Prior Coronary Artery Bypass Surgery and Risk of Death Among Patients With Ischemic Left Ventricular Dysfunction

George D. Veenhuyzen, MD; Steven N. Singh, MD; Dorothea McA reavey, MD; Brent J. Shelton, PhD; Derek V. Exner, MD, MPH

Background—Patients with ischemic LV dysfunction are at high risk of sudden death. However, no benefit from prophylactic defibrillator therapy was observed in a group of patients with LV dysfunction undergoing CABG (CABG Patch trial). Thus, the effect of CABG on future risk of sudden death in patients with LV dysfunction is of considerable interest.

Methods and Results—Mortality and modes of death in 5410 patients with ischemic LV dysfunction who were enrolled in the Studies of Left Ventricular Dysfunction (SOLVD) trials were evaluated. Outcomes of patients with (n=1870, 35%) versus without (n=3540) history of prior CABG were compared, and stratification by baseline ejection fraction (EF) values (<0.25, 0.25 to 0.30, and ≥0.30) was performed. Prior CABG was associated with a 25% (95% CI, 15% to 36%) reduction in risk of death and a 46% (95% CI, 30% to 58%) reduction in risk of sudden death independent of EF and severity of heart failure symptoms. As baseline EF declined, absolute reduction in risk of sudden death with prior CABG increased (P<0.01). No alteration in risk of death from progressive heart failure was observed with prior CABG. When these results were applied to a group of patients with LV dysfunction who had not undergone prior surgery (Coronary Artery Surgery Study Registry) predicted annual rates of death (8.2%) and sudden death (2.4%) were similar to those observed in the CABG Patch trial (7.9% and 2.3%, respectively).

Conclusions—In patients with ischemic LV dysfunction, prior CABG is associated with a significant independent reduction in mortality. These results appear to account for the lack of benefit from defibrillator therapy in the CABG Patch trial. (Circulation. 2001;104:1489-1493.)

Key Words: bypass ■ ventricles ■ mortality ■ death, sudden

Sudden cardiac death, defined as death due to a cardiac or unexplained cause within 1 hour of symptom onset,1 claims the lives of ∼400 000 North Americans each year.2 Most of these deaths are due to ventricular tachyarrhythmias,3 often in the setting of ischemic heart disease.4–7 Because myocardial ischemia appears to be an important trigger for development of ventricular tachyarrhythmias,8 the potential influence of CABG on subsequent risk of sudden death is of considerable interest. The Coronary Artery Surgery Study (CASS)9 and European Coronary Surgery Study (ECSS)10 demonstrated reductions in sudden death with surgical versus medical therapy. Because ECSS excluded patients with ejection fraction (EF) values <0.50 and CASS excluded patients with values <0.35, the effect of CABG on risk of sudden death in patients with advanced LV dysfunction is unclear.

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The CABG Patch trial failed to show a benefit from prophylactic implantable cardioverter-defibrillator (ICD) therapy in patients with LVEF values ≤0.35 and abnormal signal-averaged ECGs who were undergoing CABG.11 This finding is particularly surprising given the consistent finding that patients with pronounced LV dysfunction benefit most from defibrillator therapy.12–14 Whether lack of benefit from defibrillator therapy in CABG Patch relates to coronary revascularization or other factors is unclear but of obvious significance. The present analysis was performed to evaluate the association of prior CABG with future risk of sudden death in a well-characterized group of patients with LVEF values ≤0.35. We sought specifically to quantify the effect of prior CABG on sudden death in terms of relative and absolute benefit stratified by degree of LV dysfunction.

Methods

Studies of LV Dysfunction

Patients 21 to 80 years of age with no prior history of intolerance to enalapril and LVEF values ≤0.35 measured by radionuclide angiography, echocardiography, or contrast angiography were eligible for enrollment in the Studies of LV Dysfunction (SOLVD) trials.15–17 Those who had had a recent myocardial infarction (≤30 days), significant valvular heart disease, or another serious comorbid illness were excluded. Specific inclusion and exclusion criteria have been published.15 All SOLVD participants (n=6797) underwent detailed evaluation at entry. Patients were classified as asymptomatic or symptomatic and enrolled in the prevention or treatment trial.

