

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplement to: Coronary Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy

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## Table of Contents

|  |    |
|--|----|
| STICH Hypothesis 1 investigators, leadership, and trial committees.....  | 2  |
| Clinical Events Classification (CEC) reviewer manual.....  | 5  |
| Figure S1. Kaplan-Meier rates of death from any cause for CABG vs. MED (as-treated analysis).....  | 10 |
| Figure S2. Kaplan-Meier rates of death from any cause for CABG vs. MED (per-protocol analysis).....  | 11 |
| Table S1. Inclusion and exclusion criteria.....  | 12 |
| Table S2. Enrollment by country and by treatment.....  | 13 |
| Table S3. Left ventricular function and coronary anatomy at baseline.....  | 14 |
| Table S4. Medication use.....  | 15 |
| Table S4A. Subsequent procedures.....  | 16 |
| Table S5. Number of patients at risk, cumulative events, and cumulative withdrawals or lost to follow-up at each year following randomization..... | 17 |
| Table S6. Additional analyses on death from any cause.....   | 18 |
| Table S7. Summary of adverse events.....   | 19 |

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# Clinical Events Classification (CEC) Reviewer Manual for the Surgical Treatment for Ischemic Heart Failure Extended Study (STICHES)

## CEC Adjudication for STICHES

### PHASE 1 REVIEW

All death events will undergo Phase 1 review. Phase 1 review is defined as a process whereby two physicians, from a group of CEC physician members assigned to the project independently adjudicate death events using the event criteria listed in the charter. For the STICHES trial, the Phase 1 reviews will be completed by the same faculty physicians designated to perform Phase 2 reviews. The physicians will adjudicate death events using documentation from the eCRF, the event narratives, and other available supporting source documentation. If the Phase 1 reviewers agree in their adjudication of the death event, the event classification is complete. For difficult or complex cases, the Phase 1 reviewers can request that an event undergo Phase 2 review. Finally, all deaths adjudicated due to an Unknown cause by Phase 1 review will also undergo Phase 2 review by an Adjudication Committee.

### PHASE 2 REVIEW

Phase II review is defined as a process whereby an Adjudication Committee meeting is organized and comprised of at least 3 CEC physicians. Phase II meetings will have a preponderance of faculty members and each case will be reviewed by consensus of the Phase II reviewers. In addition to having clinical expertise, the faculty will have an understanding of CEC processes and clinical methodology. If the committee requests additional information or source documentation, then the case will be reviewed once the documentation has been obtained. The final adjudication results are recorded on a single CEC adjudication form to be completed by a Phase II reviewer. The following events will undergo Phase 2 review: Phase 1 disagreements, cases designated as difficult or complex as requested by Phase 1 review, cases designated for QC review, all deaths adjudicated due to Unknown cause by Phase 1 review.

## 1. Endpoint/Event Definitions

### Death

All deaths will be adjudicated. The STICHES CEC will categorize the cause of death as follows:

#### I. Cardiovascular Death:

##### A. Cardiac

- Sudden death – VT/ VF, Brady arrhythmia, or unknown
- Fatal pump failure

- Fatal myocardial infarction
- Other cardiac
- Cardiac procedure related death
  - PCI
  - CABG
  - Surgical ventricular reconstruction and CABG
  - ICD or bi-ventricular pacemaker
  - Other cardiac procedure related

#### **B. Vascular Death**

- Fatal CVA
- Peripheral vascular disease
- Vascular complication
- Peripheral emboli
- Venous thrombosis
- Other Vascular

### **II. Non-Cardiovascular Death**

- Infection
- Neurologic
- Pulmonary
- Renal
- Malignancy
- Other

### **III. Unknown**

#### **Mortality Definitions in Detail: Cardiovascular**

##### **Cardiac**

##### **Sudden Death:**

Defined as death that occurred suddenly and unexpectedly, in which the date of death is known. Examples of the details of sudden deaths include:

Witnessed Death due to:

- An identified arrhythmia (ECG or at least monitor recording, or monitor witnessed arrhythmia either by a medic or a paramedic).
- Cardiac arrest or cardiovascular collapse in absence of premonitory heart failure or myocardial infarction or other modes of death.
- Patients resuscitated from a sudden cardiac arrest who later die of the sequelae of the event or similar patients who die during an attempted resuscitation.

*Or*



**Unwitnessed Death:**

- Death that occurs suddenly and unexpectedly, in which date of death is unknown, but recent information identified clinical stability.

**Fatal Pump Failure:**

- Death occurring after new or worsening symptoms and/or signs of heart failure. Patients who are being treated for heart failure and who have a sudden death as the terminal event will be classified as having a pump failure related death.

**Fatal Myocardial Infarction:**

Death occurring after a documented myocardial infarction in which there is not conclusive evidence of another cause of death. Patients who are being treated for myocardial infarction and who have a sudden death as the terminal event related to the MI will be classified as having a myocardial infarction related death.

Documentation of Myocardial infarction would include:

- Autopsy evidence of a recent infarct with no other conclusive evidence of another cause of death.
- A fatal myocardial infarction may be adjudicated for an abrupt death that has suggestive criteria for an infarct but does not meet the strict definition of a myocardial infarction. The suggestive criteria is as follows:
  - Presentation of chest pain AND
  - One of the following:
    - ECG changes indicative of a myocardial injury OR
    - Abnormal markers without evolutionary changes (i.e., patient died before a subsequent draw) OR other evidence of wall motion abnormality

**Cardiac Procedure Related Death:**

Death occurring during a cardiovascular procedure (CABG, SVR, PTCA, other) or when the events leading to death are related to the procedure. The type of procedure will be specified.

(Example: A patient who had a CABG up to 15 days ago, who developed a subsequent myocardial infarction requiring inotropics, and who later died will still be classified as procedural related death.)

**Other Cardiac Death:**

Death likely due to a cardiac cause, but specific criteria for the above categories is not present.

