Supplement for:

Association of Longitudinal Changes in Left Ventricular Structure and Function with Myocardial Fibrosis: The MESA study

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The authors would like to thank Dr. John Eng (Johns Hopkins University, Baltimore, MD) for performing the correction detailed below that allowed us to compare year-0 and year-10 MRI variables, and for the preparation of this document.

BACKGROUND

The MESA cardiac MRI protocol was established in 1999 and implemented in 2000 at all sites. The protocol used the fast gradient echo (FGRE) MRI pulse sequence to obtain cine images of the heart at year-0. This pulse sequence was well validated at the time and was available at all MESA sites1.

In 2001, Carr et al. published a new method for cardiac cine MRI, the steady-state free precession (SSFP) pulse sequence2. The new method was 2.7 times faster than the prior FGRE approach, resulting in shorter breath-hold times for the MESA participants. SSFP’s other advantage is that it is not dependent on flowing blood (as is the case for FGRE). The definition between myocardial wall and blood pool is greater with SSFP compared to FGRE since fluid is intrinsically bright on SSFP images. SSFP has since replaced FGRE for routine cine cardiac MRI. The SSFP technique has been subsequently validated and found to be more reproducible with better image quality than FGRE. Thus, MESA year-10 study used SSFP cine MRI.

Unfortunately, quantification of SSFP MRI results in different left ventricular mass and volumes than using FGRE3. There are also less significant, but important differences regarding the software and readers. Newer, more rapid software methods for quantification of the MRI data were developed between 2000 and 2010. MESA year-10 used CIM 6.0 software (UniServices, Auckland, New Zealand) while MESA year-0 used MASS 4.0 software (Medis, Leiden, Netherlands). Year-10 also used different readers than year-0. Therefore, in order to compare MESA year-0 and year-10 MRI data, it was necessary to use correction equations to account for these differences.

METHODS

At baseline, Cardiac MRI was performed with 1.5-T scanners with determination of LV mass and volumes as previously described26. Briefly, a stack of short-axis images covering the entire LV was acquired using a fast gradient recalled echo sequence. The endocardial and epicardial myocardial borders were contoured using a semi-automated method (MASS 4.2, Medis, Leiden, the Netherlands). The difference between the epicardial and endocardial...
areas for all slices was multiplied by the slice thickness and section gap, and then multiplied by the specific gravity of myocardium (1.04 g/ml) to determine the ventricular mass. Papillary muscle mass was included in the LV cavity and excluded from the LV mass.

At follow-up, MESA participants without contraindications underwent CMR exams using 1.5T scanners (Avanto and Espree, Siemens Medical Systems; Signa LX, GE Healthcare) with a six-channel anterior phased-array torso coil and corresponding posterior coil elements. LV function, dimensions and myocardial mass were assessed by a cine steady-state free precession sequence. Twelve short axis slices, one 4-chamber view and one 2-chamber view were acquired as described previously. LV structural parameters (LV mass and volumes) and LV ejection fraction were measured using commercially available software (CIM v6.2, Auckland, New Zealand).

For derivation of the longitudinal conversion coefficients, data were used from the following additional readings performed.

<table>
<thead>
<tr>
<th>Data source</th>
<th>Pulse sequence</th>
<th>Reader</th>
<th>N</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 0</td>
<td>FGRE</td>
<td>Current</td>
<td>500</td>
<td>Calibration for different readers/software</td>
</tr>
<tr>
<td>Year 10</td>
<td>FGRE</td>
<td>Current</td>
<td>500</td>
<td>Calibration for different pulse sequences</td>
</tr>
<tr>
<td>Year 0</td>
<td>FGRE</td>
<td>Past</td>
<td>~75</td>
<td>Estimate of reader variability</td>
</tr>
<tr>
<td>Year 10</td>
<td>FGRE</td>
<td>Current</td>
<td>100</td>
<td>Estimate of reader variability</td>
</tr>
</tbody>
</table>

**READER CALIBRATION**

Errors-in-variables linear regression between original Exam 1 FGRE readings and re-readings of Exam 1 by current readers was performed. This gave a calibration equation that corrected for reader and software differences between year-0 and year-10 for each of the major MRI outcome variables. The errors-in-variables regression required an estimate of variability of the original year-0 FGRE readings, and this was obtained from conventional ANOVA of the year-0 reproducibility data.