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respectively. The prevention trial included 4228 patients, approximately one third of whom had New York Heart Association (NYHA) functional class II symptoms. The treatment trial included 2569 patients with mostly NYHA functional class II and III symptoms. Patients were randomized to enalapril or placebo in each trial and followed for an average of 35±14 and 33±15 months in the prevention and treatment trials, respectively.

**End Points**
Deaths were evaluated in a masked fashion by the SOLVD investigators and classified as caused by worsening heart failure, arrhythmia with worsening heart failure, arrhythmia without worsening heart failure, myocardial infarction, other cardiovascular cause, or noncardiovascular cause. Because we recognized the unavoidable difficulties of classifying modes of death as arrhythmic versus nonarrhythmic, we used 2 definitions of sudden, arrhythmic death. The limited definition of sudden death included only those deaths classified as arrhythmic without preceding signs or symptoms of worsening heart failure, whereas the broad definition included deaths classified as arrhythmic, irrespective of preceding signs and symptoms of worsening heart failure.

**Coding of Variables**
Age, LVEF, and systolic and diastolic blood pressures were assessed as continuous measures. Study drug allocation (enalapril versus placebo) and sex of each patient were coded dichotomously. Cause of LV dysfunction was determined from local investigator’s assessment to be ischemic or other. Indicator variables were used for NYHA functional class (class II versus class I and class III/IV versus class I). All remaining covariates were coded dichotomously to indicate presence or absence of a characteristic or use or nonuse of a drug at baseline.

Of the 6797 participants in SOLVD, 5423 (80%) were categorized as having ischemic LV dysfunction. Information on prior CAGB surgery was available for 5410 (99.8%) patients with an ischemic origin of LV dysfunction. Dates of surgery were available for 1632 of 1870 (87%) patients with prior CAGB, but other operative details (ie, number of grafts, type of grafts, and extent of revascularization) were not recorded. To evaluate influence of degree of LV dysfunction on outcome, patients (N=5409) were divided into 3 groups of similar size on the basis of baseline LVEF values: <0.25 (n=1532), 0.25 to 0.30 (n=1883), and >0.30 (n=1994). Baseline LVEF was missing for 1 patient.

**Statistical Analysis**
Continuous characteristics are presented as mean±SD or proportions and compared by use of paired t test or χ² test. As a result of problems with accurate classification of deaths as arrhythmic or other, the limited definition of sudden death (arrhythmia without preceding worsening heart failure) and overall mortality were used as primary outcomes. Secondary outcomes included the broad definition of sudden death (arrhythmia without regard to preceding symptoms) and other modes of death. Unadjusted survival was assessed by use of the method of Kaplan and Meier. A Cox proportional hazards model was used to evaluate the association (univariate model) and independent association (multivariate model) of prior CAGB with outcome. The primary Cox multivariate model included age, sex, NYHA functional class, and baseline LVEF. Other models included important comorbid conditions (history of hypertension and history of diabetes) and baseline medication use (β-blocker, acetylsalicylic acid [aspirin], enalapril versus placebo). Relative risk estimates and 95% confidence intervals (CI) surrounding these estimates were obtained from the Cox models. All analyses were performed by use of Stata release 6.0 software. Because of the post hoc nature of these analyses, P≤0.01 was considered significant.

**Results**
Of 5410 patients with an ischemic cause of LV dysfunction, 1870 (35%) had undergone CAGB before enrollment. Median time from CAGB to enrollment was 1.8 years (25th percentile, 6 months, and 75th percentile, 5 years). Fewer patients with prior CAGB were female, black, or smoked actively at time of enrollment (Table 1). Discrepancies in use of anticoagulants, aspirin, and digoxin also were observed among patients with versus without history of prior CAGB.