## Vascular

Vascular Disease – Death due to specific events related to vascular disease (e.g., aortic, mesenteric, renal, or peripheral). Does not include hypoperfusion or embolic sequelae of heart failure. Discrete evidence by clinical events or autopsy should be present.

## Non-Cardiovascular Death

Death due to a documented non-cardiovascular cause.

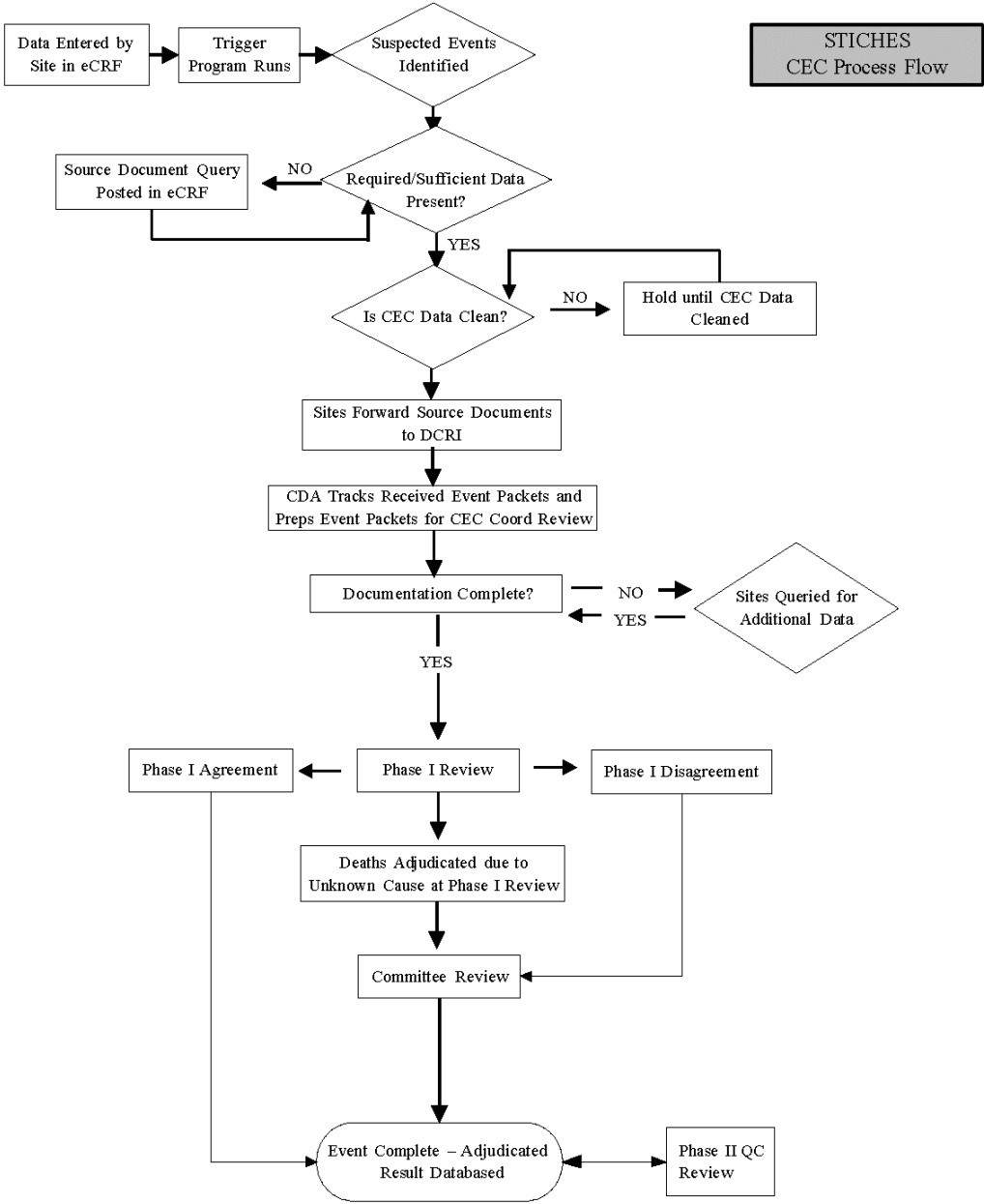
## Unknown

Defined as death in which source documentation is not sufficient to determine the cause and further information is not forthcoming

## 2. Source Documentation for CEC

| ENDPOINT | RECOMMENDED SOURCE DOCUMENTATION FOR CEC ADJUDICATION   |
|----------|---|
| Death    | <ul style="list-style-type: none"> <li>• Narrative death summary prepared by site PI/MD/designee</li> <li>• Autopsy report if applicable</li> <li>• Death/Discharge Summary upon request</li> <li>• Death Event Form</li> </ul> |

