

**HHS PUBLIC ACCESS**

Author manuscript

*Circulation*. Author manuscript; available in PMC 2018 March 21.

Published in final edited form as:

*Circulation*. 2017 March 21; 135(12): 1136–1144. doi:10.1161/CIRCULATIONAHA.116.026075.**Sudden Cardiac Death in Patients with Ischemic Heart Failure Undergoing Coronary Artery Bypass Grafting: Results from the Surgical Treatment for Ischemic Heart Failure (STICH) Randomized Clinical Trial****Meena P. Rao, M.D., MPH<sup>1</sup>, Sana M. Al-Khatib, MD, MHS<sup>1</sup>, Sean D. Pokorney, MD, MBA<sup>1</sup>, Lilin She, PhD<sup>1</sup>, Alexander Romanov, MD, PhD<sup>2</sup>, Jose C. Nicolau, MD, PhD<sup>3</sup>, Kerry L. Lee, PhD<sup>1</sup>, Peter Carson, MD<sup>4</sup>, Craig H. Selzman, MD<sup>5</sup>, Janina Stepinska, MD<sup>6</sup>, John G. F. Cleland, MD, PhD<sup>7</sup>, Wiwun Tungsubutra, MD<sup>8</sup>, Patrice M. Desvigne-Nickens, MD<sup>9</sup>, Carla A. Sueta, MD<sup>10</sup>, Matthias Siepe, MD<sup>11</sup>, Irene Lang, MD<sup>12</sup>, Arthur M. Feldman, MD<sup>13</sup>, Michael Yii, MD<sup>14</sup>, Jean L. Rouleau, MD<sup>15</sup>, and Eric J. Velazquez, MD<sup>1</sup> on behalf of the STICH trial investigators**

<sup>1</sup>Duke Clinical Research Institute and Departments of Biostatistics and Bioinformatics (KLL) and Medicine (SMA, EJV), Duke University School of Medicine, Durham, NC <sup>2</sup>State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation <sup>3</sup>Heart Institute, University of Sao Paulo Medical School, Sao Paulo, Brazil <sup>4</sup>Washington D.C. VA Medical Center, Washington, DC <sup>5</sup>Division of Cardiothoracic Surgery, University of Utah, Salt Lake City, Utah <sup>6</sup>Institute of Cardiology, Warsaw, Poland <sup>7</sup>National Heart & Lung Institute, Royal Brompton & Harefield Hospitals, Imperial College, London, United Kingdom <sup>8</sup>Siriraj Hospital, Mahidol University, Bangkok, Thailand <sup>9</sup>Division of Cardiovascular Sciences, National Heart Lung, and Blood Institute, Bethesda, MD <sup>10</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC <sup>11</sup>University

Address for correspondence: Eric J. Velazquez, MD, Duke Clinical Research Institute, P.O. Box 17969, Durham NC 27715, Phone: 919-668-8926, Fax: 919-668-7169, [eric.velazquez@duke.edu](mailto:eric.velazquez@duke.edu).

**Disclosures**

Rao: Research/Research Grant: Medtronic Foundation

Al-Khatib: None

Pokorney: Research/Research Grant: Gilead, Boston Scientific; Consulting Fees/Honoraria: Medtronic, Boston Scientific

She: None

Romanov: None

Nicolau: None

Lee: None

Carson: None

Selzman: None

Stepinska: None

Cleland: None

Tungsubutra: None

Desvigne-Nickens: None

Sueta: None

Siepe: None

Lang: None

Feldman: None

Yii: None

Rouleau: None

Velazquez: Research Grants: NHLBI, Alnylam Pharmaceuticals, Inc., Amgen, Inc., Pfizer, Novartis; Consulting Fees/Honoraria: Amgen, Inc., Expert Exchange, Merck &amp; Co., New Century Health, Novartis

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Heart Center Freiburg-Bad Krozingen, Bad Krozingen, Germany <sup>12</sup>Medical University of Vienna, Vienna, Austria <sup>13</sup>Department of Medicine, Temple University School of Medicine, Philadelphia, PA <sup>14</sup>St. Vincent's Hospital, University of Melbourne, Fitzroy, Australia <sup>15</sup>Department of Medicine, Montreal Heart Institute, University of Montreal, Montreal, QC, Canada

## Abstract

**Background**—The risk of sudden cardiac death (SCD) in patients with heart failure following CABG has not been examined in a contemporary clinical trial of surgical revascularization. This analysis describes the incidence, timing and clinical predictors of SCD after CABG.

**Methods**—Patients enrolled in the Surgical Treatment of Ischemic Heart Failure (STICH) trial who underwent CABG with or without surgical ventricular reconstruction (SVR) were included. We excluded patients with prior ICD and those randomized only to medical therapy. The primary outcome was SCD as adjudicated by a blinded committee. A Cox model was used to examine and identify predictors of SCD. The Fine and Gray method was used to estimate the incidence of SCD accounting for the competing risk of other deaths.

**Results**—Over a median follow-up of 46 months, 113 patients of 1411 patients who received CABG without (n = 934) or with SVR (n = 477) had SCD; 311 died of other causes. The mean LVEF at enrollment was 28±9%. The 5-year cumulative incidence of SCD was 8.5%. Patients who had SCD and those who did not die were younger and had fewer comorbid conditions than those who died for reasons other than SCD. In the first 30 days after CABG, SCD (n=5) accounted for 7% of all deaths. The numerically greatest monthly rate of SCD was in the 31–90 day time period. In a multivariable analysis including baseline demographics, risk factors, coronary anatomy and LV function, ESVI and BNP were most strongly associated with SCD.

