Acute Coronary Findings at Autopsy in Heart Failure Patients With Sudden Death

Results From the Assessment of Treatment With Lisinopril and Survival (ATLAS) Trial

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Background—Sudden unexpected death frequently occurs in chronic heart failure. The importance of acute coronary events in triggering sudden death (SD) is unclear.

Methods and Results—We evaluated at autopsy the prevalence of acute coronary findings (coronary thrombus, ruptured plaque, or myocardial infarction [MI]) and their relation to SD. Autopsy results in 171 patients in the randomized ATLAS trial were reviewed. The prevalence of acute coronary findings was 33%; in 54% of patients with significant coronary artery disease (CAD) who died suddenly, 32% who died of myocardial failure, but in non-CAD patients, they were present in only 5% and 10% respectively. The percentage of patients classified as dying of MI was 28% in the autopsy group versus 4% in the nonautopsied group (P<0.0001). Of the autopsied group with acute MI, 97% (31 of 32 patients) with SD and 40% (6 of 15 patients) with myocardial failure did not have the MI diagnosed during life. When undiagnosed MI was classified as “sudden unexpected” or “myocardial failure” from clinical information only, the distribution of death causes was similar in the autopsy and nonautopsied groups.

Conclusions—Acute coronary findings are frequent and usually not clinically diagnosed in heart failure patients with CAD, particularly in those dying suddenly, suggesting the importance of acute coronary events as a trigger for SD in this setting. (Circulation. 2000;102:611-616.)

Key Words: death, sudden ■ heart failure ■ ischemia

Heart failure (HF) has become an increasingly prevalent cause of death worldwide. Despite advances in therapy, mortality rates remain high, with annual rates of 10% to 20% in patients with moderately severe to severe failure. Sudden unexpected death constitutes 30% to 50% of all deaths.1 Although sudden deaths (SD) are often considered arrhythmic, the rate of acute coronary events in this setting is uncertain. Clinical studies in patients with significant coronary artery disease (CAD) without HF have implied that a primary arrhythmia without an acute ischemic event may be the primary mechanism of SD in the majority of patients.2

In autopsy series, however, acute coronary findings are often present in patients who die suddenly, particularly those with CAD.3-6 In autopsy studies, a fresh thrombus, recent myocardial infarction (MI), or plaque rupture was found in 57% to 73% of CAD patients without HF who died suddenly.3,4

The relative importance of an acute coronary event as a trigger for SD in patients with HF is currently unknown. Recurrent MI is a frequent cause of terminal myocardial failure in patients with chronic CAD but has inconsistently been described in studies of HF patients. The frequency of recurrent MI compared with other causes of death in HF is unclear because most large clinical trials have not classified MI as a cause of death. As CAD accounts for ≥50% of HF patients in the Western world, it is possible that acute coronary events contribute importantly to the progression of HF and SD.

The ATLAS (Assessment of Treatment with Lisinopril and Survival) trial provides a unique opportunity to address this issue because there were many HF patients who underwent autopsy and were classified by means of prospectively developed definitions of mode and cause of death.

Methods

ATLAS Trial Design and Results

The ATLAS trial was a prospective, international, multicenter, randomized, double-blind, parallel-group study comparing the ef-
fects on mortality and mortality plus morbidity events of a low (2.5 to 5.0 mg) to a high (32.5 to 35 mg) dose of the ACE inhibitor lisinopril in 3164 patients with moderate to severe HF caused by systolic dysfunction followed for a median of 41.2 months with 100% complete follow-up data. Primary results showed a trend to decreased mortality rate (8%) in the high-dose group and a significant 12% reduction in the risk of all-cause mortality plus all-cause hospitalization. There were 1383 deaths during follow-up (mortality rate 43.7%). Autopsy was performed in 188; data were available to determine the cause of death in 171 (12.4%) patients (present study group).