### 3. CEC Process Flow



**Figure S1. Kaplan-Meier rates of death from any cause for CABG vs. MED (As-treated analysis)**

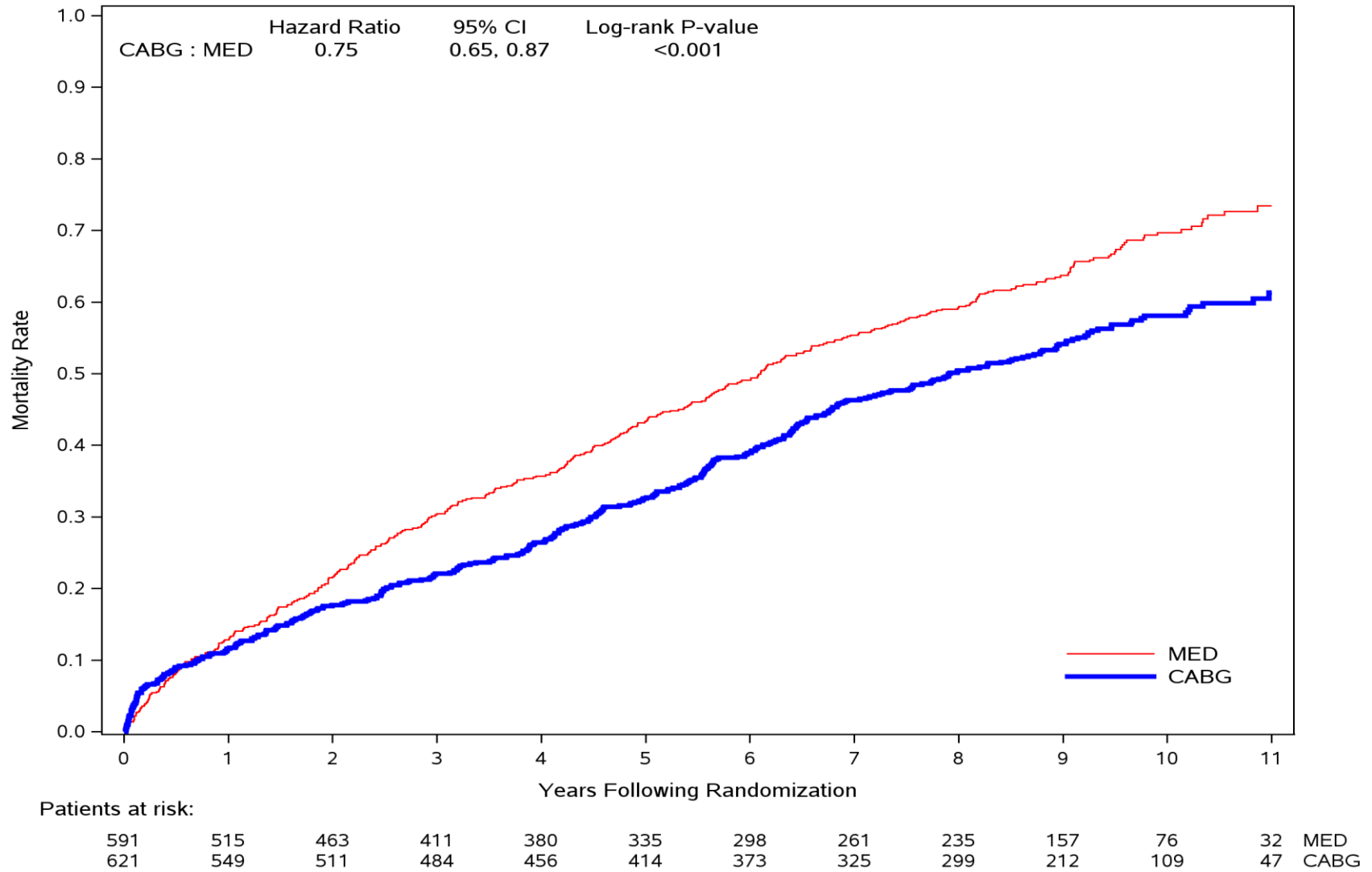
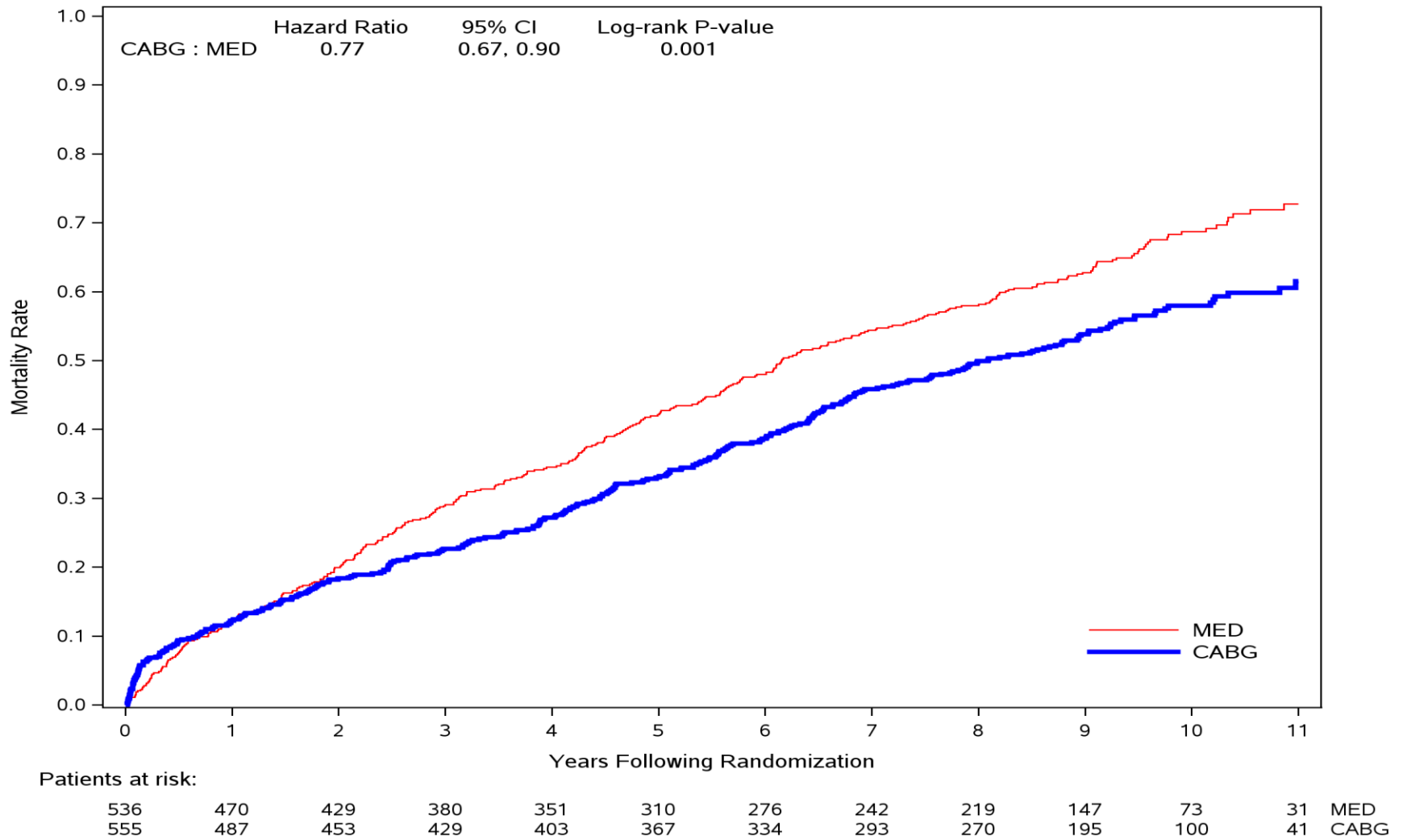