**Conclusions**—The monthly risk of SCD shortly after CABG among patients with a low LVEF is highest between the first and third month, suggesting that risk stratification for SCD should occur early in the postoperative period, particularly in patients with increased preoperative ESVI and/or BNP.

**Clinical Trial Registration**—NCT0002359 ([www.stichtrial.org](http://www.stichtrial.org))

## Keywords

Sudden Cardiac Death; Ischemic Cardiomyopathy; Heart Failure; Coronary Artery Bypass Grafting

## Journal Subject Terms

Sudden Cardiac Death; Ischemic Heart Disease; Revascularization

## Introduction

Patients with coronary artery disease and those with left ventricular dysfunction are thought to be at increased risk for sudden cardiac death (SCD).<sup>1</sup> While the implantable cardioverter-defibrillator (ICD) reduces SCD in patients with coronary artery disease and a moderately

depressed left ventricular ejection fraction (LVEF),<sup>2-5</sup> ICD implantation at the time of coronary artery bypass graft surgery (CABG) did not improve survival in a trial conducted in the 1990s.<sup>1,6</sup> While surgical revascularization may improve LVEF in a subset of patients,<sup>7</sup> strategies to predict LVEF improvement after CABG are not validated in the context of current guideline directed medical therapy. Improvement in LVEF after revascularization might render ICDs unnecessary; however, patients who undergo CABG with or without improvement in LVEF may remain at risk for SCD.<sup>8</sup> Also, there may be a delay between CABG and improvement in LVEF during which patients may be at risk for SCD.

The risk of SCD and how that risk might change over time after CABG is uncertain. Although most randomized clinical trials of primary prevention ICDs required a 90-day waiting period after CABG before implanting an ICD, the 2008 practice guidelines on device-based rhythm management did not mandate any waiting period after surgical revascularization by CABG.<sup>9</sup> Nonetheless, many major payers including the Centers for Medicare and Medicaid Services do not reimburse hospitals and health care providers for primary prevention ICDs implanted within 90 days after CABG and therefore, in the USA, ICD therapy is usually deferred. Therefore, it is important to determine the magnitude of SCD risk in heart failure patients recovering from CABG. This analysis describes the incidence, timing and clinical predictors of SCD after CABG in patients with coronary artery disease and a low LVEF.

## Methods

### Study Population

This study includes patients enrolled in the Surgical Treatment of Ischemic Heart Failure (STICH) trial with an LVEF  $\geq$  35% who underwent CABG or CABG plus surgical ventricular reconstruction (SVR). The STICH study design and results of the surgical revascularization and surgical ventricular reconstruction components have been previously described.<sup>10-13</sup> Briefly, the study enrolled patients who were candidates for at least two of the three possible therapeutic options, medical therapy alone, medical therapy plus CABG or medical therapy plus CABG and SVR. Of the 2136 patients randomized, we excluded patients who were randomized to medical therapy only (n=602), those randomized to CABG but did not receive CABG (n=74), those with ICD or pacemakers for resynchronization prior to randomization (n=44) and those who received an ICD or pacemaker after randomization but prior to CABG (n=5) leaving 1411 patients eligible for this analysis. The study complied with the Declaration of Helsinki, and the locally appointed ethics committee approved the research protocol. Informed consent was obtained from the subjects or their legally authorized representatives.

### Study Outcomes

A blinded committee adjudicated all deaths using pre-specified definitions of causes of death. SCD was defined by this committee as death that occurred suddenly and unexpectedly and judged to be due to a cardiovascular cause as previously described.<sup>14</sup>

## Statistical Analysis

Baseline or pre-operative characteristics of patients are presented as means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Data are presented for 3 groups of patients: 1) patients who had SCD, 2) patients who died of causes other than SCD, and 3) patients who did not die by the end of the study follow-up. Group comparisons with respect to baseline clinical characteristics were performed using the Kruskal-Wallis test for continuous variables and the conventional chi-square test for categorical variables.

Cox proportional hazard models were used to examine individual relationships of candidate clinical characteristics and SCD, censoring other deaths at the time of death.<sup>15</sup> Clinical characteristics included in the model were baseline patient demographics, medical history, prior cardiac procedures, presenting characteristics of heart failure (New York Heart Association [NYHA] heart failure class), Canadian Cardiovascular Society [CCS] angina, baseline laboratory measures, baseline medications, coronary anatomy, left ventricular function measures and volumes, six minute walk distance, and surgical details. Candidate variables also include biomarkers (such as B-type natriuretic peptide [BNP] and tumor necrosis factor receptor [TNFR] 1) and echocardiographic diastolic function variables such as E/A ratio, e velocity, deceleration time and right ventricular dysfunction. Of note, LVEF, end systolic volume index (ESVI) and other echocardiographic variables as above were independently measured in a blinded fashion by STICH core laboratories as previously described.<sup>16</sup>

Only a few of the included variables had greater than 2% missing data. The magnitude of missing data for the biomarkers and diastolic function parameters was high at 15–35%; this was addressed by the multiple imputation method, in which 25 multiply-imputed datasets (with missing values imputed) were created. Imputed datasets were used in the univariable and multivariable model analyses, where the results from the 25 datasets were appropriately combined. Variables with a significant ( $P<0.05$ ) or marginally significant relationship ( $P<0.10$ ) with SCD in the univariable models were included in the multivariable models. Backward elimination was used to determine factors that were statistically significant ( $p<0.05$ ) in a multivariable model for SCD.

