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# Pathogenesis of Sudden Unexpected Death in a Clinical Trial of Patients With Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure, or Both

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**Background**—The frequency of sudden unexpected death is highest in the early post-myocardial infarction (MI) period; nevertheless, 2 recent trials showed no improvement in mortality with early placement of an implantable cardioverter-defibrillator after MI.

**Methods and Results**—To better understand the pathophysiological events that lead to sudden death after MI, we assessed autopsy records in a series of cases classified as sudden death events in patients from the VALsartan In Acute myocardial infarction Trial (VALIANT). Autopsy records were available in 398 cases (14% of deaths). We determined that 105 patients had clinical circumstances consistent with sudden death. On the basis of the autopsy findings, we assessed the probable cause of sudden death and evaluated how these causes varied with time after MI. Of 105 deaths considered sudden on clinical grounds, autopsy suggested the following causes: 3 index MIs in the first 7 days (2.9%); 28 recurrent MIs (26.6%); 13 cardiac ruptures (12.4%); 4 pump failures (3.8%); 2 other cardiovascular causes (stroke or pulmonary embolism; 1.9%); and 1 noncardiovascular cause (1%). Fifty-four cases (51.4%) had no acute specific autopsy evidence other than the index MI and were thus presumed arrhythmic. The percentage of sudden death due to recurrent MI or rupture was highest in the first month after the index MI. By contrast, after 3 months, the percentage of presumed arrhythmic death was higher than recurrent MI or rupture ( $\chi^2=23.3$ ,  $P<0.0001$ ).

**Conclusions**—Recurrent MI or cardiac rupture accounts for a high proportion of sudden death in the early period after acute MI, whereas arrhythmic death may be more likely subsequently. These findings may help explain the lack of benefit of early implantable cardioverter-defibrillator therapy. (*Circulation*. 2010;122:597-602.)

**Key Words:** death, sudden ■ autopsy ■ myocardial infarction ■ heart failure ■ heart rupture

Early revascularization and the widespread use of  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, statins, and antiplatelet agents have contributed greatly to improved survival in the initial phases of acute myocardial infarction (MI)<sup>1-4</sup>; however, post-MI patients remain at substantial risk for ventricular arrhythmias and sudden cardiac death, an unpredictable complication of acute MI. Even with aggressive therapy, the risk of sudden cardiac death after MI remains high, accounting for 50% of overall mortality.<sup>5-9</sup> Long-term follow-up studies suggest that the risk of sudden cardiac death is highest in the early period after MI and declines substantially over time, particularly in patients with

reduced left ventricular function.<sup>10-15</sup> This observation has led to trials of implantable cardioverter-defibrillators (ICDs) in patients with a low left ventricular ejection fraction after MI.

## Clinical Perspective on p 602

Since the publication of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) results, which clearly demonstrated a benefit of empirical ICD therapy in patients with a left ventricular ejection fraction of 30% or less 1 month or more after MI,<sup>16</sup> ICD implantation has been recommended for almost all post-MI patients with an ejection fraction  $<30\%$ .<sup>17</sup> Yet, the Defibrillator IN Acute Myocardial Infarction Trial

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(DINAMIT)<sup>18</sup> and the Immediate Risk stratification Improves Survival (IRIS) trial<sup>19</sup> showed no improvement in mortality with early ICD placement 6 to 40 days after MI. As cardiovascular therapies evolve to target more specific mechanisms of deaths, a better understanding of specific causes of death in high-risk patients is necessary.<sup>20–22</sup> The diagnosis of sudden cardiac death within a clinical trial generally relies on source documentation that indicates that death was sudden and unexpected, because specific data relative to the mechanism, including acute MI, mechanical complication such as cardiac rupture, or arrhythmia, are rarely available. The OPTimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) review of patients on whom autopsies had been performed showed that an acute MI was found in 55% (37 of 67) of the deaths classified as sudden death.<sup>23</sup> This lack of precision in classification might have serious implications. Therefore, a better understanding of the underlying mechanisms of sudden cardiac death over time appears critical, particularly for optimization of the potential benefit of targeted strategies such as ICDs. We examined data from the VALsartan In Acute myocardial infarction Trial (VALIANT), assessed autopsy records in patients classified as having had sudden cardiac death events, and examined the influence of timing after MI on the specific cause of death derived from these autopsy reports.