### TABLE 1. Characteristics of Patients With Ischemic LV Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Prior CAGB</th>
<th>No Prior CAGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>1870</td>
<td>3540</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±9</td>
<td>60±10</td>
</tr>
<tr>
<td>Women, %</td>
<td>8</td>
<td>15*</td>
</tr>
<tr>
<td>Black race, %</td>
<td>5</td>
<td>10*</td>
</tr>
<tr>
<td>Randomization to enalapril, %</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>II</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>III/IV</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.28±0.06</td>
<td>0.27±0.06</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>125±16</td>
<td>125±17</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77±10</td>
<td>77±10</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>17</td>
<td>25*</td>
</tr>
<tr>
<td>β-blocker, %</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Potassium-wasting diuretic, %</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>69</td>
<td>43*</td>
</tr>
<tr>
<td>Anticoagulant, %</td>
<td>8</td>
<td>13*</td>
</tr>
<tr>
<td>Digoxin, %</td>
<td>32</td>
<td>28*</td>
</tr>
<tr>
<td>Antiarrhythmic drugs, %</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

*P<0.01.

Absolute Benefit
CAGB was associated with a significant reduction in the incidence of death from any cause. The largest proportion of deaths was categorized as sudden, with more than two thirds of these categorized as arrhythmic without preceding heart failure (limited definition of sudden death; Table 2). Reduction in mortality associated with prior CAGB was related largely to a lower incidence of sudden death. Incidence rates of death from progressive heart failure, myocardial infarction, and other cardiovascular causes were similar in patients with versus without history of prior CAGB.

Relative Benefit
Prior CAGB was associated with a 26% reduction in risk of death from any cause. A similar reduction in risk of death was observed after adjustment for important prognostic factors, comorbid illnesses, and baseline medication use (Table 3). Lower risk of mortality in patients with prior CAGB largely was due to significant reduction in risk of sudden death. Lower risk of sudden death was observed when either the
limited (46% reduction) or broad definition (39% reduction) was used. These reductions were not explained by important prognostic factors, comorbid illness, or baseline medication use. Prior CABG was not associated with a significant reduction in risk of death due to heart failure.

**Degree of LV Dysfunction**

Reduction in sudden death associated with prior CABG was examined in 3 groups stratified by LVEF values at baseline. Prior CABG was associated with significant reduction in risk of sudden death, regardless of definition used, in patients with the lowest (<0.25), intermediate (0.25 to 0.30), and most-preserved (>0.30) LVEF values (Table 4). As baseline LVEF declined, absolute risk reduction for sudden death significantly increased (test of trend $P<0.01$). No association was seen between prior CABG and risk of death from other cardiovascular causes, including myocardial infarction, when stratified by baseline LVEF.

**Discussion**

In patients with ischemic LV dysfunction, prior CABG is associated with a significant reduction in mortality independent of other prognostic factors. The benefit associated with prior CABG is attributable directly to a lower risk of sudden death, and relative benefit of CABG increases as LVEF declines. Death attributed to progressive heart failure is not altered significantly by prior CABG.

Prior randomized and observational analyses of the effect of CABG surgery on sudden death suggest that approximately half of all deaths among patients with CAD and impaired LV function are sudden and that total mortality and sudden death are reduced by $\geq50\%$ in patients who survive CABG surgery. The present analysis demonstrated a somewhat lower proportion of sudden deaths ($\approx40\%$ by limited definition) and smaller relative reductions in total mortality ($26\%$) and sudden death (39% by limited definition). These differences probably relate to variations in definitions of sudden death, methodology, relatively small sample sizes, and lack of adjustment for baseline differences among patients who receive CABG surgery versus medical therapy in past studies. The present analysis offers several advantages over previous studies. The SOLVD cohort is a large and well-characterized group of patients whose clinical outcomes were independently assessed in a blinded fashion. Furthermore, the medical and surgical therapies used are more similar to today’s standards than are those of studies conducted in the 1970s or earlier. Also, the use of both broad and limited definitions of sudden death avoids some of the inherent uncertainty in classifying death mode. Thus, estimates of the effect of