Given the competing risk of SCD and other modes of death, cumulative incidence rates for SCD and other death were estimated using the Fine and Gray method when SCD and other death rates were reported.<sup>17</sup> The conditional SCD rates per month for different time intervals during follow-up were calculated using the cumulative incidence rate of SCD. For each time interval, the SCD rate per month is based on the difference between the cumulative incidence SCD rates at the end and the beginning of the time interval divided by the number of months for the time interval, under the condition that the patients survived to the beginning of the time interval. Confidence intervals for the SCD rates per month were obtained using bootstrapping methods.

SAS statistical software (version 9.2 or higher) was used in all analyses (SAS Institute, Cary NC). All statistical tests were two-sided and performed at a level of significance of  $\alpha=0.05$ .

## Results

Of the 1411 patients included in this analysis, 934 patients received CABG, and 477 received CABG plus SVR. During the median follow-up period of 46 months, 234 patients (16.6%) received an ICD. There were 113 (8.0%) and 311 (22.0%) patients who died from SCD and other causes of death, respectively. Baseline or pre-operative characteristics comparing patients who died from SCD, other causes of death and those who did not die are shown in Table 1. Patients who had SCD were younger, had fewer co-morbid conditions, and lower NYHA heart failure class than those who died from other causes. Patients who died from SCD had higher diastolic blood pressure and used more digoxin. Diuretics were used more frequently in all patients who died compared with those who lived. Patients who died of causes other than SCD were more likely to have three-vessel disease compared with patients who died suddenly. While LVEF was similar in patients who died of SCD and those who died of other causes, ESVI was higher in patients who died suddenly.

Cumulative incidence rates of SCD and other death over the 5-year follow-up period after CABG are shown in Table 2. The 1-year, 3-year and 5-year cumulative incidence of SCD after CABG in this patient population with low LVEF is 2.8%, 6.1% and 8.5% respectively. The conditional risk of SCD per month over different time intervals after revascularization is shown in Figure 1. In the first 30 days after CABG, the risk of SCD was 0.35% (95% CI, 0.15%–0.85%). The risk of SCD per month was numerically highest during the 31–90 day window [0.43% (95% CI 0.21%–0.67%)], although it was only slightly higher than the risk during the first month. After 6 months, the risk per month decreased to 0.14% (95% CI 0.07%–0.24%) and remained relatively stable thereafter.

The results of the univariable analyses on the relationship between baseline characteristics and SCD are shown in Table 3. Variables that have significant ( $p < 0.05$ ) or marginally significant ( $p < 0.10$ ) association with SCD in the univariable models are listed in Table 3 by the magnitude of their univariable chi-square statistics. Of all the variables studied, baseline BNP (chi-square=16.85,  $p < 0.001$ ) and ESVI (chi-square=16.53,  $p < 0.001$ ) are the most strongly associated with SCD. Other factors found to be associated with increased SCD risk included renal function, LVEF, right ventricular dysfunction, diuretic use, coronary artery disease index, history of atrial fibrillation/flutter, mitral regurgitation, stroke and intra-aortic balloon pump use. Statin use, hyperlipidemia, sodium level and having CABG plus SVR were found to be associated with lower SCD.

Variables found to be independently and significantly associated with SCD in the multivariable model are listed in Table 4. In the final multivariable model, ESVI was the strongest factor associated with SCD followed closely by BNP. Other factors associated with SCD are statin use, Duke Coronary Artery Disease Index, baseline sodium level, history of atrial fibrillation, and having received CABG plus SVR surgery. Figure 2 shows that as the ESVI increases, the 5-year risk of SCD increases as well (12.4% vs 5.7% for those in the 4<sup>th</sup> vs. 1<sup>st</sup> quartile of ESVI). Higher BNP value, high Duke Coronary Artery Disease Index, lower sodium level, and history of atrial fibrillation were also associated with increased risk of SCD, while statin use and having received CABG with SVR appeared to be associated with a lower risk of SCD. None of the factors in the final multivariable model were highly

discriminatory between SCD and death from other causes. The c-index for the final selected multivariable model for SCD was 0.70.

## Discussion

This paper has three main findings. First, in patients with a depressed LVEF and coronary artery disease undergoing CABG with or without SVR, the 5-year cumulative incidence of SCD was 8.5%. Second, the monthly risk of SCD was greatest between the first and third months after CABG and decreased subsequently remaining nearly constant after 6 months. Third, we identified several factors that are significantly associated with the risk of SCD including baseline ESVI, BNP, statin use, the Duke coronary artery disease index, serum sodium concentration, history of atrial fibrillation/flutter and having received CABG with SVR. Of these variables, baseline ESVI and BNP were most strongly associated with SCD. While baseline or pre-operative ESVI was also associated with death from other causes, it was more strongly associated with SCD than LVEF and, therefore, may be useful for determining which post-CABG patients might benefit from early interventions to reduce the risk of SCD.

In the STICH trial, CABG with medical therapy compared to medical therapy alone significantly reduced the risk of SCD as well as pump failure death and fatal MI death with the protective effect of CABG being most prominent beyond two years after CABG.<sup>11,13,14</sup> This analysis shows the monthly risk of SCD to be greatest between the first and third months after CABG. While overall SCD numbers are a low proportion of overall deaths, this observation is important as it challenges the current practice in the United States of postponing risk stratification for SCD and supports the pursuit of identifying those patients at high risk for SCD early after CABG.