## Methods

### Patient Population

The VALIANT trial randomized 14 703 patients with clinical evidence of heart failure, left ventricular dysfunction (ejection fraction <35% on echocardiography or ventriculography, or ejection fraction <40% on radionuclide imaging), or both after an acute MI to valsartan, captopril, or both.<sup>24</sup> Details of inclusion and exclusion criteria have been published previously. Over a median follow-up of 24.7 months, there were 2878 deaths. At the discretion of treating physicians and according to local practices, an autopsy was performed in 444 (15%) of these 2878 deaths; reports were available for 398 patients (present study group). A central adjudication committee reviewed all deaths in a blinded fashion using all source documentation provided by the investigators. Autopsy records were always taken into account at the time of the final adjudication. Deaths were first classified as cardiovascular or noncardiovascular. Cardiovascular deaths were further classified as sudden cardiac death or death due to an MI, heart failure, stroke, or other cardiovascular cause. The cause of death was considered as sudden cardiac death if death occurred suddenly and unexpectedly in a patient in otherwise stable condition, with no premonitory heart failure, MI, or another clear cause of death. These could have been witnessed deaths (with or without documentation of arrhythmias) or unwitnessed deaths if the patient had been seen within 24 hours before death.

### Classification of Deaths

For the present analysis, clinical circumstances of the deaths of these 398 patients were reanalyzed in a blinded manner by a single reviewer (A.C.P.) unaware of the autopsy results and of the final adjudication. A second individual (E.B.) ensured blinding of these charts by providing the reviewer with only copies of narrative and clinical summary from the original charts. Deaths were subsequently reclassified by the same reviewer (A.C.P.) after a hiatus of several weeks but this time with knowledge of the autopsy results. Although the data presented were primarily reviewed by a single reviewer (A.C.P.) who was not a member of the original VALIANT clinical end-points committee, this reviewer (A.C.P.) presented difficult cases on an ad hoc basis to original committee members as necessary. Each autopsy report was reviewed for the cause of death: presence of index or recurrent MI, myocardial rupture, signs of

severe pulmonary congestion, stroke, and pulmonary embolism. Recurrent acute MI was defined as the presence of fresh coronary thrombus, rupture plaque, or evidence of acute new myocardial damage as stated by the examining pathologist. The diagnosis of recurrent MI was only attributed in the presence of an explicit statement by the pathologist of histological evidence of recent myocardial damage and/or the presence of fresh coronary thrombus or rupture plaque. Nonspecific and imprecise terms such as ischemia/atherosclerosis were not considered as recurrent acute MI. Other cardiovascular or noncardiovascular causes of deaths were also recorded. Patients who died suddenly without any specific autopsy evidence of an acute pathological process that explained the cause of death were presumed to have died of an arrhythmic cause; however during the first 7 days after the index MI, index MI prevented the accurate attribution of any other diagnosis by the pathologist.

### Statistical Analysis

Continuous variables were expressed as mean±SD and were analyzed with Student *t* test. Categorical variables were compared with  $\chi^2$  or Fisher exact test when appropriate. The  $\kappa$ -statistic was used to evaluate the agreement with the initial adjudication by the end-point committee. The proportions of sudden cardiac death by presumed arrhythmic death or by MI/myocardial rupture were computed among the autopsied people with circumstances of sudden death at several study time periods. For all tests,  $P<0.05$  (2-sided) was considered significant.