Figure S2. Kaplan-Meier rates of death from any cause for CABG vs. MED (Per-protocol analysis)



**Table S1. Inclusion and exclusion criteria****Inclusion Criteria**

- Women who are not of childbearing potential and men
- Age  $\geq 18$  years
- LVEF  $\leq 0.35$  measured by CMR ventriculogram, gated SPECT ventriculogram, ECHO, or contrast ventriculogram within 3 months of trial entry
- CAD suitable for revascularization

**Exclusion Criteria**

- Failure to provide informed consent
- Aortic valvular heart disease clearly indicating the need for aortic valve repair or replacement
- Cardiogenic shock (within 72 hours of randomization), as defined by the need for intra-aortic balloon support or the requirement of intravenous inotropic support
- Plan for percutaneous intervention of CAD
- Recent acute MI judged to be an important cause of LV dysfunction
- History of more than 1 prior coronary bypass operation
- Non-cardiac illness with a life expectancy of less than 3 years
- Non-cardiac illness imposing substantial operative mortality
- Conditions/circumstances likely to lead to poor treatment adherence (e.g., history of poor compliance, alcohol or drug dependency, psychiatric illness, no fixed abode)
- Previous heart, kidney, liver, or lung transplantation
- Current participation in another clinical trial in which a patient is taking an investigational drug or receiving an investigational medical device

**Medical Therapy Eligibility Criteria**

- Absence of left main CAD as defined by an intraluminal stenosis of  $\geq 50\%$
- Absence of CCS III angina or greater (angina markedly limiting ordinary activity)

**Surgical Ventricular Reconstruction Eligibility Criterion**

- Dominant akinesia or dyskinesia of the anterior LV wall amenable to SVR

Patients eligible to enter the study were first evaluated for SVR eligibility based upon dominant anterior akinesia or dyskinesia amenable to SVR. Among patients eligible to enter the study, patients with either left main CAD  $\geq 50\%$  or CCS Class  $\geq$  III angina on medical therapy were categorized as ineligible for medical therapy alone. These criteria placed patients into 1 of 3 strata.

| Stratum A      | Stratum B     | Stratum C      |
|----------------|---------------|----------------|
| MED eligible   | MED eligible  | MED ineligible |
| CABG eligible  | CABG eligible | CABG eligible  |
| SVR ineligible | SVR eligible  | SVR eligible   |

**Table S2. Enrollment by Country and by Treatment**

|           | <b>Country</b> | <b>CABG</b>        | <b>MED</b>         | <b>Total</b> |
|-----------|----------------|--------------------|--------------------|--------------|
| <b>1</b>  | Poland         | 157(49.2%)         | 162(50.8%)         | 319          |
| <b>2</b>  | India          | 81(48.8%)          | 85(51.2%)          | 166          |
| <b>3</b>  | Russia         | 66(49.6%)          | 67(50.4%)          | 133          |
| <b>4</b>  | Canada         | 60(48.8%)          | 63(51.2%)          | 123          |
| <b>5</b>  | USA            | 66(55.0%)          | 54(45.0%)          | 120          |
| <b>6</b>  | Serbia         | 37(50.0%)          | 37(50.0%)          | 74           |
| <b>7</b>  | Brazil         | 19(54.3%)          | 16(45.7%)          | 35           |
| <b>8</b>  | Australia      | 18(52.9%)          | 16(47.1%)          | 34           |
| <b>9</b>  | Germany        | 16(51.6%)          | 15(48.4%)          | 31           |
| <b>10</b> | Italy          | 17(54.8%)          | 14(45.2%)          | 31           |
| <b>11</b> | Hungary        | 13(46.4%)          | 15(53.6%)          | 28           |
| <b>12</b> | United Kingdom | 12(48.0%)          | 13(52.0%)          | 25           |
| <b>13</b> | Thailand       | 13(59.1%)          | 9(40.9%)           | 22           |
| <b>14</b> | Argentina      | 9(52.9%)           | 8(47.1%)           | 17           |
| <b>15</b> | Sweden         | 4(36.4%)           | 7(63.6%)           | 11           |
| <b>16</b> | Singapore      | 6(60.0%)           | 4(40.0%)           | 10           |
| <b>17</b> | Austria        | 4(44.4%)           | 5(55.6%)           | 9            |
| <b>18</b> | Lithuania      | 4(50.0%)           | 4(50.0%)           | 8            |
| <b>19</b> | Norway         | 3(60.0%)           | 2(40.0%)           | 5            |
| <b>20</b> | New Zealand    | 3(75.0%)           | 1(25.0%)           | 4            |
| <b>21</b> | Uruguay        | 1(25.0%)           | 3(75.0%)           | 4            |
| <b>22</b> | Malaysia       | 1(33.3%)           | 2(66.7%)           | 3            |
|           | <b>Total</b>   | <b>610 (50.3%)</b> | <b>602 (49.7%)</b> | <b>1212</b>  |

