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Recurrent infarction causes the most deaths following myocardial infarction with left ventricular dysfunction

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ABSTRACT

PURPOSE: The development of left ventricular systolic dysfunction or heart failure following an acute myocardial infarction (MI) is a powerful marker of an adverse prognosis. Recurrent MI could be an important cause of death, either directly or by provoking arrhythmias.

METHODS: The OPTIMAAL trial randomized 5477 patients with heart failure or evidence of left ventricular dysfunction following acute MI to losartan or captopril. Over a follow-up of 2.7 years, there were 946 deaths. Of the 180 (19%) of these deaths for which autopsy reports were available, acute MI was found in 57% (102 of 180) of the autopsies. By comparison, an endpoints adjudication committee using clinical data attributed death to acute MI in only 29 cases. An acute MI was found at autopsy in 55% (37 of 67) of the deaths that had been classified as due to an arrhythmia and in 81% (21 of 26) of the deaths classified as due to progressive heart failure. Including autopsy diagnoses, the rate of acute MI in patients who died suddenly was independent of the time elapsed since the index MI, but in patients not classified as dying suddenly, there was a time-related decrease in recurrent MI from 78% in the first 30 days to 30% by the end of follow-up. However, only 19% of patients who died underwent autopsy, so recurrent MI may have been substantially more common and perhaps had a different relation to time since the index MI if more patients had undergone autopsy.

CONCLUSIONS: In patients with evidence of major cardiac dysfunction after MI, recurrent MI found at autopsy is common and has often not been clinically detected.

Management strategies are often guided by an understanding of natural history, including why patients die. However, an accurate assessment of the cause of death is difficult, even when there is an international consensus on diagnostic criteria.[1-3] The use of endpoint committees, which adjudicate endpoints according to prespecified criteria based on available records, is recognized as a reasonably effective measure to improve the classification of death in clinical trials. Nevertheless, the clinical diagnosis of cause of death often remains difficult. Autopsy can make an important contribution to understanding the underlying pathophysiologic mechanisms of death. Previous trials have com-

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pared the clinical classification of death with the findings at autopsy of patients with acute myocardial infarction (MI) without heart failure[4,5] and of patients with heart failure of mixed etiology.[6] We reviewed data from all patients autopsied in the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) trial[7] to define the pathophysiologic mechanisms underlying the progression of disease in patients with evidence of major cardiac dysfunction after MI.

Methods

OPTIMAAL trial design and results

The OPTIMAAL trial was an international, multicenter, randomized trial comparing the effects of the angiotensin II antagonist losartan with the angiotensin-converting enzyme inhibitor captopril on survival of patients with heart failure or signs of left ventricular dysfunction following acute myocardial infarction (MI). Patients were enrolled within 10 days of onset of symptoms. A total of 5477 patients over age 50 years were included in the study. All patients signed informed consent.

Adjudication process

Adjudication of the clinical mode, cause, and place of death in the OPTIMAAL trial was performed by an experienced endpoint committee. Deaths were classified with and without knowledge of the autopsy to assess the relationship between clinically adjudicated endpoints and autopsy results.