## Results

### Baseline Characteristics

Baseline characteristics of the 398 patients included in the present analysis are shown in Table 1. Patients who underwent an autopsy were comparable to other patients who died with respect to gender, body mass index, systolic blood pressure, heart rate, ejection fraction, history of prior MI, use of  $\beta$ -blocker, and use of thrombolytic therapy; however, patients from the autopsy cohort were younger, more frequently white, had higher diastolic blood pressure, and were more likely to have a history of hypertension, and they were less likely to have diabetes or dyslipidemia or to have undergone primary percutaneous angioplasty. Autopsies were performed according to local practice. The majority of patients with autopsies performed (64.5%) were in Russia, where mandated autopsies were more common.<sup>25</sup>

### Clinical Classification of Deaths

The clinical classification of death in the 398 autopsies included in the present study is reported in Table 2. By clinical information only, 105 patients (26.4%) were classified as having died suddenly and unexpectedly, without any prior deterioration (6 of these who died in the first 7 days after the index MI were either already at home or died on the day of hospital discharge). Two hundred ninety-three patients had a nonsudden mode of death. Among the 398 autopsied cases, the clinical cause of death was attributed to a fatal MI in 163 cases (41%); 44 patients (11%) had a history compatible with a pump failure death, 18 (4.5%) with a stroke, and 13 (3.2%) with another cardiovascular cause of death, 10 (2.5%) died shortly after a percutaneous coronary intervention or a coronary artery bypass graft; 3 (0.8%) were presumed to have died a cardiovascular death; and the remaining 42 (10.6%) died of noncardiovascular causes.

### Autopsy-Based Adjudication in Patients With Unexpected Sudden Cardiac Death

Of 105 patients classified as having unexpected sudden cardiac death on the basis of clinical circumstances, 51 had

**Table 1. Demographic and Clinical Characteristics of Patients Who Died**

Characteristic	Autopsy Group (n=398)	Other Deaths (n=2480)	P
Age, y	67.7±10.1	70.7±10.7	<0.001
Male, %	64.6	62.7	0.51
White, %	97.5	93.6	0.021
Country, %			
Russia	64.5	19.6	<0.001
Norway	7.3	1.4	
Hungary	3.3	2.1	
Great Britain	3.3	4.1	
Canada	3.3	8.5	
United States	6.0	27.8	
Other	12.3	36.5	
Body mass index, kg/m <sup>2</sup>	27.0±4.7	27.4±5.4	0.26
Blood pressure, mm Hg			
Systolic	125.2±17.8	123.9±17.7	0.21
Diastolic	75.9±11.3	71.9±11.9	<0.001
Heart rate, bpm	79.1±13.8	78.7±13.7	0.59
LV ejection fraction, %	33±10	33±10	0.58
Qualifying MI, %			
Anterior	60.9	58.2	0.32
Inferior	37.5	31.5	0.022
Killip class, %			<0.001
I	13.9	18.2	
II	48.5	46.1	
III	30.8	25.5	
IV	6.8	10.2	
Prior MI, %	43.9	42.6	0.62
History of hypertension, %	70.6	63.1	<0.001
History of diabetes mellitus, %	21.6	33.5	<0.001
History of dyslipidemia, %	18.1	31.4	<0.001
β-Blocker, %	56.5	58.5	0.48
Primary PCI, %	3.0	8.5	<0.001
Thrombolytic therapy, %	24.9	23.9	0.69
Time to death, d	237±258	306±280	<0.001

LV indicates left ventricular; PCI, percutaneous coronary intervention.

specific acute pathological findings at the autopsy that explained the death. Six (5.7%) of these 105 patients died suddenly within 1 week of index MI; the index MI was the only finding in 3, and the remaining 3 had myocardial rupture. All of these patients were either already at home or died on the day of hospital discharge. Twenty-eight (26.6%) of the 105 patients had specific evidence of recurrent MI, 10 (9.5%) had evidence of cardiac rupture, 4 (3.8%) had evidence of overwhelming pulmonary congestion, 2 (1.9%) had evidence of another cardiovascular process (stroke or pulmonary embolism), and 1 (1%) had evidence of noncardiovascular causes of death (drug overdose). Fifty-four (51.4%) of the 105 patients had no specific autopsy evidence other than the index MI and were thus presumed to have died of arrhythmic causes (Figure 1). The clinical characteristics of the 98 patients who died suddenly of cardiac causes (either MI [n=31], myocardial rupture [n=13], or presumed arrhythmic death [n=54]) are reported in Table 3. Patients with presumed arrhythmic death had significantly lower ejection fraction (31.5±8.2% versus