**Table S3. Left ventricular function and coronary anatomy at baseline**

| Variables <sup>*,†</sup>                                | CABG<br>(N=610) | MED<br>(N=602) | Total<br>(N=1212) |
|---|-----------------|----------------|-------------------|
| <b>Left ventricular function</b>                        |                 |                |                   |
| LVEF, %   | 27 (22, 33)     | 28 (22, 34)    | 28 (22, 34)       |
| ESVI, mL/m <sup>2‡</sup>                                | 79 (61, 101)    | 77 (58, 104)   | 78 (60, 103)      |
| Akinesia or dyskinesia of anterior wall, % <sup>§</sup> | 43 (25, 57)     | 43 (25, 53)    | 43 (25, 57)       |
| <b>Mitral regurgitation</b>                             |                 |                |                   |
| None or trace   | 213 (35%)       | 222 (37%)      | 435 (36%)         |
| Mild ( $\leq 2+$ )                                      | 293 (48%)       | 261 (44%)      | 554 (46%)         |
| Moderate (3+)   | 83 (14%)        | 98 (16%)       | 181 (15%)         |
| Severe (4+)   | 21 (3%)         | 18 (3%)        | 39 (3%)           |
| Not assessed  | 0               | 3              | 3                 |
| <b>Coronary anatomy</b>                                 |                 |                |                   |
| No. of vessels with stenosis $\geq 75\%$                |                 |                |                   |
| 0   | 12 (2%)         | 13 (2%)        | 25 (2%)           |
| 1   | 136 (22%)       | 146 (24%)      | 282 (23%)         |
| 2   | 233 (38%)       | 229 (38%)      | 462 (38%)         |
| 3   | 228 (37%)       | 214 (36%)      | 442 (36%)         |
| Stenosis of left main artery $\geq 50\%$                | 18 (3%)         | 14 (2%)        | 32 (3%)           |
| Stenosis of proximal LAD $\geq 75\%$                    | 411 (67%)       | 415 (69%)      | 826 (68%)         |
| Duke CAD index (0–100)                                  | 65 (39, 77)     | 65 (39, 77)    | 65 (39, 77)       |

\*Continuous variables are presented as median (25th, 75th percentiles); categorical variables are presented as numbers with corresponding percentages.

†LVEF and ESVI are based on the best available data from STICH core labs or sites.

‡For ESVI, MED (N=553) and CABG (N=562).

§For akinesia or dyskinesia of anterior wall, MED (N=299) and CABG (N=305).

CABG denotes coronary-artery bypass grafting; CAD, coronary artery disease; ESVI, end-systolic volume index; LAD, left anterior descending; LVEF, left ventricular ejection fraction; MED, medical therapy alone.



**Table S4. Medication use**

| Medications   | CABG<br>(N=610) |            |            | MED<br>(N=602) |            |            |
|---|-----------------|------------|------------|----------------|------------|------------|
|   | Baseline        | 5-Year     | 10-Year    | Baseline       | 5-Year     | 10-Year    |
|   |                 | Follow-up* | Follow-up† |                | Follow-up* | Follow-up† |
| Beta blocker  | 507 (83%)       | 494 (90%)  | 477 (87%)  | 529 (88%)      | 506 (90%)  | 500 (88%)  |
| ACE inhibitor                                       | 514 (84%)       | 425 (77%)  | 403 (73%)  | 482 (80%)      | 430 (76%)  | 418 (74%)  |
| ARB   | 53 (9%)         | 79 (14%)   | 70 (13%)   | 62 (10%)       | 92 (16%)   | 78 (14%)   |
| ACE inhibitor or<br>ARB                             | 554 (91%)       | 487 (89%)  | 456 (83%)  | 531 (88%)      | 503 (89%)  | 483 (85%)  |
| Statin  | 483 (79%)       | 497 (90%)  | 471 (86%)  | 500 (83%)      | 491 (87%)  | 478 (84%)  |
| Antiarrhythmic                                      | 71 (12%)        | 72 (12%)   | 81 (13%)   | 57 (9%)        | 72 (12%)   | 78 (13%)   |
| Amiodarone  | 65 (11%)        | 68 (12%)   | 77 (14%)   | 53 (9%)        | 64 (11%)   | 71 (13%)   |
| Other   | 6 (1%)          | 5 (0.9%)   | 5 (0.9%)   | 6 (1%)         | 14 (2%)    | 14 (2.5%)  |
| Digoxin   | 121 (20%)       | 114 (21%)  | 113 (21%)  | 124 (21%)      | 126 (22%)  | 129 (23%)  |
| Aspirin (daily)                                     | 489 (80%)       | 460 (84%)  | 449 (82%)  | 513 (85%)      | 475 (84%)  | 466 (82%)  |
| Warfarin  | 51 (8%)         | 109 (20%)  | 101 (18%)  | 76 (13%)       | 119 (21%)  | 104 (18%)  |
| Aspirin or<br>Warfarin                              | 515 (84%)       | 504 (92%)  | 494 (90%)  | 550 (91%)      | 525 (93%)  | 514 (91%)  |
| Clopidogrel   | 106 (17%)       | 70 (13%)   | 79 (14%)   | 102 (17%)      | 92 (16%)   | 96 (17%)   |
| Diuretic<br>(loop/thiazide)                         | 399 (66%)       | 396 (72%)  | 404 (73%)  | 392 (65%)      | 398 (70%)  | 400 (71%)  |
| Diuretic<br>(potassium<br>sparing)                  | 280 (46%)       | 298 (54%)  | 297 (54%)  | 276 (46%)      | 298 (53%)  | 300 (53%)  |
| Diuretic<br>(loop/thiazide or<br>potassium sparing) | 454 (74%)       | 464 (84%)  | 460 (84%)  | 458 (76%)      | 473 (84%)  | 468 (83%)  |
| Nitrate   | 337 (55%)       | 105 (19%)  | 105 (19%)  | 309 (51%)      | 216 (38%)  | 196 (35%)  |
| Insulin   | 100 (16%)       | 102 (19%)  | 111 (20%)  | 97 (16%)       | 103 (18%)  | 108 (19%)  |
| Oral diabetic agent                                 | 139 (23%)       | 138 (25%)  | 135 (25%)  | 147 (24%)      | 141 (25%)  | 139 (25%)  |

Data presented as numbers with corresponding percentages.

