Family History and the Risk of Sudden Cardiac Death as a Manifestation of an Acute Coronary Event

Kari S. Kaikkonen, MD; Marja-Leena Kortelainen, MD; Eeva Linna, MD; Heikki V. Huikuri, MD

Background—Observational studies have suggested that a parental history of sudden death increases one’s risk of dying suddenly. This study tested the hypothesis that a family history of sudden cardiac death (SCD) is a risk factor for SCD caused by an acute coronary event.

Methods and Results—A retrospective case-control study included (1) consecutive victims of SCD (n = 1100) whose deaths were verified to be due to an acute coronary event without a history of prior myocardial infarction at medicolegal autopsy, (2) consecutive patients surviving an acute myocardial infarction (AMI; n = 1100), and (3) healthy control subjects (n = 470). Family history of AMI and SCD among the first-degree relatives was ascertained in each study group. The incidence of SCD in the 1223 first-degree relatives of SCD victims was higher (5.2%) than that in the 2326 relatives of AMI survivors (3.3%; odds ratio [OR] 1.6, 95% confidence interval [CI] 1.2 to 2.2, P < 0.01) or the 3748 relatives of controls (OR 2.2; 95% CI 1.6 to 3.0, P < 0.001). The history of SCD in 2 or more first-degree relatives was also higher (10.9%) among SCD victims than among AMI survivors (3.5%; OR 3.3, 95% CI 1.4 to 7.8, P < 0.01) or controls (1.1%; OR 11.3, 95% CI 4.0 to 31.8, P < 0.001). The family history of AMI did not differ between the SCD and AMI groups.

Male gender and current smoking were the only coronary risk factors that were more prevalent among SCD victims than among AMI survivors (P < 0.001 for both).

Conclusions—Subjects with a family history of SCD have an increased risk of dying suddenly during an acute coronary event. (Circulation. 2006;114:1462-1467.)

Key Words: death, sudden • coronary disease • genetics • epidemiology

Sudden cardiac death (SCD) due to coronary heart disease is the single most prevalent cause of death in Western societies. Despite the fact that a number of studies on SCD have been conducted during the past few decades, prevention of SCD in the general population has remained a challenge.1,2 A large number of coronary heart disease patients die suddenly without prior symptoms and before preventive efforts can be instituted.3 Another problem is the overlap between the risk factors for coronary events, acute myocardial infarction (AMI), and SCD, which makes specific identification of patients vulnerable to SCD extremely difficult.4–7

Clinical Perspective p 1467

In the Paris Prospective Study, Jouven et al8 showed that a parental history of sudden death was a risk factor for the occurrence of sudden death but was not associated with nonsudden fatal AMI. A case-control study by Friedlander et al9 also showed that a family history of AMI or sudden death was more common among victims of sudden death than among control subjects. Previous studies have not included comprehensive autopsy findings as criteria for defining the specific mode of sudden death. Therefore, it has not been well established whether there is a familial background for the occurrence of SCD as a manifestation of an acute ischemic event, which would support further research efforts on specific genetic screening for vulnerability to ischemia-induced fatal arrhythmias.

We conducted a retrospective case-control study (Finnish Genetic Study of Arrhythmic Events [FinGesture]) to elucidate the familial clustering of SCD and to investigate the possible genetic risk factors for ischemic SCD. Records of consecutive series of SCD victims and survivors of AMI without a prior history of myocardial infarction were collected from the Oulu University Hospital District in northern Finland. Only subjects with an acute coronary event verified at medicolegal autopsy were included in the SCD group. The specific aims were to investigate the role of family history as an independent risk factor for ischemic SCD and nonfatal AMI as the first manifestation of CHD.