**Table 2. Clinical Classification of Deaths**

Classification	Autopsy Group (n=398)	Other Deaths (n=2480)
Fatal MI, n (%)	163 (41.0)	425 (17.1)
SD, n (%)	105 (26.4)	872 (35.2)
Heart failure, n (%)	44 (11.0)	403 (16.3)
Stroke, n (%)	18 (4.5)	107 (4.3)
Other CV death, n (%)	26 (6.5)	330 (13.3)
Non-CV death, n (%)	42 (10.6)	343 (13.8)

SD indicates sudden death; CV, cardiovascular.

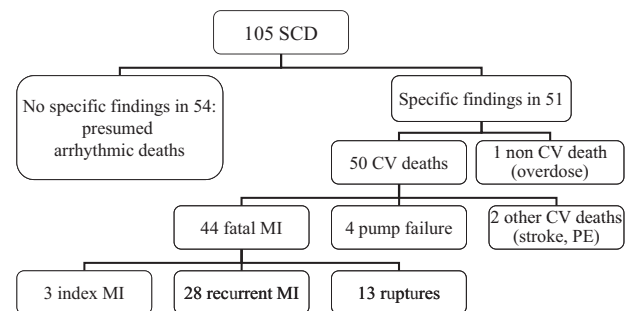
35.9±11.8%, *P*=0.035), and the mean time to death was significantly longer (306±246 versus 137±194 days, *P*<0.001) than for patients who died suddenly of MI/rupture. Because the highest percentage of autopsies occurred among Russian patients, we examined the prevalence of sudden unexpected death in Russia compared with other countries. We observed no difference in the percentage of patients with presumed arrhythmic death in Russia (34/257 [13.2%]) versus all the other countries (20/141 [14.2%], *P*=0.79).

**Autopsy-Based Adjudication in Patients Without Circumstances of Sudden Cardiac Death**

Mode of death was nonsudden in 293 patients. The most common cause of death was fatal MI in 168 patients (57.3%; myocardial rupture in 24 patients, index MI in 33, and recurrent MI in 111). The other deaths were classified as follows: pump failure in 36 patients (12.3%), stroke in 19 (6.5%), other cardiovascular deaths in 16 (5.5%), and procedure-related deaths in 10 (3.4%), whereas 3 patients (1%) were adjudicated as having had presumed cardiovascular deaths and 41 as having died of noncardiovascular causes (14%).

**Overall Clinical Adjudication of the Cause of Death Versus Autopsy-Based Adjudication**

Without knowledge of the autopsy reports, the most frequently adjudicated clinical causes of death were fatal MI in 163 patients (41%) and sudden cardiac death in 105 (26.4%). With the autopsy records, the cause of death had to be reclassified in 69 (17%) of the 398 patients, mostly because of previously unrecognized fatal MI/myocardial rupture in patients who died suddenly; the agreement between clinical adjudication without knowledge of an autopsy report and that made by the end-point committee was good (*κ*=0.74, *P*<0.0001; Figure 2). Among 212 cases of autopsy-based adjudication of fatal MI (myocardial rupture in 37 cases, index MI in 36, and recurrent MI in 139), the



**Figure 1.** Autopsy findings in 105 patients with sudden unexpected death. SCD indicates sudden cardiac death; CV, cardiovascular; and PE, pulmonary embolism.