Adjudicated clinical cause of death

The clinical cause of death was considered to be due to recurrent acute MI if any 2 of the following 3 criteria were present: abnormal values of cardiac markers (CK-MB or troponins), typical cardiac chest pain, or development of new pathological electrocardiogram (ECG) changes suggestive of ischemia or infarction: Q waves or sustained (>24 hours) ECG changes consistent with ischemic or nontransmural infarction, or new left bundle branch block, or transient current of injury (S-T elevation) on the ECG that is reversed after administration of thrombolytic therapy or coronary revascularization. The adjudicator was allowed to deviate from these criteria based on other pertinent information and clinical judgment. For example, a patient with atypical chest pain and S-T segment elevation either acutely fatal or resolving after thrombolysis or primary angioplasty, might not have evidence of abnormal values of cardiac markers or new pathological Q waves but might still be classified as a definite MI. Attribution of death to MI could occur up to 7 days following a recurrent MI if no other more proximate unrelated cause of death was evident. Death related to stroke, sudden cardiac death, or heart failure occurring within this time frame was attributed to fatal reinfarction. The cause of death was considered to be due to progressive heart failure when preceded by worsening signs and symptoms of heart failure leading to New York Heart Association class IV or circulatory collapse due to pump failure in the absence of acute myocardial reinfarction within the preceding 7 days. If a hospitalization was due to worsening heart failure but the patient later died suddenly in hospital, death was classified as due to progressive heart failure. Sudden cardiac death was classified as witnessed instantaneous or near-instantaneous death that occurred without warning or within 1 hour of nondiagnostic symptoms. The cause of death had to be considered cardiac in origin but not due to another adjudicated cause such as acute MI or progressive heart failure. Patients who were resuscitated from a cardiac arrest but subsequently died in-hospital in the absence of an identifiable cause for the arrhythmia was considered to have sudden cardiac death as the cause of death.

Adjudicated mode of death

Sudden death was classified as witnessed instantaneous or near-instantaneous death if it occurred without warning or within 1 hour of nondiagnostic symptoms or as nonwitnessed unexpected death. Nonsudden death was a death that did not satisfy these criteria.

Autopsy diagnoses

Autopsies were performed according to local routines, and diagnosis was based upon the original autopsy report. All available reports (n = 180) were assessed. Acute MI at autopsy was defined as the presence of fresh thrombus, ruptured plaque, or evidence of acute segmental myocardial damage. In addition, the examining pathologist had to state that an acute MI was present at autopsy. In the case of recurrent MI in the same territory as the index MI, recurrent MI was considered present if there was an extension of the old MI or the presence of a new fresh thrombus or ruptured plaque. Diffuse hemorrhagic areas and patchy necrosis were not considered as acute MI because these findings may have developed during a period of terminal shock with hypoperfusion. Patients with severe pulmonary congestion without evidence of acute MI on autopsy were categorized as progressive heart failure deaths if they died nonsuddenly and had been adjudicated as a progressive heart failure death before autopsy. Classification of events in the first 7 days after the index MI precluded the accurate attribution of autopsy MI to the index MI or a subsequent event in 16 deaths within the first 7 days.

Statistics

Comparison of baseline characteristics was performed with the chi-squared test for categorical variables and Student's *t* test for continuous variables. A logistic regression model was applied to test for time-related changes in autopsy findings. A two-sided *P* value of 0.05 was considered statistically significant.

Results

In the OPTIMAAL trial, 946 deaths were reported during an average follow-up of 2.7 (0.9) years. Of these 946 patients, 185 (20%) underwent autopsy, of which 180 reports, constituting 19% of all deaths, were available for analysis. Among the autopsied patients, 165 deaths occurred more than 7 days after the index MI. Patients who underwent autopsy were younger, less likely to have had a stroke before their index MI, less likely to die of an unwitnessed clinical sudden death, and more likely to die in the hospital than were patients who died but did not undergo autopsy (Tables 1 and 2).

Autopsy findings in patients with acute MI at autopsy

Acute MI was considered the primary cause of death in 102 patients following autopsy, and in most of these patients (n = 80) the recurrent MI occurred in the same territory as the index MI. Myocardial changes indicative of acute MI were present at autopsy in 86 of the 102 patients with recurrent MI, including 25 patients who had a fresh thrombus present at autopsy in the infarct-related artery. A fresh thrombus was reported in the infarct-related artery in all 16 patients without myocardial damage, all of whom had died suddenly. Only 2 patients were reported to have ruptured plaques. Severe atheromatosis or calcification was reported in 69 patients. When the 2 countries with the highest percentage of autopsies (Finland and Norway) were compared with the other countries, there was no significant ($P = 0.11$) difference in the prevalence of acute MI at autopsy in the 2 countries with the highest autopsy rate (62%; 48 of 77) compared with the other countries (53%; 55 of 103).