### TABLE 2. Cause-Specific Mortality

<table>
<thead>
<tr>
<th>Mechanism of Death</th>
<th>Prior CABG (n=1870)</th>
<th>No prior CABG (n=3540)</th>
<th>Reduction With CABG (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any mechanism</td>
<td>18.4, 6.5</td>
<td>24.3, 8.8</td>
<td>$-2.3 (-3.2, -1.4)$‡</td>
</tr>
<tr>
<td>Arrhythmia without preceding heart failure</td>
<td>4.1, 1.5</td>
<td>7.5, 2.7</td>
<td>$-1.2 (-1.7, -0.8)$‡</td>
</tr>
<tr>
<td>Heart failure with no arrhythmia</td>
<td>5.7, 2.0</td>
<td>6.4, 2.3</td>
<td>$-0.3 (-0.8, 0.2)$</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.2, 1.1</td>
<td>3.4, 1.2</td>
<td>$-0.1 (-0.5, 0.3)$</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>1.6, 0.5</td>
<td>1.6, 0.6</td>
<td>$-0.1 (-0.3, 0.2)$</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>1.8, 0.6</td>
<td>2.9, 1.0</td>
<td>$-0.4 (-0.7, -0.1)$‡</td>
</tr>
</tbody>
</table>

*Incidence per 100 person-years.  
†$P<0.01$.  
‡$P<0.001$.

### TABLE 3. Relationship Between Prior CABG Surgery and Outcome

<table>
<thead>
<tr>
<th>Relative Risk (95% Confidence Limits), %</th>
<th>All-Cause Mortality</th>
<th>Sudden Death</th>
<th>Death Attributable to Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Limited Definition</td>
<td>Broad Definition</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>$-26^* (-35 to -16)$</td>
<td>$-46^* (-58 to -31)$</td>
<td>$-39^* (-51 to -25)$</td>
</tr>
<tr>
<td>Adjusted for age, sex, LVEF, and NYHA class</td>
<td>$-25^* (-36 to -15)$</td>
<td>$-46^* (-58 to -30)$</td>
<td>$-39^* (-50 to -24)$</td>
</tr>
<tr>
<td>Add Diabetes, hypertension</td>
<td>$-25^* (-34 to -15)$</td>
<td>$-46^* (-58 to -30)$</td>
<td>$-38^* (-50 to -24)$</td>
</tr>
<tr>
<td>$\beta$-blocker, aspirin, enalapril</td>
<td>$-22^* (-31 to 11)$</td>
<td>$-44^* (-57 to -28)$</td>
<td>$-38^* (-50 to -23)$</td>
</tr>
</tbody>
</table>

*$P<0.01$.  
†$P<0.001$.  
‡$P<0.0001$.  
§$P<0.00001$.  
&$P<0.000001$.  
+$P<0.0000001$.  
##
prior CABG on risk of sudden death in the present analysis are more reliable than those of earlier studies.

**CABG Patch Trial**

Because sudden death accounts for approximately one half of all deaths in patients with advanced LV dysfunction, therapies aimed at reducing this mode of death should be expected to reduce significantly total mortality in this population. In fact, the greatest reductions in mortality associated with the use of an ICD occur in patients with advanced LV dysfunction. That the CABG Patch Trial, which enrolled patients with LVEF values ≤0.35, coronary artery disease treated with CABG surgery, and abnormal signal-averaged ECG, failed to demonstrate a survival advantage with prophylactic ICD implantation is surprising. One potential explanation for the negative result is that revascularization minimized risk of sudden death, which left little room for the potential effect of ICD therapy on sudden death and total mortality. In the control group, the 32-month incidence rates of death and arrhythmic death were 21.1%, and 6.2%, respectively.

Even if ICD prophylaxis reduced arrhythmic death by 50%, total mortality would have been reduced by only 15%. The trial was powered to show a 26% reduction in mortality at 40 months, so that the lack of a significant difference in total mortality is not surprising.

**ICD Efficacy After CABG**

Patients with LVEF values ≤0.35 treated medically in the CASS Registry had an annual mortality rate of 11.1% (Figure). On the basis of results of the present analysis, 40% of these deaths are anticipated to have been sudden (annual incidence of sudden death, 4.4%). Because CABG was associated with a 26% reduction in mortality and a 46% reduction in sudden death in the present analysis, expected post-CABG annual rate of death is ~8.2%, whereas expected post-CABG annual rate of rate of sudden death is ~2.4%

These estimates are similar to observed annual rates of death (7.9%) and arrhythmic death (2.3%) in CABG Patch patients who did not receive an ICD. Thus, that no difference was observed between the active treatment and control arms of the trial may be because CABG significantly reduced mortality, particularly sudden death, which diminished the power of the trial to show a benefit from ICD therapy. Although a 13% reduction in arrhythmic death was observed with ICD therapy in CABG Patch, the absolute difference was small (2.8%) due to the rarity of arrhythmic death in the CABG Patch cohort.