Clinical Classification of Deaths and Ischemic Events

Definitions for cause of death and MI were as follows: Sudden unexpected death was defined as death that was sudden and unexpected, including observed arrhythmic deaths and those not attributable to intractable myocardial (heart) failure or other identifiable cause. These deaths were classified as witnessed or unwitnessed and if unwitnessed, the time interval between death and the last time another individual saw the patient alive: (a) <1 hour, (b) 1 to 24 hours, or (c) >24 hours. Patients who had sudden loss of consciousness, who were successfully resuscitated, and who ultimately died of sequelae such as pneumonia were also classified as SD and formed the “>24-hour SD” group. If an autopsy was performed in a patient who died suddenly and evidence of a recent MI was found, the death was classified as secondary to MI.

Myocardial (heart) failure was defined as death from pump failure, even if the terminal event was an arrhythmia. Myocardial infarction was defined as death occurring ≤28 days after “definite” or “probable” MI. Other cardiovascular was defined as death occurring from a cardiovascular event other than those specified in the above 3 categories, including cerebrovascular accident, pulmonary or peripheral thromboembolism, cardiovascular procedural deaths from cardiac surgery, angioplasty, aortic aneurysm rupture or dissection, or other vascular causes not covered elsewhere. Noncardiovascular death was defined as death as the result of any other cause not included in the categories above.

Myocardial infarction as an ischemic event was defined as follows: a definite MI included (1) significant new Q waves with or without a typical history with characteristic rise and fall of biochemical markers, (2) a rise and fall of biochemical markers, in which the maximum value was ≥2 times the normal upper limit, with or without a typical history and/or equivocal ECG, or (3) postmortem evidence. A probable MI was defined as typical or atypical history with equivocal or no ECG abnormalities plus a typical rise and fall of biochemical markers in which the maximum value was <2 times the normal upper limit.

Clinical records were reviewed by the Endpoints Committee. If the treating physician noted the diagnosis of MI on the hospital record or biochemical markers were drawn and elevated, it was considered that the physician was aware of the possibility of an MI before death.

Autopsy Review

Each autopsy report was reviewed for the cause of death, the presence of recent and old MI, premortem coronary thrombus, plaque rupture, and the presence of significant (>70% stenosis) CAD. When CAD severity was not quantified, significant CAD was considered present if the examiner classified CAD as “severe” or “class III or IV.” Class I or II or “mild” or “moderate” obstruction was not considered significant CAD. MI was considered acute if there was a necrotic area related to a vascular territory and considered “acute” by the examiner. “Diffuse hemorrhagic areas” and “patchy necrosis” were not considered an acute MI because these findings may have developed during the period of terminal myocardial failure with hypotension. “Acute coronary findings” included premortem coronary thrombus, ruptured plaque, and/or the presence of a recent or acute MI.

TABLE 1. Distribution of Significant CAD at Autopsy Relative to Clinical Diagnosis

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Patients (n=171)</th>
<th>Patients With CAD (n=116)</th>
<th>% Patients With CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICM</td>
<td>92</td>
<td>77</td>
<td>83.4</td>
</tr>
<tr>
<td>ICM + hypertension</td>
<td>22</td>
<td>20</td>
<td>90.9</td>
</tr>
<tr>
<td>ICM + other diagnosis</td>
<td>6</td>
<td>3</td>
<td>50.0</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>29</td>
<td>8</td>
<td>27.6</td>
</tr>
<tr>
<td>Other non-CAD diagnoses</td>
<td>13</td>
<td>3</td>
<td>23.1</td>
</tr>
<tr>
<td>No diagnosis given</td>
<td>9</td>
<td>5</td>
<td>55.6</td>
</tr>
</tbody>
</table>

The underlying cause for HF was based on the investigator-provided case report form. The mode (sudden versus nonsudden) and cause of death were classified by the Endpoints Committee, who were blinded to the patient’s treatment. Consensus was reached in all cases, and deaths could be classified in 99.1% of cases.

Statistical Analysis

A χ² test for categoric and 2-tailed Student’s t test for continuous variables were used where appropriate to compare groups.

