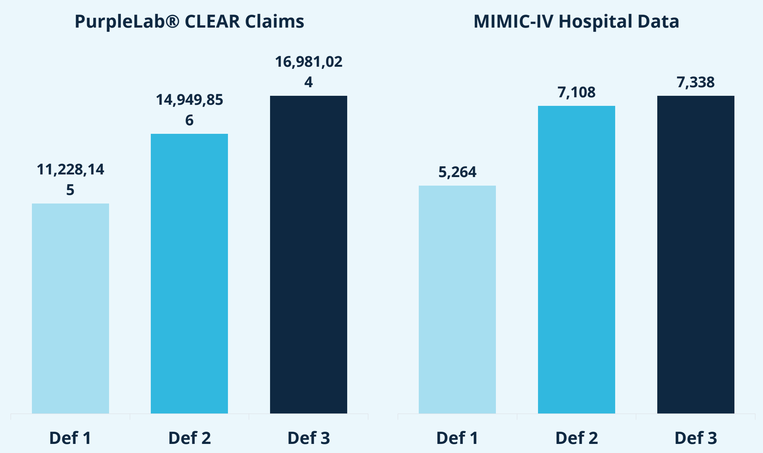

Figure 2. Number of adult patients with a documented MACE episode under each of the three MACE definitions, shown separately for each data source (note the different vertical scales).

Patients with a Documented MACE Episode

MACE definition	PurpleLab® CLEAR Claims (N=195,375,869)	MIMIC-IV (N=45,266)
Definition 1 AMI or stroke	11,228,145 (5.7%)	5,264 (11.6%)
Definition 2 AMI or stroke or CV death	14,949,856	7,108
Definition 3 AMI or stroke or all-cause death	16,981,024	7,338

Table 1. Patients with a documented MACE episode by MACE definition and data source. Percentages are of the adult population in each data source, as reported for Definition 1.

Relative Increase as Definitions Expand

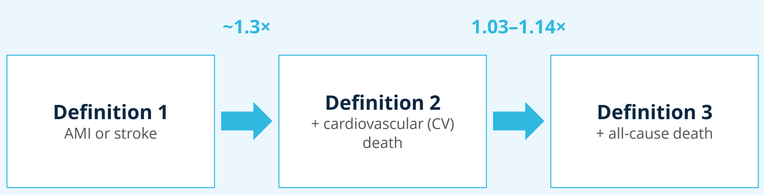

Figure 3. Adding CV death (Definition 2) resulted in ~1.3× the number of patients having a MACE episode; expansion to include all-cause death (Definition 3) resulted in 1.03–1.14× the number of patients.

CONCLUSIONS

Key Findings

- Definition 1 (AMI or stroke) identified 11,228,145 patients (5.7%) in PurpleLab and 5,264 patients (11.6%) in MIMIC.
- Adding CV death (Definition 2) resulted in ~1.3× the number of patients: 14,949,856 in PurpleLab and 7,108 in MIMIC.
- Adding all-cause death (Definition 3) resulted in 1.03–1.14× the number of patients: 16,981,024 in PurpleLab and 7,338 in MIMIC.

Clinical & Policy Implications

Future research should report complete and unambiguous CODefs for outcome measures, including the specific code lists used, so that cardiovascular outcomes research can be meaningfully compared and synthesized across studies.

REFERENCES

1. Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC Med Res Methodol. 2021;21(1):241.
2. Johnson AEW, Bulgarelli L, Shen L, et al. MIMIC-IV, a freely accessible electronic health record dataset. Sci Data. 2023;10(1):1.
3. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol. 2018;71(9):1021–1034.
4. PurpleLab, Inc. CLEAR Claims database. Available at: purplelab.com

TRANSPARENCY & REPRODUCIBILITY

Protocol: study design, computable operational definitions (CODefs™), and code lists are documented internally and available from the corresponding author on request; no separate protocol was registered. **Pre-registration:** not registered. **Data access:** MIMIC-IV is publicly available via PhysioNet under a credentialed data use agreement; PurpleLab® CLEAR Claims is available under commercial licence from PurpleLab, Inc. **Analytic code:** available from the authors on request. **Reporting:** consistent with STROBE and RECORD-PE principles.