Methods

Study Populations

The FinGesture study was started in 2000, after which all victims of sudden death autopsied at the Department of Forensic Medicine, University of Oulu, Oulu, Finland, were included in the...
Patients with a history of prior AMI were excluded from the present study. In total, 809 controls were included. Complete family history could be obtained from relatives of 138 (53%) of 259 SCD victims, 254 (51%) of 499 AMI survivors \((P=NS)\), and 470 (58%) of 809 control subjects \((P<0.01\) compared with SCD and AMI group, respectively). Diagnosis of AMI was based on standard criteria with the Finnish National Patient Register, the Hospital Discharge Register,14–16 the Causes of Death Register were used to confirm the mode of death in first-degree relatives. The quality of these registers has been validated previously.14–16 Diagnosis of AMI was based on standard criteria with the Finnish National Patient Register, the Hospital Discharge Register,14–16 the Causes of Death Register were used to confirm the mode of death in first-degree relatives. The quality of these registers has been validated previously.14–16

Family history of SCD and AMI in first-degree relatives (each biological parent, brother, sister, or child) was ascertained by mail or telephone call to the control subjects, survivors of AMI, and the closest relatives of the SCD victims with a standardized questionnaire. In cases of reported sudden death of a first-degree relative, a description of the event was elicited to confirm the mode of death. Death certificates from the Central Statistical Office in Finland and the Causes of Death Register were used to confirm the mode of death in first-degree relatives. The quality of these registers has been validated previously.14–16 Diagnosis of AMI was based on standard criteria with the Finnish National Patient Register, the Hospital Discharge Register,14–16 the Causes of Death Register were used to confirm the mode of death in first-degree relatives. The quality of these registers has been validated previously.14–16

The end-point committee reviewed all cardiac deaths and AMIs of first-degree relatives blinded to the class of the cases and used both predefined clinical criteria and death certificates in the interpretation of sudden deaths and AMIs. The same definitions for SCD regarding the time after onset of symptoms, witnessed versus unwitnessed, were used for relatives. Cases without complete information about the mode of death, including exact information on the duration of symptoms preceding death and disaggreement in the interpretation, were excluded from the study. Complete family history could be obtained from relatives of 138 (53%) of 259 SCD victims, 254 (51%) of 499 AMI survivors \((P=NS)\), and 470 (58%) of 809 control subjects \((P<0.01\) compared with SCD and AMI group, respectively).

Characterization of demographic variables and coronary risk factors was based on data obtained from the interviews with control subjects, AMI survivors, and the persons most closely related to the victim of SCD. The interviews were performed by trained interviewers using a standardized questionnaire.

Definitions and Study Design

Of the out-of-hospital SCD victims, those with (1) a witnessed sudden death within 6 hours of the onset of the symptoms or within 24 hours of the time that the victim was last seen alive in a normal state of health and (2) evidence of a coronary complication, defined as a fresh intracoronary thrombus, plaque rupture or erosion, intraplaque hemorrhage, or critical coronary stenosis (>75%) in the main coronary artery were included in the SCD group.13 Victims with a history of prior AMI, those with evidence of noncardiac cause, and victims with mechanical causes of sudden death, such as a rupture of the myocardium and/or tamponade, extensive myocardial necrosis (>50%), rupture of the entire papillary muscle, pulmonary edema, or any cause of death considered to be due to a reason other than ischemia-induced SCD, were also excluded. An end-point committee consisting of a forensic pathologist (M.-L.K.), an experienced cardiologist (H.V.H.), and the primary investigator (K.K.) defined the mode of death in each case. After the exclusions, 259 of 532 victims of sudden death were defined as having died due to an acute coronary event.

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The Ethics Committee of the University of Oulu approved the study, and the subjects or a close relative of each deceased subject gave informed consent.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