**PULSE SEQUENCE CALIBRATION**

Errors-in-variables linear regression between FGRE and SSFP readings for year-10 participants was performed. This gave a calibration equation that corrected for pulse sequence differences between year-0 and year-10 for each of the major MRI outcome variables – left ventricular (LV) mass, end-systolic volume (EDV) and end-diastolic volume (ESV). The errors-in-variables regression required an estimate of variability of the year-10 FGRE readings, and this is obtained from conventional ANOVA.

**COMBINED CALIBRATION**

Reader and pulse sequence calibration equations were algebraically combined to obtain overall equations for each of the major MRI outcome variables. This equation was used to correct original year-0 readings to be comparable to year-10 readings.
**Equations**

The correction equations used in this paper following the above methodology were:

\[
LV \text{ Mass}(SSFP@ year0) = \text{olvedm}1(FGRE@year0) \times 0.7491541082777 + 11.55746667761
\]

\[
LV \text{ EDV}(SSFP@ year0) = \text{olvedv}1(FGRE@ year0) \times 0.9576837658703 + 7.589499318002
\]

\[
LV \text{ ESV}(SSFP@ year0) = \text{olvesv}1(FGRE@ year0) \times 0.8945541670171 + 12.72954664005
\]

Please note that ejection fraction was calculated after the correction is performed from LV ESV and EDV.

**References**


**Supplemental Table S1:** LV structure and function variables from MRI and in women and men without scar (LGE -ve) and with scar (LGE+ -ve) at year 10 defined by late gadolinium enhancement (LGE).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n=874)</th>
<th>Men (n=939)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LGE –ve</td>
<td>LGE +ve</td>
</tr>
<tr>
<td>LVMi (g/m²) at year-10</td>
<td>59.2±9.3</td>
<td>70±14.4</td>
</tr>
<tr>
<td>LVMi (g/m²) at year-0</td>
<td>58.8±8.4</td>
<td>65.6±16.6</td>
</tr>
<tr>
<td>ΔLVMi (g/m²)</td>
<td>0.4±8.4</td>
<td>2.3±11.8</td>
</tr>
<tr>
<td>EDVi (ml/m²) at year-10</td>
<td>62.2±10.8</td>
<td>61±14.4</td>
</tr>
<tr>
<td>EDVi (ml/m²) at year-0</td>
<td>67.5±10.4</td>
<td>66±12.9</td>
</tr>
<tr>
<td>ΔEDVi (ml/m²)</td>
<td>-5.3±9.7</td>
<td>-5±10.4</td>
</tr>
<tr>
<td>MVR (g/ml) at year-10</td>
<td>0.97±0.18</td>
<td>1.18±0.38</td>
</tr>
<tr>
<td>MVR (g/ml) at year-0</td>
<td>0.88±0.14</td>
<td>1.02±0.29</td>
</tr>
<tr>
<td>ΔMVR (g/ml)</td>
<td>0.09±0.18</td>
<td>0.16±0.26</td>
</tr>
<tr>
<td>LVEF (%) at year-10</td>
<td>63.8±6.2</td>
<td>59.8±8.4</td>
</tr>
<tr>
<td>LVEF (%) at year-0</td>
<td>63.8±5.2</td>
<td>62.7±7.1</td>
</tr>
<tr>
<td>ΔLVEF (%)</td>
<td>0.1±6.9</td>
<td>-2.9±9.4</td>
</tr>
<tr>
<td>T1 pre-contrast (ms) at year-10</td>
<td>985±45</td>
<td>1015±49</td>
</tr>
<tr>
<td>T1 at 12’ (ms) at year-10</td>
<td>442±42</td>
<td>419±39</td>
</tr>
<tr>
<td>T1 at 25’ (ms) at year-10</td>
<td>505±42</td>
<td>489±39</td>
</tr>
</tbody>
</table>

LVMi: left ventricular mass indexed to body surface area. EDVi: end-diastolic volume indexed to body surface area. ESVi: end-systolic volume indexed to body surface area. MVR: left-ventricular mass to end-diastolic volume ratio. LVEF: left ventricular ejection fraction. T1 at 12’: T1 time at 12 minutes post contrast injection. T1 at 25’: T1 time at 25 minutes post contrast injection.
**Supplemental Table S2**: Coefficients for cross-sectional multivariable linear regression of T1 25’ times at year-10 with LV size and function at year-10, as well as T1 times at year-10 with 10-year change in LV size and function between the baseline (year 0) and follow up (year 10) CMR exams.