\*Based on the latest follow-up data in STICH follow-up, which has a median (IQR) follow-up time of 4.9 years (4.1, 6.0).

†Based on the latest follow-up data in STICHES follow-up, which has a median (IQR) follow-up time of 9.8 years (9.1, 11.0).

ACE denotes angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary-artery bypass grafting; MED, medical therapy alone.

**Table S4A. Subsequent procedures**

| <b>Subsequent Procedure</b>   | <b>CABG<br/>(N=610)</b> | <b>MED<br/>(N=602)</b> |
|-------------------------------|-------------------------|------------------------|
| CABG                          | 2 (<1%)                 | 119 (20%)              |
| Placement of LV assist device | 4 (<1%)                 | 2 (<1%)                |
| Heart transplant              | 1 (<1%)                 | 4 (<1%)                |
| PCI                           | 43 (7%)                 | 50 (8%)                |
| Placement of pacemaker        |                         |                        |
| For resynchronization (CRT)   | 42 (7%)                 | 29 (5%)                |
| For heart rate                | 47 (8%)                 | 19 (3%)                |
| ICD                           | 105 (17%)               | 118 (20%)              |
| Placement of ICD or CRT       | 122 (20%)               | 130 (22%)              |

Data presented as numbers with corresponding percentages.

CABG denotes coronary-artery bypass grafting; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LV, left ventricular; MED, medical therapy alone; PCI, percutaneous coronary intervention.

**Table S5. Number of Patients at Risk, Cumulative Events, and Cumulative Withdrawals or Lost to Follow-up at Each Year Following Randomization**

| Randomized Treatment                               | Patient Status              | Years Following Randomization |     |     |     |     |     |     |     |     |     |     |     |     |
|--|-----------------------------|-------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|  |                             | 0                             | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  |
| <b>All-cause Mortality:</b>                        |                             |                               |     |     |     |     |     |     |     |     |     |     |     |     |
| MED  | At Risk                     | 602                           | 532 | 487 | 435 | 404 | 357 | 315 | 274 | 248 | 164 | 82  | 37  | 5   |
|  | Deaths                      | 0                             | 70  | 115 | 167 | 198 | 245 | 284 | 324 | 346 | 370 | 390 | 397 | 398 |
|  | WC or LTF <sup>1</sup>      | 0                             | 0   | 0   | 0   | 0   | 0   | 3   | 5   | 8   | 11  | 12  | 12  | 12  |
| CABG   | At Risk                     | 610                           | 532 | 487 | 460 | 432 | 392 | 356 | 312 | 286 | 205 | 103 | 42  | 7   |
|  | Deaths                      | 0                             | 78  | 123 | 150 | 177 | 213 | 247 | 289 | 314 | 334 | 350 | 356 | 359 |
|  | WC or LTF <sup>1</sup>      | 0                             | 0   | 0   | 0   | 1   | 5   | 7   | 9   | 10  | 11  | 11  | 12  | 13  |
| <b>Cardiovascular Mortality:</b>                   |                             |                               |     |     |     |     |     |     |     |     |     |     |     |     |
| MED  | At Risk                     | 602                           | 532 | 487 | 435 | 404 | 357 | 315 | 274 | 248 | 164 | 82  | 37  | 5   |
|  | CV Deaths <sup>2</sup>      | 0                             | 63  | 103 | 141 | 167 | 204 | 232 | 256 | 267 | 283 | 295 | 297 | 297 |
|  | WC or LTF <sup>1</sup>      | 0                             | 0   | 0   | 0   | 0   | 0   | 3   | 5   | 8   | 11  | 12  | 12  | 12  |
| CABG   | At Risk                     | 610                           | 532 | 487 | 460 | 432 | 392 | 356 | 312 | 286 | 205 | 103 | 42  | 7   |
|  | CV Deaths <sup>2</sup>      | 0                             | 70  | 105 | 122 | 142 | 167 | 191 | 213 | 226 | 235 | 243 | 246 | 247 |
|  | WC or LTF <sup>1</sup>      | 0                             | 0   | 0   | 0   | 0   | 0   | 3   | 5   | 8   | 11  | 12  | 12  | 12  |
| <b>Mortality or Cardiovascular Hospitalization</b> |                             |                               |     |     |     |     |     |     |     |     |     |     |     |     |
| MED  | At Risk                     | 602                           | 385 | 314 | 259 | 219 | 185 | 152 | 123 | 98  | 57  | 19  | 7   | 0   |
|  | Deaths/CV Hosp <sup>3</sup> | 0                             | 217 | 288 | 343 | 383 | 417 | 447 | 476 | 499 | 512 | 522 | 524 | 524 |
|  | WC or LTF <sup>1</sup>      | 0                             | 0   | 0   | 0   | 0   | 0   | 3   | 5   | 8   | 11  | 12  | 12  | 12  |
| CABG   | At Risk                     | 610                           | 431 | 376 | 334 | 293 | 259 | 218 | 184 | 166 | 106 | 43  | 16  | 5   |
|  | Deaths/CV Hosp <sup>3</sup> | 0                             | 179 | 234 | 276 | 316 | 346 | 385 | 417 | 435 | 450 | 463 | 466 | 467 |
|  | WC or LTF <sup>1</sup>      | 0                             | 0   | 0   | 0   | 0   | 0   | 3   | 5   | 8   | 11  | 12  | 12  | 12  |