Results

Clinical Characteristics of the Study Group

Patients who died had, in general, worse baseline characteristics compared with survivors (full listing available from authors on request). They were older, more frequently in New York Heart Association class IV, with a longer duration of symptoms, and a higher prevalence of CAD. Patients undergoing autopsy, however, were similar as a group to patients who died and did not have an autopsy (full listing available from authors on request). The largest number of patients were from Sweden (n=42), Czech Republic (n=40), United States (n=24), United Kingdom (n=22), Canada (n=12), and Hungary (n=12). However, autopsy rates were quite variable, ranging from 2% (United States) to 27% (Czech Republic) (full listing available from authors on request).

Of the 171 study patients, there were 92 diagnosed clinically with ischemic cardiomyopathy (ICM) alone (54% of the study group), 17% idiopathic, 13% ICM and hypertension, 5% with no cause listed, 4% hypertension, 2% each for valvular heart disease, ICM and valvular heart disease, and other clinical combinations, and 0.6% for each of ICM plus idiopathic and ICM plus hypertension plus idiopathic (Table 1). Of those diagnosed clinically as having ICM alone (n=92) or in combination with another diagnosis (n=28), 83% actually had significant CAD at autopsy (Table 1). Of the 51 patients diagnosed clinically as having a nonischemic cause or with no diagnosis listed, 31% actually had autopsy-documented significant CAD. In summary, there were 116 patients at autopsy with significant CAD, 53 patients with normal or near-normal coronary arteries, and 2 with unclear severity of CAD.

In patients with ICM alone or in combination with another clinical diagnosis, mortality rate during the study was 48% (974 of 2035 patients) compared with 36% (409 of 1129) of non-ICM patients. The causes of death in the autopsy and nonautopsy groups are shown in Table 2 (first 2 columns). A “correction” (third column of Table 2, discussed below) assumed that autopsied patients were classified from clinical information...
alone. For the “other cardiovascular” and “noncardiovascular” deaths, the distribution of causes was similar in the 2 groups. In addition, there were similar causes of death in the patients diagnosed clinically in the ICM and non-ICM groups except that there were fewer MI deaths in the non-ICM group both in the entire cohort and the autopsied group (Table 3). This difference was magnified if patients were classified by the actual presence of CAD at autopsy rather than by clinical diagnosis (Table 3).

We investigated whether differences in causes of death could be explained by the autopsy results. Of 47 patients with MI as cause of death, 32 patients (68% of the MI group) died suddenly: In all but 1, MI was clinically unsuspected, with the autopsy findings providing the sole basis for diagnosis. Hence, if these patients had not had autopsies, they would have been classified as “sudden unexpected.” Of the 15 patients with acute MI on autopsy who died of myocardial failure, 6 (40%) were not diagnosed during life as having an ischemic event. These patients without an autopsy would have been classified as “myocardial failure.”

**Causes of Sudden Death**

SD causes in the autopsy group are shown in Table 4. Autopsy showed no specific pathology to explain SD in 51%, suggesting a primary arrhythmia, MI in 42%, with a small percentage of SD (2%) classified as noncardiovascular. One of the 2 patients had cancer. He died suddenly and unexpectedly in the hospital. This death may have reasonably been classified as “sudden unexpected.” Thus, only 1 patient with unexplained SD (1.2% of cohort), with a gastrointestinal bleed at autopsy, probably died of a noncardiovascular cause.

**Autopsy Findings**

There were 56 patients with findings suggesting an acute coronary event (33%). There were 7 patients with fresh thrombus, 1 of whom had a ruptured plaque. All had significant CAD at autopsy. There were 3 patients with fresh thrombus and acute MI; all showed significant CAD. There were 46 patients with only recent myocardial necrosis. Significant CAD was present in 42 (91.3%). The 4 non-CAD patients with recent MI had the following: (1) 3 with dilated cardiomyopathy, normal coronaries without thrombus, and myocardial necrosis and (2) 1 with endocarditis and mesenteric infarction. It should be noted that of these 56 patients found to have acute coronary findings, death was classified as MI-related in 47 patients only. Four patients were classified as myocardial failure, 1 with severe myocarditis, believed to be the primary cause of death, and a right coronary thrombus premortem but considered incidental; in the other 3, the