Adjudicated clinical cause of death vs autopsy findings

The most common adjudicated clinical causes of death before autopsy were sudden cardiac death and death from progressive heart failure (Figure 1). Following autopsy, the cause of death had to be changed in 47% (85 of 180 patients) of all patients, mostly due to undiagnosed acute MI before autopsy. Before knowledge of the autopsy findings, the most common adjudicated clinical causes of death in patients with acute MI at autopsy had been sudden cardiac death (37%; 37 of 102 patients) and progressive heart failure death (21%; 21 of 102 patients) (Figure 2). In patients with acute MI at autopsy, investigators identified a clinical event suggesting an acute MI within 30 days of death in only 20% (20 of 102 patients). Three patients were autopsied within 7 days of an out-of-hospital fatal cardiac arrest; all 3 had evidence of recurrent MI at autopsy.

Sudden mode of death and autopsy findings

Mode of death was sudden in 88 patients. The adjudicated clinical cause of death was sudden cardiac death without MI in the majority (77%; 68 of 88 patients) of such patients, but some patients were classified clinically as having had an acute MI or progressive heart failure as the cause of the sudden death. Acute MI was a common autopsy finding (60%; 53 of 88 patients) in patients who died suddenly, although this diagnosis was usually (79%; 11 of 53 patients) not recognized before death (Figure 3). In patients with sudden death due to recurrent MI by autopsy, a fresh coronary thrombus was present in 46% (24 of 53 patients) of autopsies. Among patients who died suddenly without evidence of acute MI at autopsy, 25 patients had nonspecific findings at autopsy. Other findings were cardiac rupture (n = 4), pulmonary embolism (n = 4), and stroke (n = 1). One patient committed suicide. In patients who died suddenly more than a week after randomization and who then underwent autopsy, the probability of recurrent MI at autopsy was 60% irrespective of their time of death.

Nonsudden mode of death and autopsy findings

Mode of death was nonsudden in 92 patients. The most commonly adjudicated clinical causes of death among patients dying nonsuddenly were progressive heart failure (27%; 25 of 92 patients) and noncardiovascular disease (25%; 23 of 92 patients). Acute MI was the adjudicated clinical cause of death in only 21% (19 of 92 patients) of patients who died nonsuddenly. Following autopsy, acute MI was found to be present in 53% of these patients (49 of 92 patients) and in 81% (21 of 26 patients) who had symptoms of progressive heart failure before death (Figure 4). In the 4 patients who had an adjudicated clinical diagnosis of noncardiovascular death but had acute MI at autopsy, 1 patient had cancer, 1 septicemia, and 2 had pneumonia. Over time, the relative proportion of acute MIs found at autopsy among patients with nonsudden death fell from 78% within the first 30 days of acute MI to 30% toward the end of follow-up ($P < 0.001$).

Autopsies within 1 week of index MI

During the first week following the index MI, 15 deaths resulted in autopsy. Of 6 patients who died suddenly, 3 had