1. WC = Withdrew consent; LTF = Lost to follow-up. 2. CV=Cardiovascular. 3. CV Hosp= Cardiovascular hospitalization.

**Table S6. Additional analyses on death from any cause\***

| Variable  | Hazard Ratio (95% CI)<br>CABG vs. MED | P-value |
|---|---------------------------------------|---------|
| Covariate adjusted analyses <sup>†</sup>                      |                                       |         |
| Model 1   | 0.84 (0.73, 0.97)                     | 0.019   |
| Model 2   | 0.80 (0.70, 0.93)                     | 0.003   |
| Analyses with CABG as a time-dependent covariate <sup>‡</sup> |                                       |         |
| Analysis 1  | 0.77 (0.67, 0.89)                     | <0.001  |
| Analysis 2  | 0.75 (0.65, 0.87)                     | <0.001  |
| Analysis 3  | 0.81 (0.71, 0.94)                     | 0.005   |
| Analysis 4  | 0.76 (0.66, 0.87)                     | <0.001  |
| Analysis 5  | 0.77 (0.67, 0.89)                     | <0.001  |

\*Population presented is intention-to-treat, unless otherwise specified.

<sup>†</sup>Model 1: adjusting for surgical ventricular eligibility (i.e., enrollment stratum); Model 2: Model 1+age, sex, race, baseline New York Heart Association heart failure class, myocardial infarction history, previous revascularization, best available core lab ejection fraction, number of diseased vessels, presence of chronic renal insufficiency, mitral regurgitation grade, stroke history, atrial fibrillation or flutter, baseline hemoglobin, and hyperlipidemia.

<sup>‡</sup>Analysis 1: A patient is considered to be in the CABG group at the time a patient actually received CABG.

Otherwise, the patient is considered to be in the MED group.

Analysis 2: All patients randomly assigned to CABG who actually received CABG are considered to be in CABG group at the time of randomization, all other patients are considered to be in the CABG group at and after the time of receiving surgery.

Analysis 3: All patients randomly assigned to CABG group are considered to be in CABG group at the time of randomization, but patients randomized to MED group are considered to be in the CABG group at and after the time of actually receiving CABG surgery.

Analysis 4: All patients randomly assigned to CABG who actually received CABG are considered to be in CABG group at the time of randomization. Patients randomly assigned to CABG who did not receive CABG and died within 30 days after randomization were considered to be in the CABG group from randomization until the time of their death. All other patients are considered to be in the CABG group at and after the time of receiving surgery.

Analysis 5: All patients randomly assigned to CABG who actually received CABG are considered to be in CABG group at the time of randomization. Patients randomly assigned to CABG who did not receive CABG and died within 60 days after randomization are considered to be in the CABG group from randomization until the time of their death. All other patients are considered to be in the CABG group at and after the time of receiving surgery.

CABG denotes coronary artery bypass graft; CI, confidence interval; MED, medical therapy alone.

**Table S7. Summary of Adverse Events**

| <b>Events</b>  | <b>CABG<br/>(N=610)</b> | <b>MED<br/>(N=602)</b> | <b>Total<br/>(N=1212)</b> |
|--|-------------------------|------------------------|---------------------------|
| <b>Procedure complications from operation to hospital discharge or 30 days after randomization among patients randomized to CABG and received CABG (N=555)</b> |                         |                        |                           |
| Return to operation room for bleeding  | 18 (3%)                 |                        |                           |
| Return to operation room for other reason  | 19 (3%)                 |                        |                           |
| Return to operation room for any reason  | 35 (6%)                 |                        |                           |
| Mediastinitis  | 11 (2%)                 |                        |                           |
| Other infection <sup>1</sup>   | 46 (8%)                 |                        |                           |
| Mediastinitis or other infection   | 56 (10%)                |                        |                           |
| Death or not discharged within 30 days of operation  | 52 (9%)                 |                        |                           |
|  |                         |                        |                           |
| <b>Clinical events within 30 days after randomization</b>  |                         |                        |                           |
| PA catheter placement  | 120 (20%)               | 4 (0.7%)               | 124 (10%)                 |
| Pacemaker for heart rate   | 31 (5%)                 | 3 (0.5%)               | 34 (3%)                   |
| Pacemaker for resynchronization  | 15 (2%)                 | 6 (1.0%)               | 21 (2%)                   |
| New onset atrial flutter/fibrillation  | 90 (15%)                | 3 (0.5%)               | 93 (8%)                   |
| New onset ventricular arrhythmia   | 35 (6%)                 | 4 (0.7%)               | 39 (3%)                   |
| Worsening renal insufficiency  | 35 (6%)                 | 10 (2%)                | 45 (4%)                   |
| IABP for low cardiac output  | 89 (15%)                | 5 (0.8%)               | 94 (8%)                   |
| Inotropes for low cardiac output   | 217 (36%)               | 6 (1.0%)               | 223 (18%)                 |
| Pulmonary edema requiring intubation   | 14 (2%)                 | 2 (0.3%)               | 16 (1%)                   |
| Cardiac arrest requiring CPR   | 25 (4%)                 | 2 (0.3%)               | 27 (2%)                   |
| Delirium   | 22 (4%)                 | 1 (0.2%)               | 23 (2%)                   |
|  |                         |                        |                           |
| CABG   | 0                       | 27 (4%)                | 27 (2%)                   |
| PCI  | 2 (0.3%)                | 2 (0.3%)               | 4 (0.3%)                  |
| LVAD insert  | 2 (0.3%)                | 1 (0.2%)               | 3 (0.2%)                  |
| Heart transplant   | 0                       | 0                      | 0                         |
| ICD implantation   | 12 (2%)                 | 19 (3%)                | 31 (3%)                   |
|  |                         |                        |                           |
| Death  | 22 (3.6%)               | 7 (1.2%)               | 29 (2.4%)                 |
| Acute MI   | 6 (1.0%)                | 2 (0.3%)               | 8 (0.7%)                  |
| Stroke   | 11 (1.8%)               | 1 (0.2%)               | 12 (1.0%)                 |
|  |                         |                        |                           |
| <b>Protocol Related Serious Adverse Events during the first 5 years of follow-up<sup>2</sup></b>   |                         |                        |                           |
| Major disabling stroke   | 16 (3%)                 | 16 (3%)                | 32 (3%)                   |
| New acute renal failure requiring dialysis   | 7 (1%)                  | 0                      | 7 (0.6%)                  |
| Peripheral arterial embolization requiring surgery or PCI  | 3 (0.5%)                | 4 (0.7%)               | 7 (0.6%)                  |
| Other <sup>3</sup>   | 75 (12%)                | 68 (11%)               | 143 (12%)                 |
| Cardiac Disorders <sup>4</sup>   | 48 (8%)                 | 47 (8%)                | 95 (8%)                   |
| Cardiac arrhythmias  | 25 (4%)                 | 21 (3%)                | 46 (4%)                   |
| Heart failures   | 19 (3%)                 | 18 (3%)                | 37 (3%)                   |
| Coronary artery disorders  | 7 (1%)                  | 9 (1%)                 | 16 (1%)                   |
| Myocardial disorders   | 1 (0.2%)                | 1 (0.2%)               | 2 (0.2%)                  |
| Pericardial disorders  | 1 (0.2%)                | 1 (0.2%)               | 2 (0.2%)                  |
| Cardiac disorder signs and symptoms  | 1 (0.2%)                | 2 (0.3%)               | 3 (0.2%)                  |
| Cardiac valve disorders  | 0                       | 1 (0.2%)               | 1 (0.1%)                  |