**TABLE 2. Distribution of Causes of Death**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Autopsy, % (n=171)</th>
<th>No Autopsy, % (n=1212)</th>
<th>“Corrected” Autopsy, % (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden unexpected</td>
<td>25.1</td>
<td>45.0</td>
<td>43.2</td>
</tr>
<tr>
<td>Myocardial failure</td>
<td>24.0</td>
<td>33.3</td>
<td>27.5</td>
</tr>
<tr>
<td>MI</td>
<td>27.5</td>
<td>4.1</td>
<td>5.8</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>14.0</td>
<td>5.7</td>
<td>14.0</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>9.4</td>
<td>10.1</td>
<td>9.4</td>
</tr>
<tr>
<td>Cause unknown</td>
<td>0</td>
<td>1.1</td>
<td>0</td>
</tr>
</tbody>
</table>

*The autopsy and nonautopsy groups were significantly different in causes of death (P<0.001), primarily because of the higher MI percentage in the autopsy cohort. The “correction” classified the cause of death based solely on clinical information, which erased any significant differences between the nonautopsied and autopsied groups.

**TABLE 3. Causes of Death in Patients With and Without CAD Clinically and by Cause**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Percentage of All Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients (n=974)</td>
</tr>
<tr>
<td>Sudden unexpected</td>
<td>42.5</td>
</tr>
<tr>
<td>Myocardial failure</td>
<td>32.5</td>
</tr>
<tr>
<td>MI</td>
<td>8.0</td>
</tr>
<tr>
<td>Other CV</td>
<td>6.9</td>
</tr>
<tr>
<td>Non-CV</td>
<td>9.3</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.7</td>
</tr>
</tbody>
</table>

CV indicates cardiovascular.

*ICM or non-ICM diagnoses were made by clinical evaluation.
†Includes 9 patients in autopsied group in whom clinical cause was not stated.
‡2 patients were excluded because severity of coronary disease was not clear from the autopsy report.

**TABLE 4. Causes of Sudden Death in Autopsied Patients (n=83)**

<table>
<thead>
<tr>
<th>Cause</th>
<th>n</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No specific pathology</td>
<td>42</td>
<td>50.6</td>
</tr>
<tr>
<td>MI</td>
<td>35</td>
<td>42.1</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>4</td>
<td>4.8</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Aortic aneurysm rupture</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Cancer/SD in-hospital</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

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Acute coronary findings were present in 56 (36%) of 155 patients who died of a cardiovascular cause (all cardiac except for 1 case of cerebrovascular accident with MI at postmortem as noted above) and in no patient who died of a noncardiovascular cause (P=0.003) (Figure 1, left). Acute coronary findings were more prevalent in CAD patients (P=0.001) but not confined to this group (Figure 1, middle). There was a higher prevalence (P=0.033) of acute coronary findings in patients dying suddenly than from myocardial failure (Figure 1, right). The prevalence of acute coronary findings was highest in CAD patients with SD (54%), intermediate in CAD patients who died of HF (32.1%), and infrequent in non-CAD patients dying of any cause (P=0.0001) (Figure 2). Of the 103 patients with an old MI who died suddenly (7 of 35, 28%), MI as a cause of death was 28% in the autopsy group and 4% in the nonautopsy group (P<0.001). Because it was possible that this apparent difference was due to new information obtained at autopsy, a correction was made that assumed all patients with autopsy-documented MI who died suddenly without MI being diagnosed during life (31 of 32 patients) would have been classified as “sudden unexpected,” and all patients who died from myocardial failure with unrecognized MI (6 of 15) would have been classified as “myocardial failure” deaths. The causes of death then became similar between “no autopsy” and “autopsy” groups (Table 2, third column). These data suggest strongly that the autopsy group is truly representative of all patients who died and that the differences in cause of death are due almost entirely to the underappreciation of MI as a precipitant of sudden unexpected, and to a lesser extent, myocardial failure deaths.