The best method for risk stratifying post-CABG patients for SCD is yet to be determined; however, data from this analysis may help inform this process. We identified several clinical, echocardiographic, and blood test factors that are significantly associated with SCD. Unique to our model is the incorporation of echocardiographic data, biomarker data and medications. Interestingly, beta-blocker use was not significantly associated with SCD presumably due to the very high rates of use in this patient population. The observation in this population that baseline ESVI appeared to be more strongly associated with SCD than LVEF is interesting, and probably due in part to the universally depressed baseline LVEF mandated by protocol in this cohort. Our analysis did not incorporate follow-up postoperative LVEF data including at the time of the SCD event, so any conclusions regarding relationships between post-CABG LVEF and SCD would be largely speculative.<sup>7</sup> Future studies should focus on the relationship between follow-up LVEF and risk of SCD after CABG and should explore the role of other echocardiographic parameters and other imaging modalities in the risk stratification of post-CABG patients for SCD.

Even if accurate risk stratification of post-CABG patients for SCD is achievable, there is still great uncertainty as to how one would reduce this risk shortly after CABG. The CABG-PATCH trial showed no benefit from an ICD implanted at the time of CABG.<sup>1</sup> It may be that ICD implantation at the time of CABG is only beneficial in high-risk patients. It is also



possible that the wearable defibrillator is a beneficial strategy early on with a plan to pursue an ICD if the LVEF does not improve to  $> 35\%$  more than 90 days after CABG.<sup>18</sup> The advantage of the wearable defibrillator is it is non-invasive and does not commit patients to a lifelong therapy like the ICD especially if their LVEF becomes normal or near-normal. While data on the efficacy of the wearable defibrillator in this setting are lacking, a science advisory from the American Heart Association endorsed by the Heart Rhythm Society included a IIa recommendation on the use of wearable defibrillators after revascularization.<sup>19</sup>

As a post-hoc analysis our observations must be interpreted with caution; however, this is to date the most comprehensive analysis of SCD in a post-CABG patient population. Patients enrolled in STICH may not be representative of patients seen in routine clinical practice. This analysis includes patients who received CABG and CABG plus SVR although the vast majority of patients in clinical practice receive CABG only. We pursued this approach as the overall mortality in these two groups was not significantly different with the hazard ratio for all-cause mortality of 1.0 among those randomized to CABG or CABG plus SVR.<sup>12</sup> While the rates of SCD were higher among those who received CABG than those patients who underwent CABG plus SVR, the increase in SCD was offset by a corresponding and equalizing increase in non-SCD (Table 5). Whether SVR partially mitigates SCD risk relative to CABG is consistent with the construct posited in prior reports that exclusion of LV scar may diminish the burden of ventricular tachycardia as a substrate for SCD but is of unclear clinical impact in the era of ICD availability and the results of the STICH SVR study.<sup>12,20</sup> By affecting ESVI<sup>21</sup> and hemodynamics, SVR may have an antiarrhythmic effect; alternatively, SVR may result in scar tissue at the surgical incisions creating a potentially arrhythmogenic substrate. In STICH, the SVR patients were not followed long-term; therefore we looked at SCD in a 5-year window as opposed to a 10-year window. Overall arrhythmic deaths in this analysis are a small proportion of all deaths and although SCD was centrally adjudicated using pre-specified and well-accepted criteria, not all SCD events could be attributed to a ventricular arrhythmia and such granular data were not available. Unfortunately, we did not have data on ICD shocks or aborted SCA during follow-up. Finally, our model included baseline characteristics some of which might be affected by CABG, and our analysis does not account for changes that may have resulted from CABG.

## Conclusions

Among patients with a low LVEF undergoing CABG with or without SVR, the overall risk of SCD was low relative to all deaths. The risk of SCD peaked during the first and third month post CABG and subsequently declined and remained stable after 6 months. This observation suggests that patients with ischemic cardiomyopathy who undergo CABG may need to be risk stratified and potentially treated to prevent SCD prior to 90 days after CABG. Several pre-operative clinical, echocardiographic and biochemical factors are significantly associated with the risk of SCD that could inform SCD risk stratification. Future studies should examine the relationship between follow-up LV characteristics and risk of SCD after CABG, and define the best strategies for preventing SCD early after CABG.

## Acknowledgments

### Sources of Funding

This work was supported by grants U01-HL69015, U01-HL69013, and R01-HL10583 from the National Heart, Lung, and Blood Institute/National Institutes of Health. The views expressed in this manuscript do not necessarily reflect those of the NHLBI or the NIH.