Table 1 Baseline demographics of autopsied patients vs nonautopsied nonsurvivors

	Autopsied patients (n = 180)	Nonautopsied deaths (n = 761)
	Mean ± SD or Number (%)	
Demographics		
Age	71.3 ± 9.9	74.1 ± 9.1†
Female	58 (32)	267 (35)
Male	122 (67)	494 (65)
White	179 (99)	752 (99)
Body mass index	26.0 ± 4.0	26.0 ± 4.0
Country		
Finland	32 (34)	61 (66)
Norway	45 (26)	126 (74)
Sweden	33 (18)	149 (82)
Denmark	21 (18)	94 (82)
UK and Ireland	37 (17)	181 (83)
Germany	12 (7)	149 (93)
History		
Hypertension	64 (36)	298 (39)
Previous MI	58 (32)	219 (29)
Coronary angioplasty	6 (3)	60 (8)*
Coronary artery bypass graft	8 (4)	27 (4)
Diabetes	41 (23)	165 (22)
Hypercholesterolemia	43 (24)	140 (18)
Atrial fibrillation	29 (16)	155 (20)
Ischemic heart disease	14 (8)	86 (11)
Heart failure	23 (12)	98 (13)
Stroke	8 (4)	75 (10)*
Peripheral vascular disease	7 (4)	31 (4)
Index infarction location		
Anterior or lateral	123 (67)	483 (64)
Inferior or posterior	48 (26)	212 (28)
Anterior Q-waves	77 (43)	305 (40)
Any new Q-waves	103 (57)	442 (58)
Killip Class		
I	29 (16)	138 (18)
II	106 (59)	459 (60)
III	40 (22)	145 (19)
IV	5 (3)	18 (2)
Vital signs		
Heart rate	79.9 ± 16.0	79.1 ± 15.3
Blood pressure, mm Hg	123/71	124/72
Therapy		
Captopril	81 (45)	358 (47)
Losartan	99 (55)	403 (53)
Beta-blockers	130 (72)	542 (71)
Aspirin	165 (91)	694 (91)
Warfarin	41 (23)	130 (17)
Loop diuretic	147 (82)	629 (83)
Statins	63 (35)	214 (28)

Significant differences between the two groups:
*$P < 0.05$;
†$P < 0.001$.

the adjudicated clinical diagnosis of MI and all had MI confirmed at autopsy. The remaining 3 sudden deaths had myocardial rupture without recurrent MI. Of the 9 nonsudden deaths, 7 had an adjudicated clinical diagnosis of acute MI, and all were confirmed at autopsy. One patient who had been classified as progressive heart failure death had pericardial tamponade at autopsy. The ninth patient had a procedure-related death.

Discussion

The present study demonstrates that recurrent MI is a common finding at autopsy in patients who die after an index MI, irrespective of the mode of death. However, the recurrent MI is often not recognized either because of atypical symptoms or because it presents as sudden death. The high prevalence of acute MI at autopsy is in accordance with

Table 2 Adjudicated endpoints in autopsied patients (only those included in the analysis) vs nonautopsied nonsurvivors; values are n (%)

	Autopsied patients (n = 180)	Nonautopsied deaths (n = 761)
Mode of death		
Sudden death: witnessed	87 (48)	335 (44)
Sudden death: nonwitnessed	8 (4)	88 (12)†
Nonsudden	93 (52)	426 (56)
Place of death		
In hospital	136 (76)	460 (60)‡
Out of hospital	44 (24)	301 (40)‡
Cause of death		
Non-cardiovascular death	25 (14)	129 (17)
Cardiovascular death	155 (86)	632 (83)
Sudden cardiac death	68 (38)	271 (36)
Acute MI	32 (18)	89 (12)*
Progressive heart failure	27 (15)	175 (23)*
Stroke	5 (3)	41 (5)
Other cardiovascular death	4 (5)	34 (4)
Procedure related	14 (8)	22 (3)†

Significant differences between the two groups:
*$P < 0.05$;
†$P < 0.01$;
‡$P < 0.001$.

epidemiologic data, which indicate that once an ischemic event occurs, ischemic events remain the dominant reason for later hospitalization and death in patients with heart failure.[8] Treatment with both beta-blockers and angiotensin-converting enzyme inhibitors has reduced reinfarction, sudden death, and total mortality in patients with heart failure after an MI.[9,10] Our findings are also consistent with data from 2 randomized trials of implantable cardiac defibrillators in patients with a high prevalence of left ventricular dysfunction.[11,12] Implantable cardiac defibrillators reduced all-cause mortality by reducing sudden death, but there was an increase in nonfatal acute MI in patients who received defibrillators, presumably because the device prevented deaths among patients who suffered what would otherwise have been fatal acute MI.

Comparison with other autopsy studies

The high prevalence of acute MI at autopsy in patients dying suddenly in the present study is similar in magnitude to the 57% to 73% prevalence reported previously in patients with coronary artery disease without heart failure[3,4] and the 54% prevalence in stable ischemic heart failure.[6] Hence, in a population of patients with ischemic heart disease, regardless of the severity of ventricular dysfunction, the proportion of sudden deaths that may be attributed to

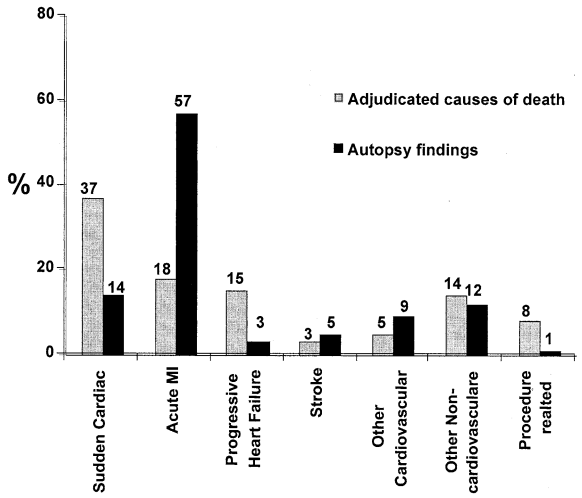

Figure 1 Causes of death in all autopsied patients (n = 180) before and after the result of autopsy was used to determine cause of death.

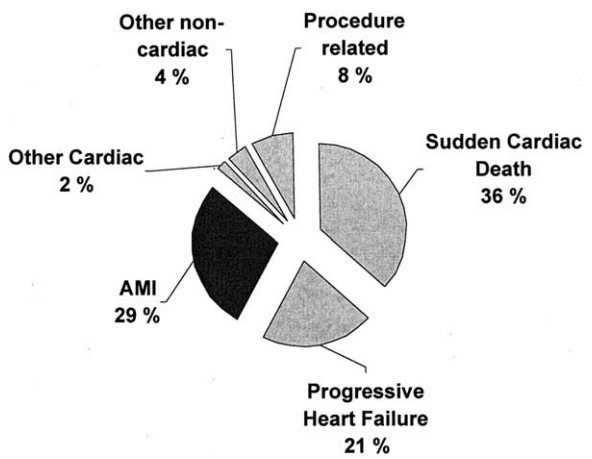

Figure 2 Adjudicated cause of death before autopsy in patients with acute MI at autopsy (n = 102).

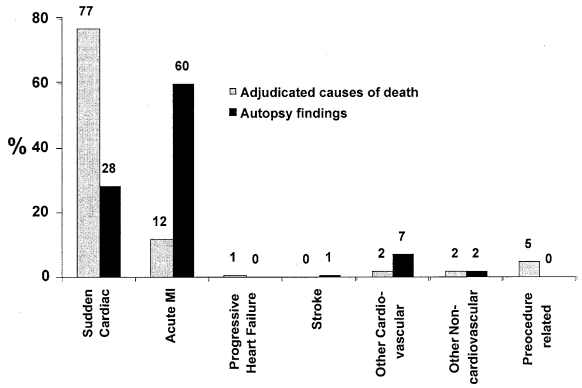

Figure 3 Adjudicated causes of death in autopsied patients with a sudden mode of death (n = 88) before and after autopsy was used to determine cause of death.

recurrent MI appears to be reasonably constant. This observation is further supported by our finding that there was no time-related trend in the prevalence of recurrent MI during our follow-up period. Acute MI was also frequently found at autopsy in patients who had symptoms of terminal progressive heart failure (81%), a higher proportion than observed in autopsied patients with coronary artery disease and death attributed to progressive heart failure in the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial (32%).[6] This difference may be due to the longer time interval between the index infarction and death among patients with ischemic heart failure in the ATLAS trial. However, because the number of patients in this subgroup in both studies was small, the results must be interpreted with caution.