**Discussion**

The present study is the first prospective, randomized, large, multicenter trial that used prespecified definitions of causes of death and a blinded Endpoints Committee to provide a relatively large sample of autopsied patients to examine causes of death in a HF population. This study demonstrates that recent coronary events are frequently unrecognized in patients with symptomatically moderate to advanced HF, especially in patients with CAD who die suddenly. These data are consistent with previous autopsy studies that have documented that a high percentage of CAD patients without HF who die suddenly also have evidence of an acute coronary event.3–6 It should be noted that recent autopsy studies of sudden cardiac death3–4 have reported a much higher incidence of ruptured plaque (57% to 81%) than we observed. However, the prevalence of acute coronary findings in CAD patients (41% in Davies’ study and 21% in Farb’s study) was
similar to the present study (44%). Cuts at millimeter distances and meticulous review of each section are required to identify accurately plaque rupture and small thrombi. Because the autopsies in our study were routine clinical examinations, the degree of detail necessary to observe ruptured plaque and small thrombi was unlikely to have been performed. An alternate hypothesis is that there was a greater delay in dying in the HF population versus the non-HF CAD group described in previous SD studies. This delay might account for the decreased prevalence of thrombus, but one would still expect the prevalence of ruptured plaque to be similar and of myocardial necrosis to be as high or even higher. This was not the case. Thus, the higher probability is that differences in methodology account for the higher prevalence of ruptured plaque and thrombus in previous studies rather than differences in patient populations or longer delay between coronary event and death.

The presence of acute coronary findings in ICM patients dying of myocardial failure is not unexpected. The most recent ischemic insult was probably the reason the patient progressed from tenuous compensation to terminal pump dysfunction. Somewhat less intuitive is the occasional patient without severe CAD at autopsy who had autopsy-documented MI. These findings may have been due to coronary embolization, an unusual sequelae of left ventricular dysfunction. In our study, patients without CAD at autopsy had a 12% prevalence of old MI, a figure similar to the 14% prevalence previously reported in patients with idiopathic dilated cardiomyopathy.

In patients with acute MI at autopsy, 79% were undiagnosed during life, many with SD and no immediate antecedent history of chest pain. If we extrapolate the findings in this study to the general HF population, it suggests that as many as half of patients with ICM who die suddenly may have had an acute ischemic event precipitating the death. Furthermore, an additional third of CAD patients dying of terminal HF may have been precipitated by an unrecognized ischemic event.

Comparison With Other Studies
This study is the first large HF trial to systematically review all autopsied patients. Thus, it is difficult to compare our results with other large randomized clinical HF trials. In previous studies, causes of death have not been described, 8-10 MI as a cause of death not included, 11-14 mode of death not described, 8 or prespecified definitions of causes of death not used or reported. 12,13,15-17 That classification of cause of death can be difficult and may be multifactorial emphasizes the importance of maximizing methods to maintain consistency across centers. In the ATLAS study, classification of cause and mode of death were prospectively developed. The Endpoints Committee required unanimity for classification; all decisions were made blinded to the patient’s drug assignment. When disagreement occurred, further information was requested and provided by individual investigators when possible, allowing for consensus in all cases and definitive classification in >99% of cases. An Endpoints Committee was not used in several frequently cited trials, 12,13,15,17-19 leading to the likelihood of inconsistent classification among centers.

Ability to Generalize Results
The most important issue in generalizing the results of this study to the HF population as a whole is whether the autopsied patients are truly representative of the spectrum of patients who die with HF. In this study a potential shortcoming is that the percentage of autopsied patients was low (<15% of all deaths). However, the autopsied patients were very similar in baseline characteristics to the nonautopsied patients who died. In the nonautopsied group, the causes of death mirror the published literature. 11,20 On the other hand, the proportions of the adjudicated causes of death was different in the autopsied versus the nonautopsied group with a higher percentage of MI as cause of death in the autopsied series. The correction that we used, that is, eliminating the influence of any new information obtained at autopsy, produced a classification of death causes that was almost identical in the autopsied and nonautopsied groups. Without this correction, the difference was due almost entirely to the underappreciation of MI as the immediate precipitant of sudden unexpected, and to a lesser extent, myocardial failure deaths. Thus, it may be surmised that our autopsy patients were, in fact, likely to be representative of the broad spectrum of HF patients included in ATLAS. The results underscore the importance of addressing the consequences of CAD in an attempt to decrease mortality rates in HF patients.