**Table 3. Clinical Characteristics of 98 Patients With Sudden Unexpected Cardiac Death**

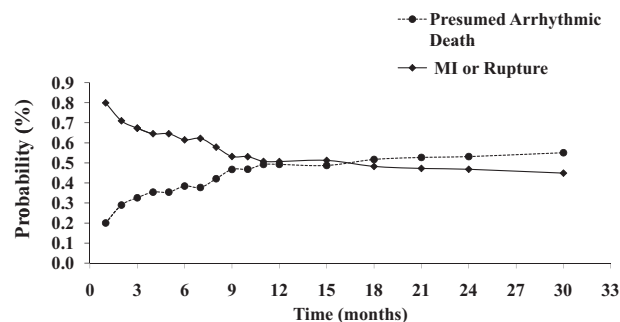
	Presumed Arrhythmic Death (n=54)	SD by MI/Ruptures (n=44)	P
Age, y	63.6±10.7	65.6±9.2	0.32
Male, %	77.7	75.0	0.75
White, %	98.1	97.7	0.36
Body mass index, kg/m <sup>2</sup>	26.0±4.2	27.9±5.1	0.048
Blood pressure, mm Hg			
Systolic	124.3±20.2	120.4±16.7	0.31
Diastolic	77.5±13.4	75.5±10.7	0.41
Heart rate, bpm	78.8±18.1	79.4±13.6	0.85
LV ejection fraction (in 59 patients), %	31.5±8.2	35.9±11.8	0.035
Qualifying MI, %			
Anterior	66.0	58.1	0.43
Inferior	30.2	47.5	0.088
Prior MI, %	35.2	29.5	0.55
History of hypertension, %	68.5	63.6	0.61
History of diabetes mellitus, %	20.4	29.5	0.29
History of dyslipidemia, %	22.6	19.1	0.67
eGFR, mL · min <sup>-1</sup> · 1.73 m <sup>-2</sup>	68.6±26.8	71.5±24.1	0.58
Primary PCI, %	6	5	0.63
Thrombolytic therapy, %	27.8	29.5	0.84
Time to death, d	306±246	137±194	<0.001

SD indicates sudden death; LV, left ventricular; eGFR, estimated glomerular filtration rate; and PCI, percutaneous coronary intervention.

mode of death was sudden and unexpected in 44 cases (21%). Autopsy-based adjudication by the single reviewer was similar to the initial adjudication by the end-point committee ( $\kappa=0.96$ ,  $P<0.0001$ ).

### Time Dependence of Sudden Cardiac Death Risk After MI

Among the 98 autopsied patients with a sudden cardiac death, the observed proportion of patients who died suddenly of recurrent MI/myocardial rupture or of a presumed arrhythmic cause was not constant over time. The rates of recurrent MI/rupture appeared highest in the early post-MI period and declined with time. In contrast, the rates of presumed arrhythmic

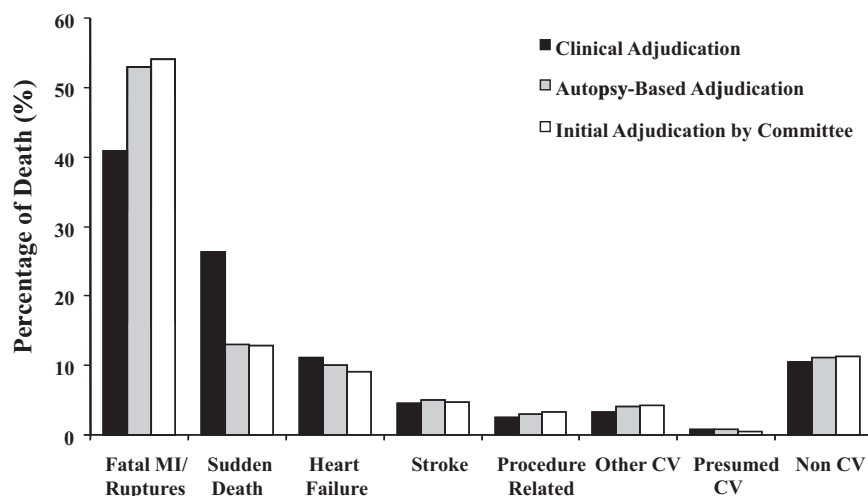


**Figure 3.** Observed proportions of sudden unexpected death by presumed arrhythmic death or by MI/myocardial rupture among 98 patients with clinical circumstances of sudden unexpected death.