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**TABLE 1. Characteristics of Study Subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Victims of SCD (N=138)</th>
<th>AMI Patients (N=254)</th>
<th>Controls (N=470)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.0 (9.2)</td>
<td>61.2 (±9.4)</td>
<td>62.5 (±5.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>124/138 (89.9)</td>
<td>185/254 (72.8)</td>
<td>&lt;0.001</td>
<td>265/470 (56.4)</td>
</tr>
<tr>
<td>BMI</td>
<td>27.3 (±4.3)</td>
<td>27.5 (±4.0)</td>
<td>NS</td>
<td>27.2 (±4.2)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>40/127 (31.5)</td>
<td>97/252 (38.5)</td>
<td>&lt;0.001</td>
<td>202/413 (48.9)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>27/127 (21.3)</td>
<td>84/252 (33.3)</td>
<td>105/413 (25.4)</td>
<td>...</td>
</tr>
<tr>
<td>Current</td>
<td>60/127 (47.2)</td>
<td>71/252 (28.2)</td>
<td>106/413 (25.7)</td>
<td>...</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>41/137 (29.9)</td>
<td>163/242 (67.4)</td>
<td>&lt;0.001</td>
<td>210/321 (65.4)</td>
</tr>
<tr>
<td>Diabetes type I or II</td>
<td>21/138 (15.2)</td>
<td>41/254 (16.1)</td>
<td>NS</td>
<td>6/419 (1.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>77/137 (56.2)</td>
<td>125/253 (49.4)</td>
<td>NS</td>
<td>149/420 (35.5)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>66/136 (48.5)</td>
<td>101/252 (40.1)</td>
<td>NS</td>
<td>...</td>
</tr>
</tbody>
</table>

NS indicates nonsignificant; BMI, body mass index. Values are expressed as mean (SD) or number of subjects (%). Probability values refer to 2-sided \(t\) test and \(\chi^2\) analyses comparing victims of SCD to AMI patients and to controls.
differed in many respects from those of SCD subjects. The risk factor profile of control subjects differed in many respects from those of SCD subjects (Table 2). However, the incidence of coronary events among first-degree relatives in general did not differentiate SCD victims from AMI survivors (Table 2). The same phenomenon was seen when the incidence of AMI among first-degree relatives was analyzed separately (Table 2). The incidence was significantly higher among first-degree relatives of both the AMI and SCD subjects than of the control subjects but did not differ between the AMI and SCD groups.

SCD among first-degree relatives of victims of SCD (5.2%) was significantly more common than SCD among the relatives of AMI survivors (3.3%) or controls (2.3%; Table 2). The OR of having had SCD among first-degree relatives was 1.6 (95% CI 1.2 to 2.2, \( P<0.01 \)) in SCD victims compared with AMI survivors and 2.2 (95% CI 1.6 to 3.0, \( P<0.001 \)) compared with control subjects. The proportion of SCD in the context of an acute coronary event (AMI or SCD) was also higher among first-degree relatives of SCD victims than among first-degree relatives of the AMI or control subjects (Table 2).

Parental history of SCD did not differ between the victims of SCD and AMI survivors, although it was higher in the SCD group than in controls (Table 3). When victims of SCD were compared with AMI survivors, the history of SCD in 1 family member did not differ significantly between the groups (OR 1.4, 95% CI 0.9 to 2.2, \( P=0.09 \)).

Statistical Analysis
Two-sided \( t \) test and \( \chi^2 \) analyses were used for comparisons between study groups. Logistic regression analysis was used to assess the significance of family history of SCD between groups after adjustment for age; gender; smoking (current smokers versus others); body mass index; history of diabetes mellitus, hypercholesterolemia, hypertension, or angina pectoris; number of first-degree relatives; and rate of adequate information on the mode of death of the family members in each group. All analyses were performed with the Statistical Package for Social Studies version 12.0 (SPSS Inc, Chicago, Ill). \( P<0.05 \) was considered significant.

Results

Patient Characteristics
The Figure shows a flow diagram of SCDs of the study population. Almost two thirds of the SCDs occurred at home, 42% of the deaths were witnessed, and resuscitation was attempted in 57% of the victims of SCD.

Demographic data and coronary risk factors are presented in Table 1. Of the common coronary risk factors, only male sex and current smoking differentiated the victims of SCD from the AMI survivors. A higher percentage of SCD victims were male. The total number of smokers (current or ex-smokers) versus nonsmokers revealed no significant difference between the SCD and AMI groups; however, the proportion of current smokers was higher in the SCD group than among AMI survivors. At the time of the ischemic event, current smoking increased the risk of SCD 2.3-fold (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.5 to 3.6, \( P<0.001 \)). Interestingly, a history of hypercholesterolemia was less common among SCD victims than AMI survivors. The risk factor profile of control subjects differed in many respects from those of SCD subjects (Table 1).