## References

1. Bigger JT. for the Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. *N Engl J Med.* 1997; 337:1569–1575. [PubMed: 9371853]
2. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. for the Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmias. *N Engl J Med.* 1996; 335:1933–1940. [PubMed: 8960472]
3. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial investigators. *N Engl J Med.* 1999; 341:1882–1890. [PubMed: 10601507]
4. Moss AJ, Zareba W, Hall JW, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002; 346:877–883. [PubMed: 11907286]
5. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. for the Sudden Cardiac Death in HF Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive HF. *N Engl J Med.* 2005; 352:225–237. [PubMed: 15659722]
6. Goldenberg I, Moss AJ, McNitt S, Zareba W, Hall JW, Andrews ML, Wilber DJ, Klein HU. for the MADIT-II Investigators. Time dependence of defibrillator benefit after coronary revascularization in the multicenter automatic defibrillator implantation trial (MADIT)-II. *JACC.* 2006; 47:1811–1817. [PubMed: 16682305]
7. Vakil K, Florea V, Koene R, Kealhofer JV, Anand I, Adabag S. Effect of coronary artery bypass grafting on left ventricular ejection fraction in men eligible for implantable cardioverter defibrillator. *Am J Cardiol.* 2016; 117:957–960. [PubMed: 26803382]
8. Samady H, Elefteriades JA, Abbott BG, Mattera JA, McPherson CA, Wackers FJTh. Failure to improve left ventricular function after coronary revascularization for ischemic cardiomyopathy is not associated with worse outcome. *Circulation.* 1999; 100:1298–1304. [PubMed: 10491374]
9. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW. American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices); American Association for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *Circulation.* 2008; 117:e350–e408. [PubMed: 18483207]
10. Velazquez EJ, Lee KL, O'Connor CM, Oh JK, Bonow RO, Pohost GM, Feldman AM, Mark DB, Panza JA, Sopko G, Rouleau JL, Jones RH. STICH investigators. The rationale and design of the Surgical Treatment for Ischemic Heart Failure (STICH) trial. *J Thorac Cardiovasc Surg.* 2007; 134:1540–1547. [PubMed: 18023680]
11. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yui M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Pranchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau. The STICH investigators.



- Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med.* 2011; 364:1607–1616. [PubMed: 21463150]
12. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, Hill JA, Menicanti L, Sadowski Z, Desvigne-Nickens, Rouleau JL, Lee KL. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med.* 2009; 360:1705–1717. [PubMed: 19329820]
  13. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doerst T, Petrie MC, Oh JK, She L, Moore VL, Desvigne-Nickens P, Sopko G, Rouleau JL. for the STICHES Investigators. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. *N Engl J Med.* 2016; 374:1511–1520. [PubMed: 27040723]
  14. Carson P, Wertheimer J, Miller A, O'Connor CM, Pina IL, Selzman C, Sueta C, She L, Greene D, Lee KL, Jones RH, Velazquez EJ. for the STICH investigators. Surgical Treatment for Ischemic Heart failure (STICH) Trial: Mode of death results. *J Am Coll Cardiol HF.* 2013; 1:1–9.
  15. Cox DR. Regression models and life tables. *J R Stat Soc Ser B.* 1972; 34:187–200.
  16. Oh JK, Pellikka PA, Panza JA, Biernal J, Attisano T, Manahan BG, Wiste HJ, Lin G, Lee KL, Miller FA, Stevens S, Sopko G, She L, Velazquez EJ. Core Lab Analysis of Baseline Echocardiographic Studies in the STICH Trial and Recommendation for Use of Echocardiography in Future Clinical Trials. *J of the American Society of Echocardiography.* 2013; 25:327–336.
  17. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999; 94:496–509.
  18. Feldman AM, Klein H, Tchou P, Murali, Hall WJ, Mancini D, Harvey M, Hellman MS, Szymkiewicz SJ, Moss AJ. WEARIT investigators and coordinators, BIROAD investigators and coordinators. Use of a Wearable Defibrillator in terminating tachyarrhythmias in patients at high risk for sudden death: results of WEARIT/BIROAD. *Pacing Clin Electrophysiol.* 2004; 27:4–9. [PubMed: 14720148]
  19. Piccini JP, Allen LA, Kudenchuk PJ, Page RL, Patel MR, Turakhia MP. American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology and Council on Cardiovascular and Stroke Nursing. Wearable Cardioverter-Defibrillator Therapy for the Prevention of Sudden Cardiac Death. A Science Advisory From the American Heart Association. *Circulation.* 2016; 133:1715–1727. [PubMed: 27022063]
  20. Sartipy U, Albage A, Straat E, Insulander P, Lindblom D. Surgery for ventricular tachycardia in patients undergoing left ventricular reconstruction by the Dor procedure. *Ann Thorac Surg.* 2006; 81:65–71. [PubMed: 16368337]
  21. Michler RE, Rouleau JL, Al-Khalidi HR, Bonow RO, Pellikka PA, Pohost GM, Holly TA, Oh JK, Dagenais F, Milano C, Wrobel K, Pirk J, Ali IS, Jones RH, Velazquez EJ, Lee KL, Di Donato M. for the STICH Investigators. Insights from the STICH trial: change in left ventricular size after coronary artery bypass grafting with and without surgical ventricular reconstruction. *J Thorac Cardiovasc Surg.* 2013; 146:1139–1145. [PubMed: 23111018]