**Table S7. Summary of Adverse Events (Continued)**

| <b>Events</b>  | <b>CABG<br/>(N=610)</b> | <b>MED<br/>(N=602)</b> | <b>Total<br/>(N=1212)</b> |
|--|-------------------------|------------------------|---------------------------|
| Respiratory, thoracic and mediastinal disorders                        | 11 (2%)                 | 4 (0.7%)               | 15 (1%)                   |
| Infections and infestations  | 8 (1%)                  | 5 (0.8%)               | 13 (1%)                   |
| Vascular disorders   | 2 (0.3%)                | 4 (0.7%)               | 6 (0.5%)                  |
| Gastrointestinal disorders   | 2 (0.3%)                | 4 (0.7%)               | 6 (0.5%)                  |
| General disorders and administration site conditions <sup>5</sup>      | 3 (0.5%)                | 3 (0.5%)               | 6 (0.5%)                  |
| Neoplasms benign, malignant and unspecified (include cysts and polyps) | 0                       | 7 (1%)                 | 7 (0.6%)                  |
| Hepatobiliary disorders  | 1 (0.2%)                | 2 (0.3%)               | 3 (0.2%)                  |
| Injury, poisoning and procedural complications                         | 2 (0.3%)                | 1 (0.2%)               | 3 (0.2%)                  |
| Nervous system disorders   | 3 (0.5%)                | 2 (0.3%)               | 5 (0.4%)                  |
| Metabolism and nutrition disorders                                     | 1 (0.2%)                | 3 (0.5%)               | 4 (0.3%)                  |
| Renal and urinary disorders  | 3 (0.5%)                | 0                      | 3 (0.2%)                  |
| Musculoskeletal and connective tissue disorders                        | 2 (0.3%)                | 0                      | 2 (0.2%)                  |
| Skin and subcutaneous tissue disorders                                 | 2 (0.3%)                | 0                      | 2 (0.2%)                  |
| Endocrine disorders  | 0                       | 1 (0.2%)               | 1 (0.1%)                  |
| Ear and labyrinth disorders  | 0                       | 1 (0.2%)               | 1 (0.1%)                  |
| Blood and lymphatic system disorders                                   | 0                       | 1 (0.2%)               | 1 (0.1%)                  |
| Psychiatric disorders  | 0                       | 1 (0.2%)               | 1 (0.1%)                  |
| Investigations   | 0                       | 1 (0.2%)               | 1 (0.1%)                  |
| Not classified by MEDRA  | 1 (0.2%)                | 0                      | 1 (0.1%)                  |
| <b>Clinical events during entire follow-up</b>                         |                         |                        |                           |
| Death  | 359 (59%)               | 398 (66%)              | 757 (62%)                 |
| Cardiovascular death <sup>6</sup>                                      | 247 (40%)               | 297 (49%)              | 544 (45%)                 |
| Sudden/arrhythmia death <sup>6</sup>                                   | 116 (19%)               | 154 (26%)              | 270 (22%)                 |
| Heart failure death <sup>6</sup>                                       | 66 (11%)                | 92 (15%)               | 158 (13%)                 |
| Acute MI   | 37 (6.1%)               | 55 (9.1%)              | 92 (7.6%)                 |
| Stroke   | 47 (7.7%)               | 41 (6.8%)              | 88 (7.3%)                 |
| Death or cardiac hospitalization                                       | 467 (77%)               | 524 (87%)              | 991 (82%)                 |
| Hospitalization (all cause)  | 349 (57%)               | 383 (64%)              | 732 (60%)                 |
| Hospitalization (cardiac)  | 278 (46%)               | 343 (57%)              | 621 (51%)                 |
| Hospitalization (heart failure)  | 157 (26%)               | 201 (33%)              | 358 (30%)                 |

<sup>1</sup> Refers to all other types of major postoperative infections (except mediastinitis), such as pneumonia, pyelonephritis, septicemia, and infections at the vein-harvest site.

<sup>2</sup> As reported in STICH database.

<sup>3</sup> System Organ Class (SOC) term from MEDRA is used here for these "Other" serious adverse event classifications.

<sup>4</sup> High Level Group Term from MEDRA is also provided for events with SOC term = "Cardiac Disorders".

<sup>5</sup> "Multiple organ failure" and "Device issue" are examples of this type of SAE.

<sup>6</sup> Cause of death is based on CEC adjudication when available; otherwise it is based on site reported data.