Family History
The incidence of coronary events, either SCD or AMI, among first-degree relatives of SCD victims and AMI survivors was significantly higher than among first-degree relatives of the control subjects (Table 2). However, the incidence of coronary events among first-degree relatives in general did not differentiate SCD victims from AMI survivors (Table 2). The same phenomenon was seen when the incidence of AMI among first-degree relatives was analyzed separately (Table 2). The incidence was significantly higher among first-degree relatives of both the AMI and SCD subjects than of the control subjects but did not differ between the AMI and SCD groups.

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**TABLE 2. History of SCD and AMI**

<table>
<thead>
<tr>
<th></th>
<th>FDR of Control (N=3748)</th>
<th>FDR of AMI (N=2326)</th>
<th>FDR of SCD (N=1223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD or AMI</td>
<td>276/3748 (7.4)</td>
<td>148/1223 (12.1)*</td>
<td></td>
</tr>
<tr>
<td>SCD</td>
<td>87/3748 (2.3)</td>
<td>64/1223 (5.2)*</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>189/3748 (5.0)</td>
<td>84/1223 (6.9)*</td>
<td></td>
</tr>
<tr>
<td>SCD proportion</td>
<td>87/276 (31.5)</td>
<td>76/262 (29.0)</td>
<td>64/148 (43.2)††</td>
</tr>
</tbody>
</table>

FDR indicates first-degree relative; MI, myocardial infarction.
Values are numbers of subjects (%). Probability values refer to \( \chi^2 \) analyses between groups.

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**TABLE 3. Family History of SCD and AMI**

<table>
<thead>
<tr>
<th></th>
<th>Control (N=470)</th>
<th>AMI (N=254)</th>
<th>SCD (N=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental SCD</td>
<td>69/470 (14.7)</td>
<td>51/254 (20.1)</td>
<td>31/138 (22.5)*</td>
</tr>
<tr>
<td>Parental MI</td>
<td>139/470 (29.6)</td>
<td>89/254 (35.0)</td>
<td>33/138 (23.9)†</td>
</tr>
<tr>
<td>SCD or AMI among FDR No</td>
<td>388/470 (82.6)</td>
<td>189/254 (74.4)</td>
<td>93/138 (67.4)</td>
</tr>
<tr>
<td>SCD or AMI among FDR 1</td>
<td>77/470 (16.4)</td>
<td>56/254 (22.0)</td>
<td>30/138 (21.7)</td>
</tr>
<tr>
<td>SCD or AMI among FDR &gt;1</td>
<td>5/470 (1.1)</td>
<td>9/254 (3.5)†</td>
<td>15/138 (10.9)§#</td>
</tr>
<tr>
<td>AMI among FDR No</td>
<td>304/470 (64.7)</td>
<td>128/254 (50.4)</td>
<td>79/138 (57.2)</td>
</tr>
<tr>
<td>AMI among FDR 1</td>
<td>144/470 (30.6)</td>
<td>78/254 (30.7)</td>
<td>39/138 (28.2)</td>
</tr>
<tr>
<td>AMI among FDR &gt;1</td>
<td>22/470 (4.7)</td>
<td>48/254 (18.9)§</td>
<td>20/138 (14.5)§</td>
</tr>
</tbody>
</table>

FDR indicates first-degree relative.
Values are expressed as number of subjects (%). Probability values refer to \( \chi^2 \) analyses between groups.

\*\( P<0.05 \) vs control; †\( P<0.05 \) vs AMI; ‡\( P<0.01 \) vs AMI; §\( P<0.001 \) vs control; #\( P<0.01 \) vs AMI.
but it was higher in victims of SCD than among controls (OR 3.4, 95% CI 1.8 to 6.5, \( P < 0.001 \); adjusted OR 2.5, 95% CI 1.1 to 5.5, \( P = 0.03 \)). There were a greater number of subjects with SCD in 2 or more first-degree relatives in the SCD group than in the AMI group (OR 3.3, 95% CI 1.4 to 7.8, \( P < 0.01 \)) or in the control group (OR 11.3, 95% CI 4.0 to 31.8, \( P < 0.001 \)). The respective ORs were 3.0 (95% CI 1.1 to 7.9, \( P = 0.03 \)) and 9.7 (95% CI 1.3 to 73.0, \( P = 0.03 \)) after adjustments for other risk factors, demographic variables, number of first-degree relatives, and rate of adequate family history obtained from each study group.

The history of more than 1 AMI among first-degree relatives was a significantly more frequent finding among AMI subjects and SCD victims than controls (OR 4.7, 95% CI 1.8 to 6.5, \( P < 0.001 \)). The respective ORs were 3.0 (95% CI 2.8 to 7.9 and OR 3.6, 95% CI 2.0 to 6.7, respectively). The AMI and SCD groups did not differ with regard to family history of AMI (Table 3).

### Discussion

The present study supports the assumption that a family history of SCD increases the risk of experiencing a cardiac arrest during an acute coronary event.\(^8,\)\(^9\) Furthermore, SCDs as a manifestation of the first acute coronary event appear to cluster in certain families, which suggests a genetic background. Apart from male gender and current smoking, the other known risk factors of coronary heart disease did not differ between victims of SCD and AMI survivors. In fact, a history of hypercholesterolemia was less common in the victims of SCD than in the other groups.

### Family History and SCD

The familial clustering of coronary heart diseases and AMI has been documented in several previous studies,\(^17\)\(^–\)\(^19\) which suggests that genetic factors influence the risk of atherosclerotic heart disease itself. However, it has not been well established whether hereditary factors predispose one to the occurrence of SCD or fatal arrhythmia during an ischemic event, or whether SCD during an ischemic event is merely an incidental phenomenon.

Studies in Seattle and Paris have reported the role of family history of sudden death as a risk factor for sudden death.\(^8\)\(^,\)\(^9\) There are some differences between the previous studies and the present study, however. Because of a lack of comprehensive autopsy evidence of the cause of sudden death, the familial background of SCD as a manifestation of an acute coronary event has remained uncertain in previous studies. In cases of sudden unexpected death, the medicolegal autopsy data, including the information on the circumstances of the death, is the best guarantee of a reliable cause-of-death diagnosis.\(^20\) A large proportion of deaths defined as sudden by clinical criteria may be due to a variety of noncardiac or nonarrhythmic causes.\(^2\) Familial clustering of sudden death in the general population may also be explained in part by inherited ion channelopathies and cardiomyopathies, which are not uncommon causes of SCD.\(^2\) In fact, about one third (31.6%) of sudden deaths defined by clinical criteria in the present study could not be defined to be due to an acute ischemic event on the basis of the autopsy results. Finally, in contrast to previous studies, only patients who experienced their first acute coronary event were included in the present study, because the risk factors and mechanisms of SCD may differ significantly between those with and without a prior AMI.

According to a follow-up study by Jouven et al,\(^8\) a parental history of sudden death is a specific risk factor for sudden death but not for the occurrence of fatal AMI. In the present study, parental history of SCD did not differ between the AMI and SCD groups. However, a familial history of AMI was generally associated with any coronary event, either AMI or SCD. This is logical in view of the assumption that certain genetic factors may predispose a person to an acute ischemic event, whereas other factors make the heart vulnerable to ischemia-induced arrhythmias and SCD during this event.

### Possible Genetic Background

Two or more SCDs in the first-degree relatives was clearly a more frequent finding among SCD victims than among AMI survivors and controls, which suggests a genetic background. In addition to genetic factors, there may also be environmental factors that cluster in families and increase vulnerability to SCD, perhaps explaining in part the observed differences in the family history of SCD between the groups.

Spooner et al\(^{21}\) have suggested 3 broad pathways by which genetic variations in physiological and pathological mechanisms may contribute to the risk for SCD: (1) atherothrombosis, (2) electrogenesis, and (3) neural regulation and control. It is obvious that underlying genetic mechanisms that predispose to SCD are multifactorial, which makes the detection of essential genetic mutations and polymorphisms difficult. Because of the definition of SCD, previous studies have included patients with heterogeneous underlying pathologies, which distorts the analysis of genetic studies of SCD even more. The present results suggest, however, that we should further study the so-far unrecognized genetic and environmental interactions that influence the vulnerability to SCD during an acute coronary event. The ongoing genetic screening of the families with a particularly high occurrence of ischemic SCD may help us to clarify in more detail the molecular and genetic background of ischemia-induced SCD.

### Study Limitations

The definition of SCD is never clear cut. It has been commonly defined in clinical studies as natural death that occurs within 1 hour of the onset of acute symptoms. This 1-hour definition is largely based on the clinical definition of SCD originally proposed by Hinkle and Thaler,\(^{22}\) but there are fewer data on the optimal time frame in cases with autopsy-defined SCD. Instead of the 1-hour definition, we used a time frame of 6 hours in cases with witnessed death and 24 hours in cases with unwitnessed death. Similar definitions have also been used in a recent study assessing autopsy-verified ischemic SCD.\(^{13}\) These definitions may be more relevant in cases of SCD caused by a specific trigger, such as a first acute coronary event,
because a large proportion of ischemic SCDs could be missed with the 1-hour definition. Furthermore, the majority of cases are probable arrhythmic deaths, when all mechanical complications are carefully excluded. However, acute pump failure cannot be definitively ruled out even when extensive autopsy findings are used.

It is assumed that the relatives of SCD victims may report selectively more SCDs (true or supposed) among their first-degree relatives than will the controls. We controlled this recall bias by asking for a short description of the reported event to confirm that the death was sudden by our criteria. In addition, death certificates from the Central Statistical Office in Finland were used to confirm the SCDs of the relatives. In these cases, the majority of victims also had undergone a medicolegal autopsy.

A relatively large proportion of the initial study populations had to be excluded by the end-point committee because of missing or inaccurate information about the exact mode of death. These strict criteria were used deliberately to avoid the selection bias of many previous studies, in which SCD was verified only by death certificates, without detailed clinical history and autopsy data.23,24 Furthermore, the proportion of accepted cases with accurate definition of the mode of death did not differ between the relatives of SCD victims and AMI survivors.

Conclusions

The primary prevention of SCD has thus far focused mainly on prevention of coronary deaths in general and on implantation of cardioverter-defibrillators for high-risk patients. On the basis of the present study, subjects prone to ischemic SCD can also be identified by obtaining a detailed family history with regard to SCD. In particular, the risk of SCD appears to be high if 2 or more first-degree relatives have experienced SCD. In these individuals, special attention should be given to the prevention of their first acute coronary event. Future studies will show whether genetic screening can play a role in identifying the subjects at high risk for cardiac arrest during an ischemic event.

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Disclosures

None.

References

Sudden cardiac death (SCD) due to coronary heart disease is the single most prevalent cause of death in Western societies. Despite a number of studies and trials aimed at reducing the incidence of SCD during the past few decades, prevention of SCD in the general population has remained a challenge. A large number of coronary heart disease patients die suddenly without prior symptoms and before preventive efforts can be instituted. Another problem is the overlap between the risk factors for coronary events, acute myocardial infarction, and SCD, which makes specific identification of patients vulnerable to SCD extremely difficult. On the basis of the results of the present study, a detailed family history of SCD can help identify subjects at risk. Subjects who have had 2 or more sudden deaths among their first-degree relatives have a more than 3-fold risk of dying suddenly if they experience an acute coronary event. These findings suggest that detection and aggressive treatment of risk factors for acute coronary events is particularly important for subjects with a family history of SCD. Further research is needed to identify potential environment-gene interactions that predispose a person to sudden death during an acute coronary event.
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