Definition of SD
The definitions of sudden unexpected death and other death causes are crucial in placing our results in perspective. The present study differs in some minor respects from the most frequently used definition of SD, requiring death to occur within 1 hour and be witnessed with some caveat to deal with an unwitnessed death. The underlying concept was, however, retained in this study. Our definition tacitly acknowledged the reality that many SD are not witnessed and that the circumstances surrounding the event require evaluation to determine if the death was truly unexpected and sudden. In the present study, we also included patients who died in hospital from sequelae of earlier sudden collapse after successful resuscitation. This was done under the assumption that the sudden hemodynamic destabilization from the collapse was the direct precipitant of the terminal event. The CAST and CAMIAT trials considered any successful resuscitation as an end point, whereas we counted only those patients who eventually died after resuscitation. 21,22 If we would have used a more restricted definition of <1 hour with or without witnesses, our results would not have substantially changed as <5% of the SD patients had “delayed SD.” It should also be noted that in several studies in the HF population, there have been modifications of the definition of SD. Death occurring during sleep in an ambulatory patient with unchanged symptoms was assumed to be sudden in most cases in our series; it probably has been considered as such in other studies but has rarely been explicitly stated. Unwitnessed deaths with adequate circumstantial information suggesting SD were so classified in several other studies. 4,8,15

Other Triggers and Causes of SD
The similar frequency of SD in the non-CAD and CAD patients without acute coronary findings at autopsy empha-
sizes that triggers other than an acute coronary event are clearly operative in SD in HF patients. Our data also demonstrate that unexpected SD may on occasion be related to a vascular catastrophe and only very rarely to a noncardiovascular cause.

Therapeutic Implications
Our findings have important therapeutic implications. Death may be precipitated in approximately one third of HF patients from acute coronary events. Therefore, improved strategies to prevent or more adequately treat ischemia may be important. It should be emphasized that the accuracy of diagnosing CAD clinically was only moderate in this study. If differentiating a coronary from noncoronary cause has therapeutic implications, coronary arteriography should be recommended whenever a HF-related cause is in doubt. In the ATLAS trial, although two thirds of the patients had ICM clinically as their cause of HF, only 40% were taking aspirin. Furthermore, the interaction of aspirin and an ACE inhibitor remains unclear, and other antplatelet agents such as clopidogrel may have more of a role when an ACE inhibitor is used. β-Blockers were used in only a small fraction of cases, although they have been found to be efficacious in improving symptoms and longevity. Similarly, cholesterol-lowering agents may be appropriate in view of data showing a decrease in secondary coronary events in patients with elevated or average cholesterol levels, although data in HF patients are limited.

Study Limitations
Limitations of this study include the relatively low percentage of autopsies and the varying degrees of description and detail on autopsy reports. The possibility exists that autopsies were done for special reasons, and the study group is not representative. This possibility is lessened by the similar clinical characteristics of the autopsied and nonautopsied groups, the broad geographic area represented by study patients, the common disease process, and modes of death. The relative underrepresentation of North American patients autopsied may have affected the findings, but this is unlikely because ~20% of all study patients were from North America.

Conclusions
In summary, acute coronary events are frequent in HF patients who die suddenly and may be a trigger of sudden, and to a lesser extent, progressive myocardial failure deaths, particularly in patients with ICM. Careful attention to this issue, including a more aggressive use of agents known to be protective against subsequent ischemic events, may allow for improvement in prognosis.

Acknowledgments
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