Implications of the current study

Our data demonstrate that despite improved diagnostic tools, standard diagnostic criteria, and an endpoint committee, recurrent MI remains very much under-diagnosed among both patients who died suddenly and those who died of progressive heart failure. When death occurs outside of the hospital, information is frequently lacking on prodromal symptoms; an electrocardiogram and cardiac biomarkers are rarely obtained.[7,13] Arrhythmias, which often occur early after the onset of ischemia, may further confuse the picture.[9,14] In most of these patients, autopsy will be the only way of making the correct diagnosis. Of note are that nearly all acute MIs that were diagnosed at autopsy but had been missed clinically occurred in patients whose adjudicated clinical cause of death were cardiovascular death, so the broad category of clinical cardiovascular death was rather accurate and may represent a more robust endpoint to be reported in clinical trials irrespective of their autopsy rates.

The large proportion of deaths attributed to recurrent MI in the present study suggests that ischemic events are important precipitating factors for death and that prevention of recurrent MI may be the primary objective in prolonging survival in this population. The high percentage of recurrent MI in patients suffering a sudden cardiac death suggests that sudden cardiac death frequently is not a random electrical event but that it may relate to acute coronary syndromes. Trials of implantable cardiac defibrillators probably represent the best opportunity for unraveling the pathophysiologic mechanisms of sudden death in patients with ischemic heart failure, so the integration of autopsies into these trials should be encouraged.

Study limitations

Although only a minority of patients in OPTIMAAL had an autopsy, the proportion of autopsies in the current trial (19%, 180 of 941 deaths) is relatively large compared with other trials such as the ATLAS trial (12%; 171 of 1383 deaths).[6] However, because only a minority of patients were autopsied, and because autopsy cases were not randomly selected, the precise percentages that are reported for cause and mode of death by autopsy are not as accurate as they would have been with a higher percentage of autopsies. However, when only cases from the two countries with the highest proportion of autopsies (Finland [34%; 32 of 94 deaths] and Norway [26%; 45 of 172 deaths]) were analyzed, the results were consistent with our overall findings. Furthermore, our results are consistent with previous reports.[4-6,15]

There also are limitations related to the diagnosis of acute MI at autopsy: infarcted myocardium cannot usually be detected on routine examinations until 4–6 hours after the triggering event,[16] the time from onset of a thrombotic occlusion until autopsy is important for the detection of thrombus because the thrombus may rapidly lyse,[17] and the presence of ruptured plaque is difficult to assess, especially in the presence of coronary calcification.[18] In the present study, only 2 patients were reported to have ruptured plaques. The occurrence of ruptured plaque was difficult to assess because extensive coronary calcification was present in 68% (n = 69) of our patients. However, major problems

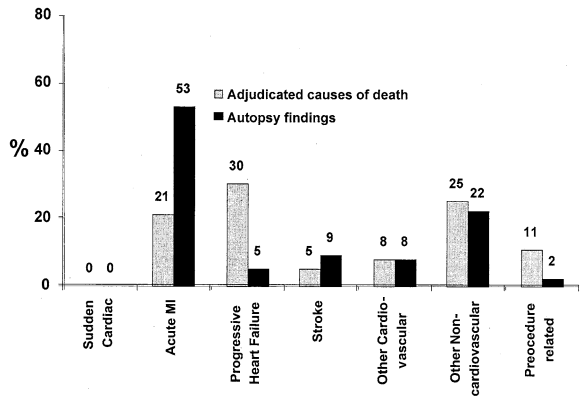

Figure 4 Adjudicated causes of death in autopsied patients who did not have a sudden mode of death (n = 92) before and after autopsy was used to determine cause of death.

related to autopsy examinations 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.

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