**Mechanism of Benefit From CABG**

In the present analysis, reduction in mortality associated with prior CABG was due primarily to a reduction in sudden death. Arrhythmic death most often is due to ventricular tachycardia that degenerates into ventricular fibrillation. Ventricular tachycardia is thought to occur when transient conditions superimpose on an anatomic substrate capable of supporting reentry. Acute ischemia produces abrupt reductions in local action potential duration and transmembrane resting potential and amplitude. These electrophysiological changes lead to a reduced time course of repolarization and upstroke velocity. Slow conduction and unidirectional block, which are required for reentry, then can exist adjacent to areas of normally perfused myocardium. CABG surgery is effective for relief from ischemia and may prevent sudden death by reducing acute ischemic events that may serve as triggers for lethal ventricular arrhythmias.

**Limitations**

Examining the effect of CABG surgery on mortality in a cohort of patients who have already survived CABG surgery ignores the influence of perioperative mortality. However, perioperative mortality now can be as low as 5.2% for CABG surgery in patients with severe LV dysfunction (EF <30%). Furthermore, CABG surgery was not a randomized event in the SOLVD trials, which leaves the possibility that confounding influences other than CABG surgery itself may be responsible for observed differences in mortality. However,

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**TABLE 4. Reduction in Sudden Death Risk With CABG, by Degree of LV Dysfunction**

<table>
<thead>
<tr>
<th>Baseline LVEF (No. of Patients)</th>
<th>Limited Definition (95% Confidence Limits)</th>
<th>Broad Definition (95% Confidence Limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute Reduction* Relative Reduction, %</td>
<td>Absolute Reduction* Relative Reduction, %</td>
</tr>
<tr>
<td>&gt;0.30 (n=1994)</td>
<td>-1.0† (-1.6 to -0.4) -52† (-72 to -19)</td>
<td>-1.0† (-1.7 to -0.4) -40† (-59 to -13)</td>
</tr>
<tr>
<td>0.25 to 0.30 (n=1883)</td>
<td>-1.1† (-1.8 to -0.3) -44† (-64 to -13)</td>
<td>-1.4† (-2.5 to -0.4) -39† (-58 to -11)</td>
</tr>
<tr>
<td>&lt;0.25 (n=1532)</td>
<td>-1.6† (-2.8 to -0.5) -38† (-58 to -9)</td>
<td>-1.7† (-3.2 to -0.3) -33† (-53 to -6)</td>
</tr>
</tbody>
</table>

*Rate per 100 person-years.
†P<0.01.
differences in outcome were not explained by differences in important prognostic factors (age, sex, LVEF, and NYHA functional class), concomitant illness, or medication use.

We acknowledge that any clinical definition of sudden death is imprecise\textsuperscript{28} and that overall mortality is a cleaner measure of therapeutic efficacy.\textsuperscript{29} Thus, we used both broad and limited definitions of sudden death. Despite the use of differing definitions, the effect of prior CABG on outcome was similar. Moreover, alterations in the risk of sudden death mirrored alterations in overall mortality.

The intent of the present analysis was to provide further insight into potential mechanisms of benefit from CABG. Although observational studies may provide reliable estimates of treatment efficacy,\textsuperscript{30,31} we recognize that a large, adequately powered randomized trial of CABG versus medical therapy would be required. However, because of the demonstrated efficacy of CABG surgery in terms of overall mortality in patients with more-preserved LV function,\textsuperscript{9,10} the appropriateness of such a study is questionable.

Conclusions

The present analysis confirms the benefit of CABG surgery on improved prognosis, provides a current estimate of treatment efficacy, and extends findings of past studies by addressing the influence of revascularization on sudden and other modes of death in patients with advanced LV dysfunction. CABG surgery is associated with a reduced risk of sudden death, which is most pronounced among patients with the worst LV function. This effect, which may explain the negative results of the CABC Patch Trial, should be considered in the planning of randomized trials of patients with advanced LV dysfunction who are receiving surgical revascularization.

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References

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