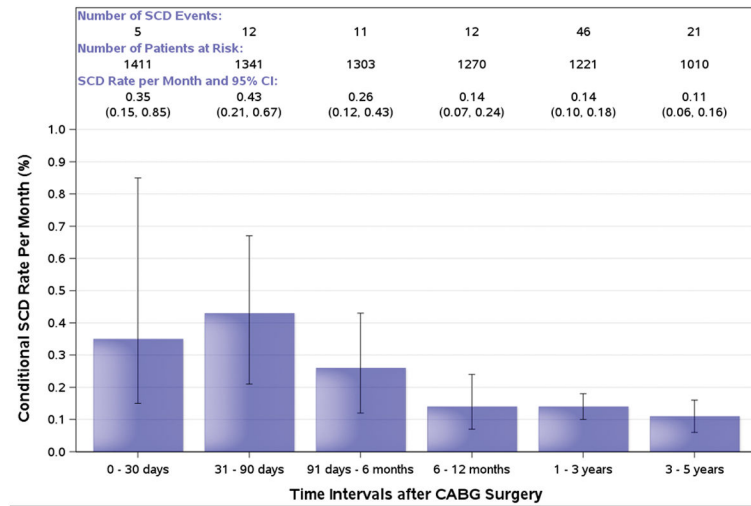
### Clinical Perspective

#### What is new?

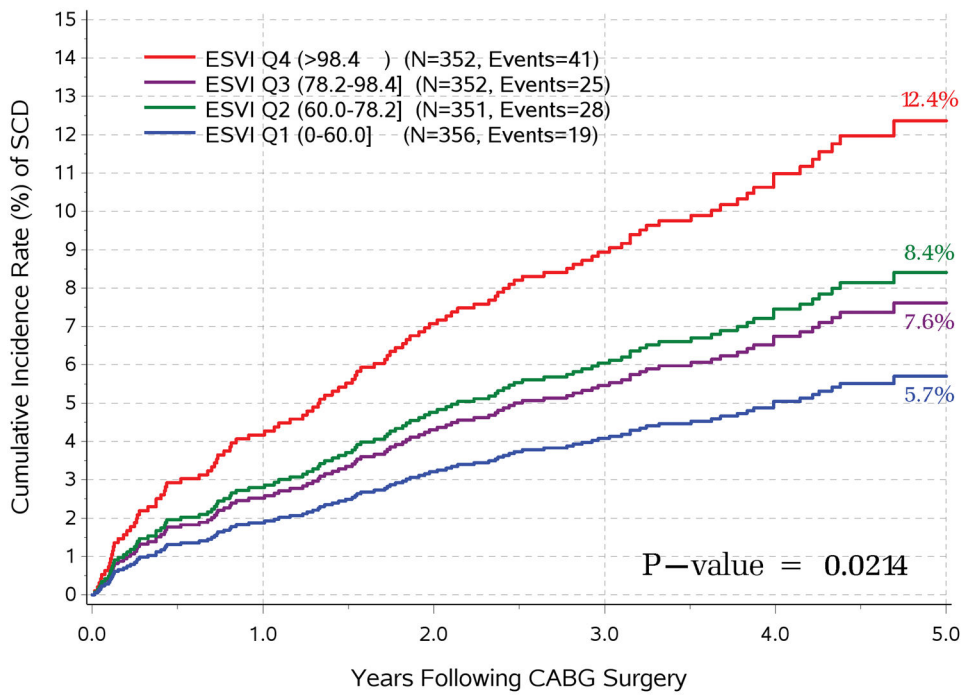
- The timing of sudden cardiac death (SCD) in patients with heart failure and coronary disease was found to be highest during the first and third months after coronary artery bypass surgery (CABG).
- In this analysis, several clinical, echocardiographic and biochemical factors were found to be significantly associated with the risk of SCD particularly preoperative ESVI and/or BNP.

#### What are the clinical implications?

- Patients with ischemic cardiomyopathy who undergo CABG may need to be risk stratified prior to 90 days after CABG to help prevent SCD.
- Pre-operative clinical predictors can help inform early SCD risk stratification.



**Figure 1.** Conditional risk of sudden cardiac death per month for different time intervals after coronary artery bypass graft surgery



**Figure 2.** Cumulative incidence rates of sudden cardiac death after coronary artery bypass grafting by ESVI quartiles

Baseline characteristics of patients who, after CABG with or without SVR, died suddenly compared with those who died of other causes and those who did not die

Table 1

| Characteristics: No. (%)      | All patients (N=1411) | SCD (n=113) | Other deaths (n=311) | No death (n=987) | p-value |
|-------------------------------|-----------------------|-------------|----------------------|------------------|---------|
| Age                           | 61 ± 10               | 61 ± 10     | 65 ± 9               | 60 ± 9           | <0.001  |
| Male                          | 1212 (86)             | 99 (88)     | 268 (86)             | 845 (86)         | 0.836   |
| White                         | 1153 (82)             | 93 (82)     | 270 (87)             | 790 (80)         | 0.026   |
| Medical History               |                       |             |                      |                  |         |
| Stroke                        | 94 (7)                | 11 (10)     | 35 (11)              | 48 (5)           | <0.001  |
| Diabetes                      | 518 (37)              | 44 (38)     | 140 (45)             | 335 (34)         | 0.002   |
| Hypertension                  | 839 (59)              | 61 (54)     | 197 (63)             | 581 (59)         | 0.174   |
| Hyperlipidemia                | 947 (67)              | 65 (58)     | 199 (64)             | 683 (69)         | 0.017   |
| Peripheral vascular disease   | 208 (15)              | 20 (18)     | 64 (21)              | 124 (13)         | 0.002   |
| Chronic kidney disease        | 108 (8)               | 15 (13)     | 45 (15)              | 48 (5)           | <0.001  |
| Atrial flutter/fibrillation   | 161 (11)              | 18 (16)     | 59 (19)              | 84 (9)           | <0.001  |
| Prior CABG                    | 36 (3)                | 2 (2)       | 16 (5)               | 18 (2)           | 0.005   |
| NYHA heart failure class      |                       |             |                      |                  | <0.001  |
| I                             | 132 (9)               | 9 (8)       | 22 (7)               | 101 (10)         |         |
| II                            | 655 (46)              | 57 (50)     | 124 (40)             | 474 (48)         |         |
| III                           | 560 (40)              | 41 (36)     | 134 (43)             | 385 (39)         |         |
| IV                            | 64 (5)                | 6 (5)       | 31 (10)              | 27 (3)           |         |
| Diastolic blood pressure      | 74 ± 11               | 75 ± 10     | 73 ± 12              | 75 ± 11          | 0.052   |
| Three vessel coronary disease | 909 (64)              | 70 (62)     | 218 (70)             | 621 (63)         | 0.060   |
| LVEF%                         | 28 ± 9                | 26 ± 9      | 26 ± 8               | 29 ± 9           | <0.001  |
| ESVI                          | 83 ± 32               | 93 ± 37     | 89 ± 35              | 79 ± 31          | <0.001  |
| EDVI                          | 116 ± 40              | 127 ± 42    | 124 ± 44             | 112 ± 38         | <0.001  |
| BNP                           | 442 ± 501             | 622 ± 609   | 568 ± 664            | 381 ± 403        | <0.001  |
| Mitral regurgitation          |                       |             |                      |                  | <0.001  |
| None or Trace                 | 513 (37)              | 36 (32)     | 90 (29)              | 387 (39)         |         |
| Mild ( 2+)                    | 655 (47)              | 51 (46)     | 153 (50)             | 451 (46)         |         |