| Variable | Cross-sectional | | Longitudinal | | | | | | |
|----------|-----------------|---|---|---|---|---|
|          | Uni  | Multi | $r^2$ | Uni  | Multi | $r^2$ | Uni  | Multi | $r^2$ |
| **WOMEN** | | | | | | | | | |
| LVMi     | 0.95† | 1.07† | 0.49 | 0.66† | 0.99† | 1.07† | 0.48 |
|          | (0.58,1.32) | (0.75,1.4) | (0.26,1.06) | (0.61,1.37) | (0.68,1.45) | | |
| EDVi     | 0.84† | 0.60† | 0.47 | 0.23 | 0.63† | 0.55† | 0.47 |
|          | (0.54,1.13) | (0.36,0.84) | (-0.11,0.58) | (0.35,0.92) | (0.25,0.86) | | |
| MVR      | -14.665 | -1.16 | 0.45 | 6.19 | -9.51 | -0.13 | 0.44 |
|          | (-33.25,3.92) | (-17.20,14.87) | (-13.08,25.47) | (-17.54,17.28) | | |
| LVEF     | 0.38 | 0.099 | 0.45 | 0.20 | -0.02 | 0.08 | 0.45 |
|          | (-0.16,0.92) | (-0.32,0.52) | (-0.28,0.68) | (-0.57,0.60) | (-0.36,0.53) | | |
| **MEN**  | | | | | | | | | |
| LVMi     | 0.44† | 0.46† | 0.22 | 0.47† | 0.35* | 0.73† | 0.33 |
|          | (0.19,0.70) | (0.19,0.73) | (0.17,0.76) | (0.05,0.65) | (0.43,1.03) | | |
| EDVi     | 0.22* | 0.16 | 0.2 | -0.01 | 0.16 | 0.16 | 0.31 |
|          | (0.02,0.42) | (-0.04,0.36) | (-0.22,0.21) | (-0.08,0.37) | (-0.07,0.38) | | |
| MVR      | -1.45 | 2.52 | 0.2 | 9.68 | -0.57 | 6.63 | 0.31 |
|          | (-13.66,10.76) | (-10.16,15.20) | (-2.00,21.36) | (-17.11,15.98) | (-5.87,19.14) | | |
| LVEF     | 0.82† | 0.36 | 0.21 | 0.60† | 0.07 | 0.45* | 0.31 |
|          | (0.41,1.23) | (-0.06,0.79) | (0.23,0.97) | (-0.48,0.63) | (0.03,0.86) | | |

Coefficients and 95% confidence intervals (in brackets) for multivariable linear regression models to assess the cross-sectional associations, and baseline and change associations of CMR variables with T1 post-contrast 25’ times at year 10. Multivariable models adjusted for risk factor values at year-10 for cross-sectional associations. For associations with baseline (BL) and change ($\Delta$) in values, models adjusted for baseline value and change in value of covariates. Additionally, models adjusted for gadolinium dose and glomerular filtration rate at year-10 for post-contrast T1 times. * if p<0.05, † if p<0.001.

LVMi: left ventricular mass indexed to body surface area (g/m²). EDVi: end-diastolic volume indexed to body surface area (ml/m²). MVR: left-ventricular mass to end-diastolic volume ratio (g/ml). LVEF: left-ventricular ejection fraction (%).
**Supplemental Table S3**: Coefficients for multivariable logistic regression relating presence of scar defined by LGE at the follow up year-10 exam with LV mass indexed (allometric approach).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cross-Sectional Associations with Baseline and Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uni</td>
</tr>
<tr>
<td>WOMEN</td>
<td></td>
</tr>
<tr>
<td>LVMIa</td>
<td>0.05†</td>
</tr>
<tr>
<td></td>
<td>(0.02,0.07)</td>
</tr>
<tr>
<td>MEN</td>
<td></td>
</tr>
<tr>
<td>LVMIa</td>
<td>0.04†</td>
</tr>
<tr>
<td></td>
<td>(0.03,0.05)</td>
</tr>
</tbody>
</table>

Coefficients and 95% confidence intervals (in brackets) for multivariable logistic regression models to assess the cross-sectional associations, and baseline and change associations of LV mass indexed (allometric approach) with the presence of scar as assessed by LGE at year 10. Multivariable models adjusted for risk factor values at year-10 for cross-sectional associations. For associations with baseline (BL) and change (Δ) in values, models adjusted for baseline value and change in value of covariates. * if $p<0.05$, † if $p<0.001$. 
**Supplemental Table S4**: Coefficients for cross-sectional multivariable linear regression of T1 12’ times at year-10 with LV mass indexed (allometric approach) at year-10, as well as T1 times at year-10 with 10-year change in LV mass indexed (allometric approach) between the baseline (year 0) and follow up (year 10) CMR exams.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cross-sectional</th>
<th>Longitudinal</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uni</td>
<td>Multi</td>
<td>r²</td>
<td>Uni</td>
<td>Multi</td>
<td>r²</td>
</tr>
<tr>
<td>WOMEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMIa</td>
<td>1.00</td>
<td>0.79†</td>
<td>0.46</td>
<td>0.50†</td>
<td>0.81†</td>
<td>0.85†</td>
</tr>
<tr>
<td></td>
<td>(0.74,1.25)</td>
<td>(0.57,1.01)</td>
<td></td>
<td>(0.23,0.77)</td>
<td>(0.55,1.08)</td>
<td>(0.58,1.12)</td>
</tr>
<tr>
<td>MEN</td>
<td>0.43</td>
<td>0.37†</td>
<td>0.28</td>
<td>0.38*</td>
<td>0.21</td>
<td>0.59†</td>
</tr>
<tr>
<td>LVMIa</td>
<td>(0.23,0.63)</td>
<td>(0.16,0.57)</td>
<td></td>
<td>(0.14,0.61)</td>
<td>(-0.03,0.46)</td>
<td>(0.34,0.84)</td>
</tr>
</tbody>
</table>

Coefficients and 95% confidence intervals (in brackets) for multivariable linear regression models to assess the cross-sectional associations, and baseline and change associations of LV mass indexed (allometric approach) with T1 post-contrast 12’ times at year 10. Multivariable models adjusted for risk factor values at year-10 for cross-sectional associations. For associations with baseline (BL) and change (Δ) in values, models adjusted for baseline value and change in value of covariates. Additionally, models adjusted for gadolinium dose and glomerular filtration rate at year-10 for post-contrast T1 times. * if p<0.05, † if p<0.001.
Figure S1: Plots showing scatter plots and linear fits for men (red line) and women (blue line) with LV structure and function parameters at year-10 on the x-axis and post-contrast T1 times in ms at 12 minutes at year-10 on the y-axis.
Figure S2: Plots showing scatter plots and linear fits for men (red line) and women (blue line) with 10-year change in LV structure and function parameters on the x-axis and post-contrast T1 times in ms at 12 minutes at year-10 on the y-axis.
**Figure S3:** Plots showing scatter plots and linear fits for calibrated baseline and follow-up LV structure and function parameters on the y-axis and y-axis respectively.
MESA CRITERIA FOR EVENTS

Each potential event is reviewed and classified using standardized criteria. A reviewer’s classification of an event applies only to the specific hospitalization or outpatient situation under review. Unless the review is for death, a reviewer should not be concerned if there is a history of prior incident events identified in the records or in MESA reviews. Each event should be judged separately as “Definite,” “Probable,” or “No/Absent” for a new incident event.

CRITERIA FOR NONFATAL EVENTS

Nonfatal events include MI, resuscitated cardiac arrest, angina, congestive heart failure, peripheral vascular disease (PVD), stroke, and TIA. In addition, MESA records revascularization procedures. MESA is purposefully not identifying asymptomatic coronary or ventricular disease as an end point because of concerns about potential bias.

CRITERIA FOR MYOCARDIAL INFARCTION

The criteria for myocardial infarction (MI) include information about chest pain, cardiac enzymes, and ECGs. The MESA MI criteria have been adapted from the Atherosclerosis Risk in Communities (ARIC) study. The source for the ARIC criteria is: “ARIC Protocol 3, Surveillance Component Procedures, Version 4.0” (October 1997).

**Chest pain:** Chest pain is defined as an episode of ischemic pain, tightness, pressure, or discomfort in the chest, arm, or jaw. Other atypical pains identified as due to coronary ischemia may qualify. If there is a clear noncardiac cause, chest pain is considered to be absent. Duration of pain is not considered part of the chest pain criteria.

**Enzyme criteria:** Table S5 shows the enzyme criteria in the absence of coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Equivocal is between "above normal" and "twice the upper limit of normal," and abnormal is greater than "twice the upper limit of normal."

When (non-CABG or non-PTCA) muscle trauma is present, enzymes are downgraded to equivocal. Enzymes collected during the 48 hours following a CABG or PTCA will be classified differently from the scheme described in Table S5. For PTCA, levels of CK or MB above three times the upper limit of normal (ULN) within 48 hours of the procedure will be categorized as abnormal. MB will take precedence over CK if both are available. These abnormal enzymes would not be “downgraded to equivocal” on the basis of the procedure. Similarly for CABG, levels of MB above five times the ULN within 48 hours of the procedure will be categorized as abnormal. Total CK will not be used for post-CABG enzymes. These abnormal enzymes would not be “downgraded to equivocal” on the basis of the surgical procedure.

After 48 hours, the standard enzyme criteria would again apply. Other new measures, such as myoglobin or MB subforms, may need to be added in the future and will be added as necessary with the same criteria for equivocal (between "above normal" and "twice the upper limit of normal") and abnormal (greater than "twice the upper limit of normal").
### Supplemental Table S5. MESA Algorithm to Classify Cardiac Enzymes as Abnormal, Equivocal, or Normal

<table>
<thead>
<tr>
<th>Enzyme Value</th>
<th>There is (a) no known muscle trauma/hemolysis and (b) no PTCA or CABG in past 48 hours*</th>
<th>Muscle trauma/liver/hemolytic disease exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB = present where present or absent</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>CK-MB ≥ 2× ULN (upper limit of normal)</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>CK-MB** ≥ 10% Total CK, if no ULN is given</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Total CK ≥ 2× ULN and LDH ≥ 2× ULN</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>LDH 1 : LDH 2 &gt; 1</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>LDH 1 ≥ 2× ULN if LDH 2 is missing</td>
<td>Abnormal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Total CK ≥ 2× ULN or LDH ≥ 2× ULN</td>
<td>Equivocal</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal &lt; Total CK &lt; 2× ULN and Normal &lt; LDH &lt; 2× ULN</td>
<td>Equivocal</td>
<td>Normal</td>
</tr>
<tr>
<td>5% Total CK &lt; CK-MB† ≤ 9% Total CK or CK-MB “weakly present”</td>
<td>Equivocal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Normal &lt; CK-MB &lt; 2× ULN</td>
<td>Equivocal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Normal &lt; LDH 1 &lt; 2× ULN</td>
<td>Equivocal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Data present, but insufficient for above criteria</td>
<td>Incomplete</td>
<td>Incomplete</td>
</tr>
<tr>
<td>Normal &lt; Troponins &lt; 2× ULN</td>
<td>Equivocal</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Troponins &gt; 2× ULN</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Troponins &lt; ULN</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>CK-MB &lt; ULN</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>All other results</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*PTCA–abnormal in first 48 hours requires Troponins or LDH 1 or CK or CK-MB > 3× ULN; equivocal requires 1-3× ULN. CABG–abnormal in first 48 hours requires Troponins or LDH 1 or CK-MB > 5× ULN; equivocal requires 1-5× ULN. † CK and CK-MB must be in same units for this criterion.

**ECG criteria:** The following ECG tracings are identified by the Field Center and scanned:
- The first two codable ECGs after admission;
- The last codable ECG recorded before discharge; and
- The last codable ECG recorded on day 3 (or the first ECG thereafter) following admission or an in-hospital event.

The Coordinating Center provides the scanned ECGs to the Events Review Committee. Committee members (Physician Reviewers) will review the ECGs and classify them into the categories listed below using clinical criteria.

In addition, MESA will do a central reading of ECGs. This will only be done on events reviewed by the committee for MI, to provide a more standardized serial ECG interpretation that includes the baseline exam ECG as well as the hospital ECGs. Criteria for standardized coding at the ECG Reading Center are provided in Appendix A. These criteria are based on the modification of Minnesota rules for serial ECGs.

**MI criteria:** Table S6 shows the diagnostic categories of MI according to the ECG criteria, enzyme categories, and chest-pain history.

**Supplemental Table S6.** MESA Diagnostic Criteria for Hospitalized MI

<table>
<thead>
<tr>
<th>Cardiac Pain Present</th>
<th>Cardiac Enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG Pattern</strong>*</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Evolution of Major Q-Wave</td>
<td>Definite MI</td>
</tr>
<tr>
<td>Evolution of ST Elevation with or without Q-wave Or New LBBB</td>
<td>Definite MI</td>
</tr>
<tr>
<td>Evolution of ST-T Depression/inversion alone Or Evolution of Minor Q-waves alone</td>
<td>Definite MI</td>
</tr>
<tr>
<td>Single ECG with Major Q-Wave Or Single ECG with LBBB, described as new</td>
<td>Definite MI</td>
</tr>
<tr>
<td>Normal, Absent, Uncodable, other</td>
<td>Probable MI</td>
</tr>
</tbody>
</table>

**Criteria for Resuscitated Cardiac Arrest**

A category of resuscitated cardiac arrest is an additional nonfatal outcome. This diagnosis is reserved for patients who were in full arrest (asystole or ventricular fibrillation and pulseless) and who underwent cardiopulmonary resuscitation (including cardioversion) successfully. Cardiac arrest secondary to noncardiac conditions, such as respiratory arrest, should not be classified as resuscitated cardiac arrest. Because post-arrest enzymes are
difficult to interpret, in general, attempts to classify MI will not be made in patients with resuscitated cardiac arrest. Patients who never awaken and go on to die during a subsequent hospitalization would not qualify for the diagnosis of resuscitated cardiac arrest. Patients who never awaken and go on to die will be classified according to their cause of death (see Section 4.2). To classify an event as a resuscitated cardiac arrest, all of the criteria below must be met:

- The absence of a clear-cut noncardiac cause. Presence of cardiac symptoms (e.g., chest pain) is confirmatory but not necessary.
- The person must have lived at least 24 hours after resuscitation.

**CRITERIA FOR ANGINA**

The MESA criteria for both inpatient and outpatient angina were adapted from the Women’s Health Initiative (WHI). In MESA, angina is a symptomatic event generally involving ischemic chest, left arm, or jaw pain, though the symptoms may be "atypical." Atypical anginal symptoms can include shortness of breath, exertional dyspnea, epigastric discomfort, and back pain, in addition to pain that is isolated to the arm or the jaw.

Physician adjudicators categorize angina events as “definite,” “probable,” and “no angina” based on clinical judgment. In addition, reviewers record the criteria met during the hospitalization or outpatient medical visit:

a. Physician diagnosis of angina and receiving medical treatment for angina (e.g., nitrates, beta-blockers, or calcium-channel blockers)
b. CABG surgery or other revascularization procedure
c. 70% or greater obstruction of any coronary artery per angiography
d. Horizontal or down-sloping ST-segment depression or abnormal ST elevation of ≥1 mm on exercise or pharmacological stress testing with pain
e. Scintigraphic or echocardiographic stress test positive for ischemia
f. Resting ECG shows horizontal or down-sloping ST depression or abnormal ST elevation ≥1 mm with pain that is not present on ECG without pain

Reviewers check all criteria that apply. This approach has the advantage of easily permitting a range of analyses based on definitions of angina that include "soft" criteria (#a only) or various types of "hard" criteria (#b–f). In general, the original report of the procedure should be reviewed rather than accepting references in discharge summaries to the results of diagnostic or therapeutic procedures. However, if an original full report is not available, convincing reference to the procedure results in the discharge summary is acceptable.

Given its difficult diagnosis, angina must retain a stringent criteria standard. All of the following guidelines below should be followed:

a. Clear and thorough documentation of symptoms is needed to identify an event as “definite angina.” Even if a test such as an ETT lists “angina” or “chest pain” as its indication, angina should not be ruled unless there is additional, explicit information from the physician regarding symptoms. Likewise, a test showing positive ischemia
or the performance of a further procedure (e.g., catheterization) is not enough to
rule for angina if other MESA criteria are not met.

b. Only code an event as angina if it is distinct from an MI.
c. Reviewers should not angina as part of pain symptoms of an MI.

Angina will require clinical symptoms to be considered a MESA event. If there is only a
physician diagnosis/treatment, then the diagnosis cannot be "definite." If there is more
than just a physician diagnosis, then the reviewer can assign "definite" instead of
"probable."

**Unstable angina:** There is no formal separate classification for unstable angina. The
suggested definition is “nonelective admission (discharge) to the hospital for acute angina
and not codable as definite or probable MI.”

**Revascularization:** Revascularization will be documented on its own, as a category
separate from other events. In cases where revascularization was performed without
clinical symptoms, the reviewers will record the revascularization, but not record angina. A
reviewer’s classification of revascularization applies only to the specific hospitalization or
outpatient situation under review. A reviewer should not be concerned if there is a history
of prior revascularization(s) identified in the records or in MESA reviews.

**Criteria for Congestive Heart Failure (CHF)**
The MESA criteria for CHF were adapted from the WHI. MESA identifies both inpatient and
outpatient diagnoses of heart failure. Physician reviewers categorize CHF events as
"definite," "probable," and "no CHF." A diagnosis of "definite" or "probable" CHF requires
clear and thorough documentation of symptoms, as asymptomatic disease is not a MESA
endpoint. (A ruling of "definite" requires more than a physician diagnosis.) Reviewers
record the adapted MESA criteria for CHF met:

a. CHF diagnosed by physician, and patient receiving medical treatment for CHF (e.g.,
diuretics, digitalis, vasodilators, beta-blockers, or ACE inhibitors)
b. Pulmonary edema/congestion, by CXR
c. Dilated ventricle or poor left ventricular function (e.g., low ejection fraction or wall
motion abnormalities), by echocardiography, radionuclide ventriculogram
(RVG)/multigated acquisition (MUGA), or other contrast ventriculography, or
evidence of left ventricular diastolic dysfunction.

Reviewers will check all criteria that apply. This approach has the advantage of easily
permitting a range of analyses based on definitions of heart failure that include "soft"
criteria (#a only) or various types of "hard" criteria (#b–c).

In general, the reviewer should examine the original report of a procedure rather than
accept references to results of the diagnostic or therapeutic procedures in discharge
summaries. If an original full report is not available, convincing reference to the procedure
results in the discharge summary is acceptable.

**Criteria for Claudication or Peripheral Vascular Disease (PVD)**
The MESA criteria for claudication have been adapted from the WHI. Claudication is a symptomatic event and in MESA refers to only the lower body—typically exertional leg pain relieved by rest. Outpatient records of claudication will not be sought in MESA unless they include a major outpatient diagnostic procedure such as angiography or angioplasty. Physician adjudicators categorize potential MESA PVD events as “definite,” “probable,” and “no PVD” based on clinical judgment. A ruling of “definite PVD” requires more than a physician diagnosis. Good documentation of symptoms is needed. Even if a test such as a Doppler lists “PVD” or “claudication” as its indication, PVD should not be ruled unless there is information documenting symptoms or treatment for PAD.

Physician adjudicators also subclassify PVD as:

- a. Lower extremity claudication
- b. Atherosclerosis of arteries of the lower extremities
- c. Arterial embolism and/or thrombosis of the lower extremities
- d. Abdominal aortic aneurysm

Reviewers also record the PVD criteria met:

- a. Ultrasonographically- or angiographically-demonstrated obstruction or ulcerated plaque (≥50% of the diameter or ≥75 of the cross-sectional area) demonstrated on ultrasound or angiogram of the iliac arteries or below
- b. Absence of pulse by Doppler in any major vessel of the lower extremities
- c. Exercise test that is positive for lower extremity claudication
- d. Surgery, angioplasty, or thrombolysis for peripheral vascular disease
- e. Amputation of one or more toes or part of the lower extremity because of ischemia or gangrene
- f. Exertional leg pain relieved by rest and at least one of the following: (1) claudication diagnosed by physician AND (2) ankle-arm blood pressure ratio ≤0.8
- g. Surgical or vascular procedure for abdominal aortic aneurysm
- h. Doppler, angiogram, CT, or MRI examination positive for abdominal aortic aneurysm

Criteria for Stroke and TIA

All potential cerebrovascular events are classified as “stroke,” “transient ischemic attack” (TIA), or “not a cerebrovascular event.” All events classified as stroke will be further classified by type: subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, brain infarction, or unknown. Criteria for TIA, stroke, and type of stroke are provided below. Criteria for infarct subtype are provided in Appendix B. Symptomatic retinal infarction should be classified as "brain infarction" but requires documentation by an ophthalmologist. "Brain Infarct Subtypes" should also be coded for a symptomatic retinal infarction.

**TIA**

One or more episodes of focal neurologic deficit

**AND**
Lasting more than 30 seconds

AND

Complete resolution of focal neurologic deficit within 24 hours

AND

No clinically relevant lesion on brain imaging*

OR

Brain imaging not done

AND

None of the following features: clonic jerking, conjugate eye deviation, prolonged focal seizure with spread, scintillating scotoma, headache with nausea and vomiting, or immediately-preceding head trauma

**Stroke**

Rapid onset of neurologic deficit, headache, or meningismus

AND

Neurologic deficits not secondary to brain trauma (closed head injury), tumor, infection (e.g., encephalitis or meningitis), or other nonvascular cause. (But clinical evidence or suspicion of embolic stroke secondary to SBE *would* be counted as stroke)

AND

Clinically relevant lesion on brain imaging*

OR

Duration greater than 24 hours

OR

Death within 24 hours

**Criteria for Stroke Types**

*Subarachnoid Hemorrhage (SAH)*

Clinical presentation with sudden onset of a headache, meningismus, loss of consciousness, or coma. Focal neurologic deficit may also be present.

*Clinically relevant lesion on brain imaging: Imaging finding judged to be consistent with signs and symptoms regardless of timing of brain imaging (i.e., less or greater than 24 hours), regardless of stroke type (i.e., with or without blood), and regardless of imaging technique (i.e., cranial computed tomography [CT scan] or cranial magnetic resonance imaging [MRI]).*
Consistent imaging findings with blood mainly in the subarachnoid space (basal cistern or convexity) or isolated intraventricular hemorrhage

OR

Cerebral fluid bloody or xanthochromic on direct nontraumatic examination

OR

Surgical or autopsy evidence of subarachnoid hemorrhage

Intraparenchymal Hemorrhage (IPH)
Clinical presentation of focal neurologic deficit; coma may be present

AND

Consistent imaging findings with mainly intraparenchymal, dense hemorrhage

OR

If no imaging, cerebral spinal fluid bloody or xanthochromic on direct nontraumatic examination

OR

Surgical or autopsy evidence of intraparenchymal hemorrhage

Other Hemorrhage (OH)
Insufficient data to classify subarachnoid or intraparenchymal hemorrhage

AND

Imaging shows blood in the parenchyma, subarachnoid space, or both

OR

Cerebrospinal fluid bloody or xanthochromic on direct nontraumatic examination

OR

Surgical or autopsy evidence of blood in parenchyma, subarachnoid space,

OR

both

Brain Infarction (INF)
Not meeting criteria for SAH, IPH, or OH

AND
Clinical presentation of focal neurologic deficit; coma may be present

AND

Consistent imaging findings without clinically relevant lesion or with clinically relevant mainly nonhemorrhagic lesion or hemorrhagic lesion indicating a hemorrhagic infarction

OR

Surgical or autopsy evidence of brain infarction

Other Stroke Type (OS)
Not meeting criteria for SAH, IPH, OH, INF.

[Examples: venous thrombosis with bleed, arterial dissection.]

Unknown Stroke Type
Insufficient data to classify type as SAH, IPH, OH, INF, or OS

[Examples: No work-up was done.]

Criteria for Deaths
Deaths are classified, using criteria provided below, into the following fatal event categories:

a. Atherosclerotic CHD Death, with subclassifications of “definite fatal MI,” “definite fatal CHD,” and “possible fatal CHD”
   b. Stroke Death
   c. Other Atherosclerotic Disease Death (noncoronary/nonstroke)
   d. Other Cardiovascular Disease Death
   e. Non-Cardiovascular Disease Death

Those in categories a, c, and d are categorized according to timing from onset of last episode of symptoms to death (<5 min, 5 min to 1 hr, 1 to 24 hr, >24 hr, unknown). They are also classified as to most important mechanism(s) thought to cause death (more than one may apply):

a. Primary arrhythmic death: death <5 minutes without preceding symptoms of ischemia or heart failure
   b. Secondary arrhythmic/mechanical death: death with preceding symptoms of ischemia or heart failure, but not directly due to shock or low output state
   c. Congestive heart failure – death due to shock or low output state, including pre-renal azotemia
   d. Cardiac procedure such as CABG, angioplasty or stent
   e. Hemorrhage from thrombolytic therapy
   f. Unknown or uncertain

Criteria for Atherosclerotic Coronary Heart Disease Death
Requires the absence of known nonatherosclerotic or noncardiac cause of death.
**Definite Fatal MI**
Any in-hospital death that meets criteria for MI

**OR**
Out-of-hospital death with a documented MI within previous 28 days

**Definite Fatal CHD**
Does not qualify as a “definite fatal MI”

**AND**
Chest pain within previous 72 hours

**OR**
History of CHD

**Possible Fatal CHD**
Does not qualify as “definite fatal MI” or “definite fatal CHD”

**AND**
Underlying cause of death included in: ICD-10 codes I20–I25, I46, I51.6, R96,

**OR**
R98–R99

**Criteria for Stroke Death**
a. Stroke occurrence and type determined by stroke event adjudication: subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, brain infarction, other stroke type, or unknown stroke type
b. Mechanism of death is recorded as due to critical brain injury or as secondary to complications such as infections (lungs, urine, skin), pulmonary embolism, or arrhythmia. Critical brain injury can be lethal either because of the size of the infarct or bleed with herniation, or because of the location in the brain stem.

**Criteria for Other Atherosclerotic Disease Death**
If not codable, as above, reviewers can assign “Other Atherosclerotic Disease Death” based upon clinical judgment. Such criteria would include: complications of aneurysm, ischemia of any organ or limb leading to death, etc.

**Criteria for Other Cardiovascular Disease Death**
If not codable, as above, reviewers can assign “Other Cardiovascular Disease Death” based upon clinical judgment. Such criteria would include: pulmonary embolism, valvular heart disease, etc.

**Criteria for Other Death**
None of the above causes of death assigned, or a strong history of a likely cause of death that is not CHD.

Use official ICD-10 code (usually indicated on the death certificate).