Alcohol septal ablation for obstructive hypertrophic cardiomyopathy
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Chapter 9

Long-term clinical outcome after alcohol septal ablation for obstructive hypertrophic cardiomyopathy: Results from the Euro-ASA registry

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Submitted
Abstract

**Background:** The first cases of alcohol septal ablation (ASA) for obstructive hypertrophic cardiomyopathy (HCM) were published two decades ago. Although the outcomes of single-centre and national ASA registries have been published, the long-term safety and efficacy of the procedure are still debated.

**Methods:** We report long-term outcomes from the largest multi-centre ASA registry (EuroASA registry).

**Findings:** A total of 1275 (58±14 years, median follow-up 5·0 years) highly symptomatic patients treated with ASA were included. The 30 day post-ASA mortality was 1%. Overall, 171(13%) patients died during follow-up, indicating a post-ASA all-cause mortality rate of 2·42 deaths per 100 patient-years. Survival rates at 1, 3, 5, and 10 years after ASA were 98%, 94%, 89%, and 77%, respectively. In multivariate analysis, independent predictors of all-cause mortality were age at ASA (p<0·01), septum thickness before ASA (p<0·01), and NYHA class before ASA (p=0·047); all-cause mortality was also independently associated with the left ventricular (LV) outflow tract gradient at the last clinical check-up (p=0·048). ASA reduced the LV outflow tract gradient from 67±36 to 16±21 mmHg (p<0·001) and NYHA class from 2·9±0·5 to 1·6±0·7 (p<0·001). At the last check-up, 89% of patients reported dyspnoea of NYHA class ≤2, which was independently associated with LV outflow tract gradient (p<0·001).

**Interpretation:** The Euro-ASA registry demonstrated low peri-procedural and long-term mortality after ASA. This intervention provided durable relief of symptoms and a reduction of LV outflow tract obstruction in selected and highly symptomatic patients with obstructive HCM. As the post-procedural obstruction is independently associated with both worse functional status and prognosis, the choice of optimal therapy should be focused on the complete elimination of LV outflow tract gradient.

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Introduction
Hypertrophic cardiomyopathy (HCM) is characterised by the presence of an increased thickness of the left ventricular (LV) wall that is not solely explained by abnormal loading conditions, including hypertension and/or valvular diseases (1-2). Two-thirds of patients with HCM have evidence of LV outflow tract obstruction, which is usually based on basal septal hypertrophy in combination with elongated mitral leaflet(s), causing systolic anterior motion of the mitral valve (1-3). In patients who remain highly symptomatic despite optimal medical therapy, surgical myectomy has been traditionally performed to relieve obstruction and its associated symptoms (1-2). Alcohol septal ablation (ASA) was introduced two decades ago by Ulrich Sigwart in The Lancet as an alternative percutaneous technique (4). He demonstrated that the injection of a small amount of desiccated alcohol into an appropriate septal branch of the left anterior descending artery is followed by basal septal necrosis and subsequent shrinkage, resulting in a decrease in LV obstruction. Although encouraging results of single-centre or national ASA registries have been repeatedly published (5-14), the long-term safety and efficacy of the procedure were debated continuously over the following decades (1, 15-16). Twenty years after the introduction of ASA, we therefore report long-term outcomes from the largest multinational ASA registry (Euro-ASA registry) to date.