| Characteristics: No. (%)     | All patients (N=1411) | SCD (n=113) | Other deaths (n=311) | No death (n=987) | p-value |
|------------------------------|-----------------------|-------------|----------------------|------------------|---------|
| Moderate (3+)                | 188 (13)              | 19 (17)     | 46 (15)              | 123 (13)         |         |
| Severe (4+)                  | 46 (3)                | 6 (5)       | 20 (7)               | 20 (2)           |         |
| Medications                  |                       |             |                      |                  |         |
| Beta-blocker                 | 1202 (85)             | 96 (85)     | 247 (79)             | 859 (87)         | 0.004   |
| Digoxin                      | 230 (16)              | 25 (22)     | 61 (20)              | 144 (15)         | 0.024   |
| ACE-I/ARB                    | 1249 (89)             | 95 (84)     | 277 (89)             | 877 (89)         | 0.301   |
| Antiarrhythmic drug use      | 165 (12)              | 17 (15)     | 48 (15)              | 100 (10)         | 0.021   |
| Statin                       | 1090 (77)             | 78 (69)     | 228 (73)             | 784 (79)         | 0.008   |
| Diuretic (loop/thiazide)     | 861 (61)              | 84 (74)     | 224 (72)             | 553 (56)         | <0.001  |
| Diuretic (potassium sparing) | 566 (40)              | 45 (40)     | 154 (50)             | 367 (37)         | <0.001  |

CABG=coronary artery bypass graft, NYHA=New York Heart Association, EF=ejection fraction, ESVI=end systolic volume index, EDVI=end diastolic volume index, BNP=B-type Natriuretic peptide, ACE-I= angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker



**Table 2**

Cumulative Number of Events and Cumulative Incidence Rate (%) of Sudden Cardiac Death and Other Death for Different Time Points after Surgery among 1411 Patients

| Time after Surgery | Sudden Cardiac Death        |  | Other Death                 |  |
|--------------------|-----------------------------|--|-----------------------------|--|
|                    | Cumulative Number of Deaths | Cumulative Incidence Rate (%) and 95% CI | Cumulative Number of Deaths | Cumulative Incidence Rate (%) and 95% CI |
| 30 days            | 5                           | 0.4 (0.2, 0.9)                           | 65                          | 4.6 (3.7, 5.7)                           |
| 90 days            | 17                          | 1.2 (0.7, 2.0)                           | 90                          | 6.4 (5.2, 7.7)                           |
| 6 months           | 28                          | 2.0 (1.4, 2.8)                           | 114                         | 8.1 (6.8, 9.6)                           |
| 1 year             | 40                          | 2.8 (2.1, 3.8)                           | 148                         | 10.5 (9.1, 12.0)                         |
| 3 years            | 86                          | 6.1 (4.9, 7.6)                           | 231                         | 16.4 (14.6, 18.5)                        |
| 5 years*           | 107                         | 8.5 (7.2, 10.1)                          | 300                         | 25.3 (22.9, 28.0)                        |

\* There were 6 sudden cardiac deaths and 11 other deaths happened during the follow-up period that was "> 5 years" after the surgery.