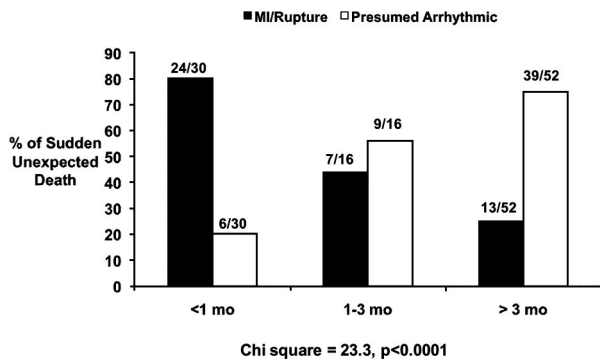
mic death increased over time (Figure 3). Indeed, the percentage of sudden cardiac death due to recurrent MI or rupture was highest in the first month after the index MI and declined substantially over time. By contrast, the percentage of presumed arrhythmic death increased significantly over time. Within the first month, only 20% of the sudden deaths were considered presumed arrhythmic compared with up to 75% beyond 3 months ( $\chi^2=23.3$ ,  $P<0.0001$ ; Figure 4).

### Discussion

The present study demonstrates that recurrent MI or cardiac rupture accounted for a high proportion of deaths among patients who died suddenly and unexpectedly after acute MI and underwent autopsy. Among 105 sudden deaths based on clinical circumstances, autopsy suggested the following causes: 3 index MIs in the first 7 days (2.9%), 28 recurrent MIs (26.6%), 13 cardiac ruptures (12.4%), 4 pump failures (3.8%), 2 other cardiovascular causes (stroke or pulmonary embolism; 1.9%), and 1 noncardiovascular cause (1%). Fifty-four cases (51.4%) had no acute specific autopsy evidence other than the index MI and were thus presumed arrhythmic. Specific autopsy-defined causes of sudden death such as recurrent MI or cardiac rupture appeared to be highest in the early post-MI period and were less frequent later, which suggests that arrhythmic death may be more likely subse-



**Figure 2.** Causes of death in all autopsied patients (n=398) based on clinical information only (black bars), based on autopsy findings (gray bars), and after initial adjudication by the end-point committee (white bars). CV indicates cardiovascular.



**Figure 4.** Percentage of sudden death by presumed arrhythmic death or MI/myocardial rupture over time in 98 patients.

quently. These findings may help explain the lack of benefit observed in recent early post-MI ICD trials.

The high prevalence of acute MI at autopsy in patients in the present study who died suddenly is consistent with the 54% to 60% prevalence reported in previous trials.<sup>23,26</sup> Indeed, the OPTIMAAL trial randomized 5477 patients with heart failure or evidence of left ventricular dysfunction after acute MI and observed 946 deaths. Autopsy reports were available in 180 (19%) of these deaths, of which only 67 (37%) had been adjudicated as sudden death. Their review of patients with autopsy results showed that an acute MI was found in 55% (37 of 67) of the deaths classified as sudden death, which is consistent with the present data; however, in their study, the proportion of sudden deaths attributed to recurrent MI appeared to be reasonably constant over time. Recurrent MI or mechanical complications such as cardiac rupture may indeed mimic sudden cardiac death and be unrecognized in the absence of autopsy records. The clinical diagnosis of the cause of death remains a difficult exercise, even with international consensus on diagnostic criteria and the use of end-point committees.<sup>27–29</sup> In most cases, autopsy is the only way to make an accurate diagnosis and to obtain a better assessment of the underlying mechanisms of deaths. However, diagnosis of recent MI by autopsy remains a challenge when death occurs early after the index MI. Index MI can still be confused by the pathologist as a new MI, obviously more likely sooner after the index event than later.

In the present series, 49% of the patients who died suddenly had acute structural abnormalities at autopsy. Patients who died suddenly of presumed arrhythmic death were similar to those who died suddenly of other causes with the exception of having a lower baseline ejection fraction and a longer time until death. The rate of primary angioplasty or thrombolysis was similarly low in the 2 groups. Our inability to distinguish these 2 groups of patients may reflect our lack of sophisticated measures of the risk of arrhythmia. Although depressed left ventricular function identifies patients with increased mortality risk and is widely used as a determinant of risk after MI, it does not allow a distinction to be made between patients who will die of arrhythmia and those who will die of other cardiovascular causes.<sup>10,30,31</sup>

The results of the present study suggest that recurrent MI may be responsible for a substantial number of cases of sudden cardiac death early after the index MI, with the risk of

sudden cardiac death by presumed arrhythmic mechanisms becoming more predominant only after several months. The large proportion of sudden cardiac death attributed to recurrent MI suggests that recurrent infarction may be especially important in the post-MI population. Moreover, in the present series, 13 patients who died suddenly had evidence of myocardial rupture by autopsy. Taken together, these findings may help explain the lack of benefit of early ICD therapy observed in the DINAMIT<sup>18</sup> and IRIS<sup>19</sup> trials, although this finding does not necessarily preclude benefit, because patients with acute MI may still die of cardiac arrhythmia.

Some limitations and strengths of the present analysis should be noted. Only a small percentage of the patients who died (444 [15%] of 2878) had an autopsy; nevertheless, the present series is relatively large compared with other recent cardiovascular trials that have reported autopsy findings, such as OPTIMAAL (180/946, 19%)<sup>23</sup> and the Assessment of Treatment with Lisinopril And Survival (ATLAS; 171/1383, 12%).<sup>26</sup> Autopsies were not assigned randomly, and there were clear geographic differences in the acquisition of autopsies; nevertheless, patients who underwent autopsy were very similar to those who did not with respect to baseline characteristics. Finally, autopsies were performed according to clinical practice, and the quality of these examinations varied. We must recognize and acknowledge that a large proportion of the autopsies were performed in 1 country, Russia, and their quality was not controlled. This is a main limitation of the data analysis. However, major problems related to autopsy are likely to result in underestimation of the prevalence of acute MI, so our key finding may be more conservative than what would be found if autopsies had a higher sensitivity for finding acute MI.

In summary, in patients with left ventricular dysfunction, heart failure, or both, recurrent MI or cardiac rupture accounts for a high proportion of deaths in patients who die suddenly and unexpectedly in the early period after acute MI, whereas arrhythmic death may be more likely subsequently. These findings may help explain the lack of benefit of early ICD therapy and underscore the importance of developing strategies to prevent recurrent ischemia to decrease the incidence of sudden cardiac death.

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## Disclosures

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### CLINICAL PERSPECTIVE

Sudden unexpected death is highest in the early post-myocardial infarction period. Yet, the Defibrillator in Acute Myocardial Infarction Trial and the Immediate Risk Stratification Improves Survival Trial showed no improvement in mortality with early placement of an implantable cardioverter-defibrillator 6 to 40 days after myocardial infarction. The Optimal Trial in Myocardial Infarction With Angiotensin II Antagonist Losartan review of patients with autopsies showed that an acute myocardial infarction was found in 55% (37 of 67) of the deaths classified as sudden death. This lack of precision in classification might have serious implications. To better understand the pathophysiological events that lead to sudden unexpected death after myocardial infarction, we assessed autopsy records in a series of cases classified as sudden cardiac death in patients from the Valsartan in Acute Myocardial Infarction Trial. The present study demonstrates that recurrent myocardial infarction or myocardial rupture account for a high proportion of sudden unexpected deaths in the early period after acute myocardial infarction, whereas arrhythmic death may be more likely subsequently. These findings may help explain the lack of benefit of early implantable cardioverter-defibrillator therapy.