Methods

Patients
A total of 1275 (58±14 years, 49% females), highly symptomatic, consecutive patients treated with ASA were included. Ablations were performed in ten centres from seven European countries (Bad Oyenhausen – Germany; Prague, Brno, Trinec – Czech Republic; Copenhagen, Gentofte – Denmark; Nieuwegein – the Netherlands; Innsbruck – Austria; Warsaw – Poland; Oslo – Norway) between January 1996 and February 2015. All patients had been prospectively included in institutional registries and subsequently also in the Euro-ASA registry. Individual centres began with the ASA programme in the years 1996–2005. The diagnosis of obstructive HCM was made by cardiologists experienced in managing patients with this disease, based on typical clinical, electrocardiographic, echocardiographic and/or cardiac magnetic resonance imaging features, with ventricular myocardial hypertrophy (LV wall thickness ≥15 mm) occurring in the absence of any other cardiac or systemic disease that could have been responsible for the hypertrophy. Alcohol septal ablation was offered to highly symptomatic adult patients in functional (NYHA) class III/IV, who were refractory or intolerant to medical therapy. In exceptional cases, patients with severe angina pectoris or
documented exertional syncope were also included. The maximal (provocable) LV outflow tract gradient had to be $\geq 50$ mmHg in the absence of severe mitral valve disease or other indication for cardiac surgery. Decisions regarding the choice for a transcatheter or surgical approach were made after a detailed multidisciplinary evaluation and a consensus amongst experts in the management of HCM, based on clinical experience at the individual sites.

Alcohol septal ablation technique

All interventions were performed by experienced interventional cardiologists. Details of the ASA technique have been published in the past (4, 17-18). Although there were some small differences in ASA technique amongst sites, all ablations were guided by myocardial contrast echocardiography and the volume of injected alcohol was gradually decreased over time (19-20). Blood was withdrawn for MB fraction of creatine kinase (CK-MB) in the two days post-ASA.

Follow-up

There were differences in post-ASA follow-up between centres participating in the registry. Generally, all patients had a routine check-up 3–6 months after ASA and then every year. Patients with an implanted pacemaker or cardioverter-defibrillator (ICD) were evaluated for both implant function and memory, including registration of discharge. The survival of patients treated in the Czech Republic and Denmark were continuously checked in the National Database of the Departed. The survival of patients treated in other countries was updated in 2014–2015, either by clinical visit, telephone call, or mail communication. For deceased patients who died beyond study institutions, interviews or mail communication with the general practitioner or next of kin was performed to discover the cause of death.

Endpoints and definitions

In this study, we wanted to determine: i) relationships between alcohol dose injected during ASA, improvement of LV outflow tract pressure gradient and the occurrence of complete heart block, ii) clinical outcome in patients treated with ASA, iii) the post-ASA rates of all-cause mortality and sudden mortality events, iv) predictors of mortality events and clinical outcome. All-cause mortality was defined as death due to any cause. Sudden mortality events included sudden deaths, appropriate ICD discharges and successful resuscitations. Sudden death was defined as sudden and unexpected death within one hour after a witnessed collapse in a previously stable patient or death that occurred during sleep. In patients with an implanted ICD, device interventions triggered by ventricular fibrillation (VF) or ventricular tachycardia (VT) were considered appropriate. Cardiovascular death was defined as death related to any cardiovascular disease, including heart failure, infective endocarditis or stroke.
The relative delta pressure gradient was used to express the percentage reduction of left ventricular outflow gradient and was defined as follows: (pressure gradient at baseline – pressure gradient at last clinical check-up)/pressure gradient at baseline.

Statistical analysis

All data was evaluated by two independent statisticians. It was presented as means ± standard deviation (±SD) and/or medians with interquartile range (IQR). Kolmogorov–Smirnov tests, Student t-tests, Wilcoxon tests, Mann–Whitney tests, logistic regression, linear regression, nonparametric regression (LOWESS – locally weighted scatterplot smoothing), median regression, Cox proportional hazard regression, Kaplan–Meier survival analysis, log rank tests for trend and chi-square tests were used as appropriate. The following clinical and echocardiographic variables with a potential impact on patient outcome were chosen and evaluated, firstly in a univariate model: age, gender, baseline and residual dyspnoea in NYHA class, baseline and residual left ventricular pressure gradient, baseline and residual septal thickness, amount of alcohol injected during ASA. Variables with a p value < 0·15 were then entered into a multivariate analysis, which was performed using a backward stepwise multiple Cox’s regression or logistic regression. A probability of less than 0.05 was considered statistically significant. All reported p-values were two-sided. The statistical software GraphPad, release 6·05 (GraphPad Software, La Jolla, CA, USA), was used.

Results

Baseline characteristics and ASA procedures

A total of 1275 consecutive patients underwent ASA (49% women, 3·7% with implanted pacemaker, 4·1% with implanted ICD). Baseline clinical and echocardiographic characteristics of the patient cohort are summarised in Table 1.

Volumes of injected alcohol were 2·2±0·9 ml (median 2 ml, IQR 1·5–2·5 ml) with a subsequent CK-MB peak of 2·9±2·2 μkat/l (Czech centres, upper limit of normal was 0·42 μkat/l) or 141±211 IU/l (remaining centres, upper limit of normal was 80 IU/l). The relationship between alcohol dose and relative delta pressure gradient is expressed in Figure 1. In multivariate analysis, the relative delta pressure gradient was independently associated with the amount of injected alcohol (HR 1·77, 95% CI 1·07–2·47; p<0·001), septum thickness at the last check-up (HR 0·22, -0·37- -0·54; p <0·001), and also NYHA class at the last check-up (HR -1·43,95% CI -2·44- 0·43; p =0·005). Although higher doses of alcohol were more effective in decreasing LV outflow tract gradient, they were also associated with a
higher occurrence of the complete heart block (HR 1.19, 95% CI 1.05-1.35; p=0.006) (Figures 1 and 2).

A total of 13 (1%) patients died within one month of ASA; four patients died of heart failure, three patients of pulmonary embolism, two patients of cardiac tamponade, one patient of sepsis, one patient of stroke, one patient of carcinoma, and one patient of sudden death (VF). Intra-procedural or early post-procedural (48 hours) sustained VT/VF requiring electrical cardioversion occurred in 16 patients (1.3%) and a further 4 (0.3%) patients required electrical cardioversion between two and 30 days after ASA. The most frequent complication was a transient peri-procedural complete heart block. This occurred in 468 (37%) patients until 30 days after ASA, with 151 (12% of all patients) patients subsequently requiring permanent pacemaker implantation.

Clinical outcome

At the last clinical check-up (median 3.9 years, IQR 1.4–7.4), ASA had reduced LV outflow tract gradient from 67±36 to 16±21 mmHg (p<0.001) and NYHA class from 2.9±0.5 to 1.6±0.7 (p<0.001) (Table 1); 89% of patients reported dyspnoea of NYHA class ≤2, and 86% of patients experienced improvement of ≥1 class of NYHA. According to multivariate analysis, NYHA class ≤2 at the last clinical check-up with the absence of myectomy or mortality event during follow-up was independently associated with LV outflow tract gradient at the same check-up (HR 0.98, 95% CI 0.97–0.99; p<0.001).

Up to the last clinical examination, 87 (7%) patients underwent a re-ASA procedure and 42 (3%) patients primarily treated by ASA subsequently underwent myectomy. Of 110 (9%) patients with an implanted ICD, 52 (4%) patients underwent implantation before and 58 (5%) after ASA. Some clinical data was missing for 105 (8%) patients.

Survival after ASA

The median of follow-up for survival was 5.0 years, (IQR 2.1–8.2 years). Five (0.4%) patients were lost to long-term follow-up. Overall, 171(13%) patients died during 7057 patient-years of follow-up, indicating a post-ASA all-cause mortality rate of 2.42 deaths per 100 patient-years (95% CI, 2.07–2.82) (Figure 3). Survival rates are summarised in Table 2. According to multivariate analysis, independent predictors of all-cause mortality were higher age at ASA (HR 1.06, 95% CI 1.05–1.08; p<0.001), septum thickness before ASA (HR 1.05, 95% CI 1.01–1.09; p<0.001), and NYHA class before ASA (HR 1.5, 95% CI 1.00–2.10; p=0.047); all-cause mortality was also independently associated with LV outflow tract gradient at the last check-up (HR 1.01, 95% CI 1.00–1.01; p=0.048). The survival of patients, divided in three groups according to LV outflow tract gradient at the last clinical
check-up (\(\leq 29\) mmHg, 30-59 mmHg, \(\geq 60\) mmHg), is available in Figure 4. After adjustment for age at ASA, septum thickness before ASA and NYHA class before ASA, 10-year all-cause mortality rates were 75%, 72%, and 55%, respectively.

A total of 197 (15%) patients experienced all-cause death or appropriate ICD discharge during 7055 patient-years of follow-up, indicating the rate of mortality events as 2.84 per 100 patient-years (95% CI, 2.46–3.27) (Figure 5). In multivariate analysis, independent predictors of these mortality events were higher age at ASA (HR 1.05, 95% CI 1.04–1.07; \(p < 0.001\)), and septum thickness before ASA (HR 1.06, 95% CI, 1.03–1.1; \(p=0.001\)); mortality events were also independently associated with LV outflow gradient at the last check-up (HR 1.01, 95% CI 1.00–1.01; \(p=0.02\)). Figure 6 depicts the mortality events subdivided by cause.

Sudden mortality events (sudden death, first appropriate ICD discharge or successful resuscitation) occurred in 68 (5.3%) patients, indicating the rate as 0.98 per 100 patient-years (95% CI, 0.76–1.12) (Figure 7); 43% of these patients survived the first event. The only independent predictor of sudden mortality events was the septum thickness before ASA (HR 1.07, 95% CI 1.01–1.12; \(p=0.014\)).

Sudden or cardiovascular death occurred in 82 (6.4%) patients, which means an annual mortality rate of 1.16 (95% CI, 0.92–1.44) per 100 patient-years. Mortality events at least partially attributable to HCM (peri-procedural events, sudden mortality events or cardiovascular death) occurred in 108 (8.5%) patients, which means the annual mortality rate 1.58 (95% CI, 1.29–1.90) per 100 patient-years.

**Discussion**

The Euro-ASA Registry was designed as a large, multinational, European registry to identify long-term outcome and its predictors in patients after ASA for highly symptomatic obstructive HCM. Two decades after the introduction of ASA, we can report the following principal findings: i) higher doses of alcohol are more effective in decreasing LV outflow tract gradient, but they are also associated with a higher occurrence of peri-procedural complete heart block; ii) LV outflow gradient is lowered by 76%, and 86% of patients experience improvement of \(\geq 1\) class of NYHA; iii) the more pronounced reduction of LV outflow tract gradient is associated with the lower resultant NYHA class; iv) the 30-day post-procedural mortality rate is 1%, and 12% of treated patients require an early post-procedural pacemaker implantation; v) the annual post-ASA mortality rate is 2.4% and risk of a sudden
mortality event is 1% per year; vi) the all-cause mortality is independently associated with the residual LV outflow tract gradient.

Based on data from smaller studies describing similar haemodynamic results with the use of low or high doses of intracoronary alcohol (19-20), the low doses (1-2 ml) have become standard in most ASA centres. The current registry suggests that higher doses of alcohol were slightly more effective in decreasing LV outflow tract gradient. This has significant clinical consequences, because the lower LV outflow tract gradient was associated both with better functional class and survival. On the other hand, the advantage of higher alcohol doses was balanced by a higher risk of peri-procedural complete heart block. Based on our findings, we believe that doses of alcohol ranging between 1·5 and 2·5 ml are well balanced in terms of efficacy and safety for most patients. Nevertheless, the optimal dose of alcohol can vary for each individual patient depending on the severity of their symptoms, acceptability of procedural risk and LV morphology.

Procedure-related mortality was believed to be low even in the first decade after ASA introduction, with a reported mean value of approximately 1·5% (21). In this registry, we found the 30-day post-ASA all-cause mortality to be even lower (1%) including non-cardiovascular mortality. On the other hand, the complication rate related to ASA is still not negligible and we have to bear in mind that one-tenth of patients will have to subsequently undergo pacemaker implantation, and some patients (1·6%) will suffer from early post-procedural ventricular arrhythmias. Fortunately, the initial fears of a plethora of late ventricular dysfunction and arrhythmias, or an increased rate of sudden death (15-16) have not been fulfilled in our observation. In this registry, with a follow-up exceeding 7000 patient-years, the rate of sudden mortality events was 1% per year, including 0·6% of sudden deaths, which is less than or similar to results presented in other HCM registries containing HCM patients without previously performed ASA (22-24). The combined rate of sudden and cardiovascular mortality reported here (1·2%) is also relatively low and may not even be entirely attributable to HCM.

In the arena of HCM prognostication and choosing the optimal septal reduction therapy, there is still a knowledge gap with regard to post-procedural mortality and comparison of ASA and myectomy. Long-term survival in the current study was comparable with similar reports of patients treated by myectomy. In this study (n=1275, mean age at ASA 58 years) 10-year survival was 77%, compared to two surgical Mayo Clinic studies (25-26) with survival rates of 77% (Schaff et al., 749 patients, mean age at surgery 52 years), and 83% (Ommen et al., 289 patients, mean age at surgery 45 years). Similarly, the North American ASA Registry
(874 patients, mean age at ASA 55 years) demonstrated a 9-year survival of 74% (5). An identical 10-year survival of 77% was also reported by Sorajja in 544 consecutive patients with obstructive HCM (mean age 59 years), who were mildly symptomatic or asymptomatic and did not require septal reduction therapy (27). All this data, albeit reported from cohorts with a lower number of patients, seems to be consistent with our results and suggests that the long-term survival of patients treated by both techniques of septal reduction therapy is similar. This view has also been confirmed by several meta-analyses (28-29).

Prediction of post-ASA clinical outcome is challenging because of the marked heterogeneity of the treated HCM cohort. In this study, the independent predictors of all-cause mortality were higher age, septum thickness and functional class before ASA, and the only predictor of sudden mortality events was septum thickness before ASA. In the context of known risk factors of long-term mortality for HCM patients these results are not surprising, however, the residual LV outflow tract gradient at the last clinical examination was also independently associated with all-cause mortality and all-cause mortality plus risk of appropriate ICD discharge. Our results thus suggest that the increase in residual LV obstruction by each mmHg was associated with a 1% increase in risk of all-cause death. It is worth noting that in post-myectomy patients an association of incomplete relief of the outflow obstruction with worse survival has also been demonstrated (30).

Based on these findings, we may speculate that with the exception of ICD implantation for prevention of sudden cardiac death, the reduction of LV gradient is the most important therapeutic procedure affecting the long-term survival of highly symptomatic obstructive HCM patients, and that the means used to accomplish this are less important. In other words, it does not matter whether the obstruction is eliminated by means of myectomy or ASA, the most important objectives are the safety of the procedure and the final haemodynamic result. We cannot be sure that the current results are entirely generalisable since the patients have been referred to tertiary centres that have great experience with HCM. The key factor influencing the results of ASA is probably the optimal selection of HCM patients who are appropriate for this therapy. Typically, patients with less basal hypertrophy, long mitral leaflets, and marked hypertrophy of (bifid) papillary muscles are good candidates for septal myectomy and surgical procedures on mitral valve and/or papillary muscles (3). On the other hand, patients with hypertrophy localised mainly in the basal part of the septum without elongated mitral leaflets may be effectively and safely treated by ASA.
Chapter 9

Conclusion
Patients diagnosed and treated in tertiary centres focusing on HCM have both low peri-procedural and long-term mortality after ASA. Higher doses of alcohol are slightly more effective in reducing LV obstruction and result in a higher incidence of peri-procedural complete heart blocks. Since the post-procedural obstruction is independently associated with both worse functional status and prognosis, the choice of optimal therapy should be focused on the complete elimination of LV outflow tract gradient.
Research in Context

Evidence before the study
We searched PubMed on June 26, 2015, for clinical trials with the terms “hypertrophic cardiomyopathy”, “alcohol septal ablation”, “registry” and “survival”, with no language restrictions. We identified a multicentre North American Registry (n=874, mean follow-up 2·1 years) (5) and a German TASH Registry (n=264, in-hospital results) (6). In addition, we found several major institutional and multi-centre studies (7-14) in PubMed.

Two-thirds of the patients with HCM display evidence of obstruction in LV at rest or after provocation (1-2). As first demonstrated two decades ago (4), the injection of a small amount of desiccated alcohol into an appropriate septal branch of the left anterior descending artery is followed by basal septal necrosis with its subsequent shrinking and decrease in LV obstruction (alcohol septal ablation – ASA). Although observational data suggested favourable outcomes of ASA (5-6), the long-term results are still a matter of debate (1, 15-16).

Added value of this study
We report long-term outcomes of ASA and their predictors from the largest multi-centre ASA registry (Euro-ASA registry, n=1275, mean follow-up 5·5 years). Doses of alcohol ranging between 1·5 and 2·5 ml were well balanced in terms of efficacy and safety for most patients. ASA lowered LV outflow tract gradient by 76%, and 86% of the patients experienced an improvement of ≥1 of NYHA functional class. The annual post-ASA mortality rate was 2·4% and the risk of sudden mortality event was 1% per year. Both the all-cause mortality and better functional status were independently associated with LV outflow tract gradient at the last clinical examination of the patient.

Implications of all available evidence
Alcohol septal ablation performed in dedicated centres is a safe and effective procedure for symptomatic obstructive HCM patients. The post-ASA residual obstruction is a significant factor influencing functional status and long-term survival. Appropriate pre-procedural patient selection, and if possible complete elimination of the obstruction, should therefore be pursued for the optimal improvement of long-term survival.
Acknowledgments
The authors are grateful to statisticians Eva Hansvenclova and Dr Marek Maly for their assistance with statistical analysis. The authors also thank colleagues responsible for the HCM clinics in all participated centres.

Conflict of interest: None
Table 1. Clinical and echocardiographic characteristics at baseline and last clinical check-up.

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<th>Baseline</th>
<th>Follow-up</th>
<th>P-value</th>
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<tr>
<td>Age, years</td>
<td>58 ± 14</td>
<td>63 ± 13</td>
<td>&lt;0.001</td>
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<tr>
<td>Dyspnoea, NYHA class</td>
<td>2.9 ± 0.5</td>
<td>1.6 ± 0.7</td>
<td>&lt;0.001</td>
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<td>Angina, CCS class</td>
<td>1.3 ± 1.2</td>
<td>0.7 ± 0.8</td>
<td>&lt;0.001</td>
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<tr>
<td>Episodes of syncope, %</td>
<td>22</td>
<td>7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular outflow tract gradient, mmHg</td>
<td>67 ± 36</td>
<td>16 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter, mm</td>
<td>43 ± 6</td>
<td>46 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>70 ± 10</td>
<td>66 ± 10</td>
<td>&lt;0.001</td>
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<tr>
<td>Basal septum thickness, mm</td>
<td>20 ± 4</td>
<td>15 ± 4</td>
<td>&lt;0.001</td>
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**Table 2. Event-free survival rates after ASA**

<table>
<thead>
<tr>
<th>Event</th>
<th>Survival rates (95% CI)</th>
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<tr>
<td></td>
<td>1 year</td>
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<tr>
<td>All-cause death</td>
<td>98% (96%-98%)</td>
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<tr>
<td>All-cause death or appropriate ICD discharge</td>
<td>97% (96%-98%)</td>
</tr>
<tr>
<td>Sudden mortality event</td>
<td>99% (98%-99%)</td>
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Figure 1. Relationship between alcohol dose, relative delta pressure gradient and complete heart block.
Figure 2. Lowess curve describing relationship between alcohol dose and the occurrence of peri-procedural complete heart block.
Figure 3. Kaplan-Meier survival curve describing all-cause mortality with 95% confidence intervals.
Figure 4. Relationship between survival in groups divided according to the left ventricular outflow tract pressure gradient (LVOTO) at the last clinical check-up.
Figure 5. Kaplan-Meier survival curve describing all mortality events including appropriate ICD discharges and resuscitations with 95% confidence intervals.
Figure 6. Causes of death after ASA.
Figure 7. Kaplan-Meier survival curve describing all sudden mortality events including appropriate ICD discharges and resuscitations with 95% confidence intervals.
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