**Table 3**

Baseline variables predicting sudden cardiac death in univariate analyses

| Variable                                       | Wald Chi-Square | HR   | 95% CI     | p-value |
|--|-----------------|------|------------|---------|
| BNP in 100pg/ml increment*                     | 16.85           | 1.21 | 1.10–1.33  | <0.001  |
| ESVI in 20 ml/m <sup>2</sup> increment         | 16.53           | 1.22 | 1.11–1.35  | <0.001  |
| Creatinine (mg/dL)                             | 13.02           | 1.58 | 1.23–2.03  | <0.001  |
| LVEF in 5% increment                           | 10.75           | 0.83 | 0.74–0.93  | 0.001   |
| Duke CAD index in 10 point increments          | 10.62           | 1.15 | 1.06–1.26  | 0.001   |
| Chronic renal insufficiency                    | 9.63            | 2.37 | 1.37–4.08  | 0.002   |
| TNF receptor*                                  | 9.54            |      |            | 0.009   |
| 1000–1800 in 200pg/mL increments               |                 | 1.16 | 1.00–1.34  |         |
| >1800 in 200pg/mL increments                   |                 | 1.02 | 1.00–1.04  |         |
| Diuretics (loop/thiazide or potassium sparing) | 8.34            | 2.01 | 1.25–3.23  | 0.004   |
| Statin   | 6.66            | 0.59 | 0.40–0.88  | 0.010   |
| RV dysfunction*                                | 6.22            | 1.33 | 1.06–1.65  | 0.013   |
| New onset ventricular arrhythmia               | 6.15            | 5.97 | 1.45–24.53 | 0.013   |
| Hyperlipidemia                                 | 5.91            | 0.63 | 0.43–0.91  | 0.015   |
| Atrial flutter/fibrillation                    | 5.60            | 1.84 | 1.11–3.04  | 0.018   |
| Mitral regurgitation*                          | 5.31            | 1.31 | 1.04–1.64  | 0.021   |
| E/A ratio overall*                             | 5.20            |      |            | 0.074   |
| 1.6–2.0 in 0.1 increments                      |                 | 1.19 | 1.03–1.39  |         |
| >2.0 in 0.1 increments                         |                 | 0.96 | 0.90–1.02  |         |
| Sodium in mEq/L                                | 4.40            | 0.95 | 0.91–1.00  | 0.036   |
| E velocity in m/s*                             | 4.29            | 2.29 | 1.04–5.04  | 0.039   |
| Deceleration time in 10ms increments*          | 4.06            | 0.91 | 0.84–1.00  | 0.044   |
| Stroke   | 3.53            | 1.82 | 0.97–3.38  | 0.060   |
| Received mitral valve procedure                | 3.46            | 1.54 | 0.98–2.44  | 0.063   |
| Received CABG + SVR                            | 3.43            | 0.66 | 0.42–1.02  | 0.064   |
| IABP for low cardiac output                    | 3.03            | 1.97 | 0.92–4.24  | 0.082   |

BNP=B-type natriuretic peptide, ESVI=end systolic volume index, LVEF=left ventricular ejection fraction, CAD=coronary artery disease, TNF=tumor necrosis factor, RV=right ventricle, CABG=coronary artery bypass graft, SVR=surgical ventricular reconstruction, IABP=intra-aortic balloon pump

HR=hazard ratio, CI=confidence interval

Variables with 10 or more patients with missing data are marked by “\*”. The number and percent of patients with missing data are as follows: BNP: 493 (34.9 %); TNFR1: 493 (34.9%); Deceleration time: 434 (30.8%); E/A ratio: 402 (28.5 %); E velocity: 337 (23.9% ); RV dysfunction: 209 (14.8%).

**Table 4**

Baseline variables predictive of sudden cardiac death in a multivariable model

| Variable                               | Wald Chi-Square | HR   | 95% CI    | p-value |
|--|-----------------|------|-----------|---------|
| ESVI in 20 ml/m <sup>2</sup> increment | 9.59            | 1.18 | 1.06–1.31 | 0.002   |
| BNP in 100 pg/mL increment up to 750   | 9.51            | 1.16 | 1.06–1.28 | 0.002   |
| Statin use                             | 7.52            | 0.57 | 0.38–0.85 | 0.006   |
| Duke CAD index in 10 point increments  | 5.71            | 1.11 | 1.02–1.22 | 0.017   |
| Sodium in mEq/L                        | 5.21            | 0.95 | 0.90–0.99 | 0.023   |
| History of atrial fibrillation/flutter | 5.01            | 1.79 | 1.08–2.98 | 0.025   |
| Received CABG+ SVR                     | 4.02            | 0.64 | 0.41–0.99 | 0.045   |

ESVI=end systolic volume index, BNP=B-type natriuretic peptide, CAD=coronary artery disease, CABG=coronary artery bypass graft, SVR=surgical ventricular reconstruction

HR=hazard ratio, CI=confidence interval

**Table 5**

Cumulative Incidence Rate (%) of Sudden Cardiac Death and Other Death for Different Time Points after Surgery by Treatment Received

| Time after Surgery | Cumulative Incidence Rate (%) and 95% CI |                  |                   |                   |
|--------------------|--|------------------|-------------------|-------------------|
|                    | SCD                                      |                  | Other Death       |                   |
|                    | CABG (N=934)                             | CABG+SVR (N=477) | CABG (N=934)      | CABG+SVR (N=477)  |
| 30 days            | 0.4 (0.2, 1.0)                           | 0.3 (0.1, 0.6)   | 4.4 (3.5, 5.6)    | 5.0 (3.9, 6.4)    |
| 90 days            | 1.4 (0.8, 2.2)                           | 0.9 (0.5, 1.6)   | 6.1 (5.0, 7.4)    | 6.9 (5.3, 9.0)    |
| 6 months           | 2.3 (1.6, 3.3)                           | 1.4 (0.9, 2.4)   | 7.7 (6.4, 9.4)    | 8.7 (6.7, 11.3)   |
| 1 year             | 3.2 (2.4, 4.4)                           | 2.0 (1.3, 3.1)   | 10.1 (8.6, 11.8)  | 11.3 (9.2, 14.0)  |
| 3 years            | 7.0 (5.5, 8.8)                           | 4.4 (3.0, 6.6)   | 15.8 (13.9, 17.9) | 17.7 (14.8, 21.1) |
| 5 years            | 9.6 (7.8, 11.8)                          | 6.1 (4.1, 9.1)   | 24.4 (21.6, 27.6) | 27.2 (23.1, 32.0) |

SCD=sudden cardiac death, CABG=coronary artery bypass graft, SVR=surgical ventricular reconstruction, CI=confidence interval

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript