

1 A worldwide survey on incidence, management and prognosis of oesophageal fistula formation following  
2 atrial fibrillation catheter ablation: The POTTER-AF study

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25

1 **Abstract**

2  
3 **Aims:** Oesophageal fistula represents a rare but dreadful complication of atrial fibrillation  
4 catheter ablation. Data on its incidence, management and outcome are sparse.

5 **Methods and results:** This international multicenter registry investigates the characteristics of  
6 oesophageal fistulae after treatment of atrial fibrillation by catheter ablation. A total of 553,729  
7 catheter ablation procedures (radiofrequency: 62.9%, cryoballoon: 36.2%, other modalities:  
8 0.9%) were performed at 214 centers in 35 countries. In 78 centers 138 patients (0.025%,  
9 radiofrequency: 0.038%, cryoballoon: 0.0015% ( $p < 0.0001$ )) were diagnosed with an oesophageal  
10 fistula. Periprocedural data were available for 118 patients (85.5%). Following catheter ablation,  
11 the median time to symptoms and the median time to diagnosis were 18 (7.75, 25; range: 0-60)  
12 days and 21 (15, 29.5; range: 2-63) days, respectively. The median time from symptom onset to  
13 oesophageal fistula diagnosis was 3 (1, 9; range: 0-42) days. The most common initial symptom  
14 was fever (59.3%). The diagnosis was established by chest computed tomography in 80.2% of  
15 patients. Oesophageal surgery was performed in 47.4% and direct endoscopic treatment in  
16 19.8%, and conservative treatment in 32.8% of patients. The overall mortality was 65.8%.  
17 Mortality following surgical (51.9%) or endoscopic treatment (56.5%) was significantly lower as  
18 compared to conservative management (89.5%) (odds ratio 7.463 (2.414, 23.072)  $p < 0.001$ ).

19 **Conclusions:** Oesophageal fistula after catheter ablation of atrial fibrillation is rare and occurs  
20 mostly with the use of radiofrequency energy rather than cryoenergy. Mortality without surgical  
21 or endoscopic intervention is exceedingly high.

22



1 **Keywords:** Atrial fibrillation, catheter ablation, radiofrequency energy, oesophageal fistula

2

### 3 **Introduction**

4 Invasive treatment of atrial fibrillation (AF) by catheter ablation based pulmonary vein isolation  
5 (PVI) is being increasingly performed worldwide. Catheter ablation has shown high procedural  
6 and long-term follow-up success rates for treatment of paroxysmal and persistent AF.<sup>1</sup> In general,  
7 the rate of severe peri- and postprocedural complications is low and several technical  
8 improvements, novel technologies and energy sources have increased the safety profile of this  
9 treatment strategy. However, oesophageal fistula (OF) is a devastating and potentially lethal  
10 complication of AF ablation procedures. Its incidence is known to be low and has been reported  
11 to range between 0.02% and 0.1% of cases, with a high mortality of 50% to 83%.<sup>2, 3, 4, 5</sup> Since OF is  
12 a rare complication, only limited information based on case reports, case series, and nationwide  
13 registries with a limited number of patients on its incidence, management, and outcome is  
14 available in the recent literature.<sup>2,3,6,7,8,9,10-12</sup> The largest survey to date was conducted in 2015  
15 and included 33 patients with OF after AF ablation.<sup>3</sup> Meanwhile, the total number of AF ablation  
16 procedures has significantly increased. Additionally, AF ablation technologies have rapidly  
17 changed with increasing numbers of cryoballoon ablations, contact force guidance, and high-  
18 power short-duration based radiofrequency (RF) ablations.<sup>13-15</sup> The aim of this worldwide study  
19 was to evaluate the incidence, management and outcome of OF after catheter ablation  
20 procedures for AF or atrial tachycardia (AT) treatment.

21

22

## 1 **Methods**

2

### 3 Study design:

4 The POTTER-AF (PrOgnosis following oesophageal fisTula formaTion in patients undergoing  
5 cathetER ablation for AF) study is designed as an international, multi-center, anonymized registry  
6 study to evaluate the incidence, management and outcomes of post-procedural OF after catheter  
7 ablation of AF. The survey was conducted at the Department of Rhythmology at the Lübeck  
8 University Heart Center under the auspices of the Working Group of Cardiac Electrophysiology of  
9 the German Cardiac Society (AGEP, DGK). Experienced electrophysiological centers from all  
10 around the world were invited to participate. The registry was approved by the local ethical  
11 review board of the University of Lübeck, Germany (AZ 21-291). Each participating center was  
12 responsible for its ethics approval by the local ethics committee. The study has been performed  
13 in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its  
14 later amendments. All patient information was anonymized. The POTTER-AF study has been  
15 registered at [clinicaltrials.gov](https://clinicaltrials.gov) (NCT05273645). Each participating center provided data on the  
16 total number of patients treated with catheter ablation for AF or AT. Additionally, patients`  
17 baseline characteristics, periprocedural characteristics, and follow-up data were assessed for  
18 patients with OF according to a standardized and uniform online questionnaire survey  
19 (SurveyMonkey). Data acquired via SurveyMonkey were assessed for an individual patient level  
20 and used for further analysis. The inclusion criteria were patients with an OF (which included  
21 atrio-oesophageal fistula, oesophago-pericardial fistula, or oesophageal perforation) after  
22 catheter ablation for AF treatment. There were no exclusion criteria for this study. The primary

1 endpoint was the occurrence of OF following catheter ablation for AF or AT treatment. The  
2 secondary endpoints were the diagnosis and management of OF as well as outcome and  
3 mortality.

#### 4 5 Data management

6 Data were retrospectively and electronically collected. The analysis was performed using  
7 anonymized data only. The described data were retrospective data derived from the clinical  
8 routine of the participating centers, including routine follow-up visits. All the members of the  
9 research team were obliged to secrecy. All data were protected from unauthorized external  
10 access, as only members of the research team were permitted and enabled access to these data.

#### 11 12 Statistical analysis:

13 All categorical variables were reported as absolute and relative frequencies and were compared  
14 using Fisher's exact test or the Chi-square test. Continuous variables were tested for normal  
15 distribution using the Shapiro-Wilk test. They were reported as mean  $\pm$  standard deviation (SD)  
16 in the case of normal distribution, otherwise as median and interquartile range (first quartile,  
17 third quartile). Continuous variables were compared using the non-paired Student's *t*-test when  
18 normally distributed and the corresponding non-parametric test (Mann-Whitney U test)  
19 otherwise.

20 The association between different parameters and death was assessed using binary logistic  
21 regression and is reported as odds ratio (OR) and 95% confidence intervals (CI).

1 Variables with a p-value <0.1 in the univariable model and considered clinically important for the  
2 outcome were included in a multivariable binary logistic regression model.

3 All parameters with perfect collinearity were excluded from the logistic regression analysis and  
4 were reported descriptively. The variables eligible for multivariable logistic regression are: age,  
5 structural heart disease, left ventricular ejection fraction, coronary artery disease, congestive  
6 heart failure, duration of hospitalization, use of conscious sedation, use of thermal probe,  
7 anatomical pulmonary vein isolation, diagnostic method (computed tomography [CT], septic  
8 shock, coma, cardiac arrest, oesophageal surgery, direct oesophageal surgery without endoscopic  
9 treatment, conservative treatment). All p-values are two sided. A p-value of <0.05 was considered  
10 statistically significant. All statistical analyses were performed using SPSS version 28.0 (IBM SPSS  
11 Statistics).

## 12 **Results**

### 13 Patients' population

14 A total of 609 experienced electrophysiological centers around the world were invited to  
15 participate in this study (**Figure 1**). Data on overall conducted AF or AT catheter ablation  
16 procedures were obtained from 214 (35%) centers in 35 countries across 5 continents. The full  
17 list of centers included in this study is available in the supplements (**Supplements Table 1**). A total  
18 of 553,279 patients underwent catheter ablation procedures for AF or AT treatment between  
19 1996 and 2022. The mean percentage of energy source was RF in 62.9±29.8%, cryoballoon in  
20 36.2±30%, laserballoon in 0.6±3% and others in 0.3±1.3%. A total of 138 patients (0.025%) from  
21 78 centers (21 countries) experienced postprocedural OF (**Figure 2**). The incidence of RF was

1 0.038%, while for cryoballoon it was 0.0015% ( $p < 0.0001$ ). For other modalities the incidence was  
2 0.02%.

3 Periprocedural data, management, and outcomes were available for 118 patients (18 countries),  
4 while relevant data were not available for 20 patients (14.5%). The final diagnoses were atrio-  
5 oesophageal fistula in 113/118 (95.8%) patients, oesophago-pericardial fistula in 4/118 (3.4%)  
6 patients and oesophageal perforation in 1 (0.8%) patient. The baseline characteristics are shown  
7 in **Table 1**. Forty-seven percent were female, with a mean age of  $62.0 \pm 11.4$  years. A history of  
8 oesogastric pathology was reported in 8% of the patients, and 23% reported a preprocedural  
9 proton pump inhibitor therapy.

10 The highest amount of OF per center was five in one center. The maximum incidence of OF at the  
11 specified time was 0.4%, whereas the minimum incidence per study center was 0.0066% ( $p < 0.01$ ).

12

### 13 Periprocedural characteristics

14 Procedural data are presented in **Table 2**. In 114/118 patients (96.6%) the catheter ablation  
15 energy source was RF; contact force measuring catheters were used in 46% of them. The median  
16 RF power when ablating at the posterior wall was 30 (interquartile range: 25, 30) W. Besides PVI,  
17 additional left atrial (LA) lines were deployed in 45.5% of RF patients. Ablation of a roof line was  
18 performed in 30.9%, a posterior line was performed in 24.5% and ablation of complex  
19 fractionated atrial electrograms at the posterior wall was performed in 15.2% of patients.

20 In 3/118 patients (2.5%), a cryoballoon (n=1: 1<sup>st</sup> generation, Arctic Front cryoballoon, Medtronic  
21 Inc. and n=2: 2<sup>nd</sup> generation Arctic Front Advanced cryoballoon, Medtronic Inc.) was used for PVI.

1 The minimal reported temperature was  $-69^{\circ}\text{C}$  during cryoballoon application to the RIPV. No  
2 oesophageal temperature probe was utilized in any of the cryoballoon OF cases. In 1/118 patients  
3 (0.8%) the laserballoon ablation (HeartLight, Cardiofocus) was used. The maximal laser energy at  
4 the posterior wall was reported to be 10 W and the maximal oesophageal temperature as  
5 measured via an oesophageal temperature probe was reported to be  $37.1^{\circ}\text{C}$ . An oesophageal  
6 temperature probe was utilized in 24.6% of the total OF population and data concerning the  
7 esophageal temperature was available for 15.3% of patients. The mean maximum measured  
8 temperature was  $40.2\pm 2.2^{\circ}\text{C}$ . A total of 74.6% reported postprocedural proton pump inhibitor  
9 therapy.

10

### 11 Patient presentation

12 The findings on patients' presentation, diagnostic modality and complications are depicted in  
13 **Figure 3**. The median time between the procedure and earliest onset of symptoms was 18 (7.75,  
14 25) days (range: 0-60 days), and the median time between the procedure and OF diagnosis was  
15 21 (15, 29.5) days (range: 2-63 days). The median time from first symptom onset to OF diagnosis  
16 was 3 (1, 9) days (range: 0-42 days). One OF occurred on Day 2 (RF, non-contact force catheter,  
17 maximum of 25 W at posterior wall, PVI only). The first symptoms occurred already on Day 1  
18 (fever, neurological symptoms, multi-organ dysfunction, septic shock, and death before  
19 interventional or surgical treatment). Two further OF were diagnosed on Day 4 and two OF on  
20 Day 5. All early diagnosed patients reported symptoms (fever and neurological symptoms).

21 In patients treated with endoscopy alone, oesophageal surgery, or conservative treatment, the  
22 median time between the procedure and the earliest onset of symptoms was 10 (6, 15), 18 (11,

1 22.5) and 20.5 (10, 29) days, respectively ( $p=0.03$ ). The median times between the procedure and  
2 OF diagnosis were 18 (10, 25), 21 (15, 29) and 26.5 (19, 32) days, respectively ( $p=0.03$ ).

3 The primary initial symptoms were fever ( $n=70$ , 59.3%), chest pain or odynophagia ( $n=64$ , 54.2%)  
4 and neurological symptoms (stroke or seizures) ( $n=52$ , 44.1%). Other symptoms were reported in  
5 74 patients (62.3%: dyspnea, nausea, syncope, cough, AF, hematemesis, confusion, vomiting, ST-  
6 elevation myocardial infarction, and aphasia). The symptoms occurred either in isolation or in  
7 association with one another. In one patient (0.8%), no symptoms were reported. Diagnosis was  
8 made by routine endoscopy on Day 10. In this case a RF contact force measuring catheter with a  
9 maximum of 48 W at the posterior wall during deployment of a posterior line was utilized. After  
10 endoscopic treatment via clipping no sequelae were reported.

11 The diagnosis was established by chest CT in 93 (80.2%) patients, with cerebral CT or cerebral  
12 magnetic resonance imaging in 40 (34.5%), with echocardiography in 29 (25%), with endoscopy  
13 in 24 (20.7%) patients, and other, in 20 (17.2%, autopsy, pericardiocentesis, lumbar puncture,  
14 cardiac surgery) of patients. Diagnosis was established using either an isolated modality or a  
15 combination of several modalities.

### 16 Clinical course, management and outcome

17 During the clinical course, delayed complications were stroke or cerebral hemorrhages (25/107,  
18 23.4%), severe sepsis or septic shock (62/107, 57.9%), coma (50/107, 46.7%), cardiac arrest  
19 (20/107, 18.7%), gastrointestinal bleeding (18/107, 16.8%), cardiac tamponade (12/107, 11.2%),  
20 or others in 31/107 (29%). A total of 5/107 (4.7%) patients reported no complications. In two of  
21 those patients the OF was detected during routine endoscopic ultrasound assessment and was  
22 treated by endoscopic clipping and endoscopic stenting with no and minor sequelae, respectively.

1 In one patient, a CT scan was performed due to confusion. After detection of an OF, the patient  
2 was treated with endoscopic stenting followed by oesophageal surgery with minor long-term  
3 sequelae. Gastric liquid pericardial effusion was detected in two patients, both treated with  
4 oesophageal surgery and did not report any sequelae.

5 All patients were treated with intravenous antibiotic therapy. Among 116 patients diagnosed with  
6 OF, and treatment data available, n=38 (32.8%) were treated conservatively, without endoscopic  
7 of surgical treatment attempts, and n=34 (89.5%) of them died during follow-up. One patient  
8 (2.6%) had severe sequelae and three (7.9%) reported no long-term sequelae.

9 A total of 31 (26.7%) patients were initially treated with endoscopic therapy (oesophageal stenting  
10 (n=28), clipping (n=2) or vacuum-assisted-closure therapy (n=1)). Due to their critical condition,  
11 17/31 (54.8%) died or had severe sequelae (3/31, 9.7%). Minor sequelae were reported in 4/31  
12 (12.9%) patients, while 7/31 (22.6%) had no sequelae. The oesophageal stent was removed in  
13 4/31 (12.9%) patients after 30 – 75 days.

14 Isolated endoscopic therapy was performed in 23 (19.8%) patients (mortality: 13/23, 56.5%);  
15 whereas in eight patients the initial endoscopic therapy was switched to a surgical approach due  
16 to limited benefit (mortality: 4/8, 50%).

17 A total of 55/116 (47.4%) patients were treated using an oesophageal surgical approach. In one  
18 patient treated with oesophageal surgery, the data concerning mortality were not available. A  
19 total of 28/54 (51.9%) patients treated surgically died. A direct surgical approach without a  
20 previous endoscopic treatment attempt was conducted in 47/116 (40.5%) patients. In this group  
21 24/46 (52.2%) died. In terms of mortality, there were no significant differences between patients  
22 who underwent a direct surgical approach and those who underwent a direct endoscopic



1 approach ( $p=0.801$ ). The overall mortality was 77/117 (65.8%), 11/117 (9.4%) and 11/117 (9.4%)  
2 experienced long term major and minor sequelae, respectively. Only 18/117 (15.4%) reported no  
3 long-term sequelae. The mortality following surgical (51.9%) or endoscopic treatment (56.5%)  
4 was significantly lower than that following conservative management (89.5%), (OR 7.463 (2.414,  
5 23.072)  $p<0.001$ ), **Figure 4**. The median time to death was 28.5 days (19.3, 42).

6 In order to better understand the differences between patients receiving conservative treatment  
7 and those receiving surgical/endoscopic treatment, the comparison between the two populations  
8 in terms of baseline characteristics, procedural data, complications and survival was performed  
9 (**Supplements Table 4**). It is important to note that the patients receiving conservative treatment  
10 had a longer time to initial symptoms (20.5 (10, 29.8) vs. 15 (6, 21.8) days;  $p=0.037$ ) and a longer  
11 time until OF diagnosis (26 (18, 33.5) vs. 19 (13, 28.5) days;  $p=0.019$ ), as compared to those  
12 receiving surgical/endoscopic treatment. Moreover, the patients receiving invasive treatment  
13 were more likely to be diagnosed by means of chest CT (86.8% vs. 65.8%;  $p=0.013$ ) and less likely  
14 to be diagnosed by other methods. In terms of complications, the patients receiving  
15 surgical/endoscopic treatment were less likely to have a diagnosis of stroke during the clinical  
16 course as compared to those treated conservatively (14.7% vs. 39.5%;  $p=0.008$ ).

#### 17 Subgroup analysis of survivors vs non-survivors

18 A detailed comparison of survivors and non-survivors is shown in **Supplements Table 2**.  
19 Concerning baseline characteristics, atrio-oesophageal fistula, older age, reduced left ventricular  
20 ejection fraction and coronary artery disease showed significantly higher values in terms of  
21 mortality while an oesophageal-pericardial fistula ( $n=4$  patients, 100% survival) showed a  
22 significantly lower mortality. An anterior line showed significantly higher mortality. The

1 occurrence of septic shock, coma, cardiac arrest and gastrointestinal bleeding was significantly  
2 higher in the non-survivors while the rate of patients with no complications was significantly  
3 higher in the survivors. Patients with any interventional or surgical treatment, patients with  
4 oesophageal surgery as well as patients with direct oesophageal surgery without previous  
5 stenting or clipping showed a significantly lower mortality.

6 To identify mortality associated factors, a simple (univariable) binary logistics regression was  
7 performed (**Supplements Table 3**). For identified factors with a p-value of  $<0.1$  and considered  
8 of clinical importance for the prognosis, a multivariable binary logistic regression was  
9 conducted.

10 Although not significant, yet a trend towards a lower mortality was observed for the use of an  
11 esophageal probe (OR: 0.449,  $p=0.068$ ) in the univariable logistic regression. After including this  
12 variable in the multivariable model, it was significantly associated with lower mortality (OR: 0.231,  
13  $p=0.012$ ). Moreover, the use of conscious sedation and the treatment via oesophageal surgery  
14 were associated with better survival (**Table 3**).

## 1 Discussion

2 Oesophageal fistula represents a rare but dreadful complication of AF catheter ablation. The  
3 incidence varies between different studies; however, it may be underreported and the true  
4 incidence is unknown. This fearful complication is associated with a very high mortality rate.<sup>2 3 4</sup>

5 <sup>5</sup> Due to the limited number of cases, data concerning the incidence, management, and outcome  
6 of OF are sparse. Therefore, this complication requires an international worldwide effort to allow  
7 for a better understanding of the factors contributing to its occurrence and the optimal  
8 management strategies. To address these issues, the POTTER-AF study was conducted.

9 The major findings were: (i) the incidence of OF after catheter ablation for AF/AT treatment was  
10 0.025% with an incidence of 0.038% for RF and 0.0015% for Cryoballoon ( $p < 0.0001$ ); (ii) the  
11 median time to symptoms (18 (7.75, 25) days), and the median time to diagnosis (21 (15, 29.5)  
12 days) occurred relatively late after the procedure, while the median time from first symptom  
13 onset to OF diagnosis was 3 (1, 9) days (range: 0-42 days); (iii) the most common initial symptom  
14 was fever (59.3%); (iv) the diagnosis was established using chest CT in 80.2%; (v) oesophageal  
15 surgery was performed in 47.4% and a direct endoscopic treatment was conducted in 19.8%, and  
16 conservative treatment was conducted in 32.8% of cases; (vi) the overall mortality was 65.8%,  
17 18.8% experienced long term sequelae; (vii) mortality following surgical (51.9%) or endoscopic  
18 treatment (56.5%) was significantly lower as compared with conservative management (89.5%)  
19 ( $p < 0.001$ ); and (viii) the multivariable binary logistic regression found the conscious sedation and  
20 the use of thermal probe, as well as the treatment by means of oesophageal surgery as  
21 significantly associated with a better prognosis in terms of survival (Structured Graphical  
22 Abstract).

1  
2 This worldwide survey provides the largest dataset on OF today. It reports important data to allow  
3 a better understanding of the incidence, management and outcomes of OF occurring after AF/AT  
4 ablation. With 0.025%, the incidence of OF is in line with recent literature of a nationwide survey  
5 from France (incidence of 0.026%), which was calculated from 33 OF in 129,286 AF/AT ablations  
6 procedures.<sup>3</sup> Other surveys with limited patients number reported on incidences of between  
7 0.016% and 0.15%.<sup>2,7,16</sup>

#### 8 9 Impact of the energy source in oesophageal fistula formation

10 Although OF has been mainly reported for RF based catheter ablation procedures, the latest  
11 findings suggest that OF also may occur in cryoballoon and other balloon based ablation  
12 procedures.<sup>10,17</sup> The incidence of OF following cryoballoon based ablation was reported as  
13 <0.0001%, which maybe reflects the frequent use of oesophageal temperature probes during  
14 cryoballoon based procedures.<sup>10</sup> The POTTER-AF study evaluated an OF in a total of 3 patients  
15 after cryoballoon based PVI which only reflects 2.5% of the analysed population. The incidence of  
16 RF (0.038%) was significantly higher than that of cryoballoon (0.0015%,  $p < 0.0001$ ). This difference  
17 might partially be explained by additional ablation of LA lines in RF patients, yet most likely not  
18 completely. With a reported cryoballoon temperature of a minimum of  $-69^{\circ}\text{C}$ , which is far below  
19 the suggested minimum temperature of  $-60^{\circ}\text{C}$  for the Arctic Front Advanced cryoballoon, the  
20 combination of a temperature cut-off and the utilization of an oesophageal temperature probe  
21 might prevent OF in cryoballoon procedures. In 1/118 patients (0.8%) the laserballoon ablation  
22 was used. The maximal laser energy at the posterior wall was reported to be 10 W, which is in  
23 line with the recommendations.<sup>18</sup>

1 Since RF is still the most common energy source for cardiac ablation procedures, and the main  
2 proportion of patients included in the POTTER-AF study suffered OF after RF based catheter  
3 ablation. The latest observations on pulsed field ablation based catheter ablation suggested that  
4 this novel non-thermal energy source might reduce oesophageal injuries and potentially OF due  
5 to its selectivity to cardiomyocytes.<sup>19</sup>

6  
7 Prevention of oesophageal fistula  
8 Utilization of oesophageal temperature probes is a common strategy to monitor the oesophageal  
9 temperature and potentially prevent oesophageal injuries. While for cryoballoon and  
10 laserballoon based ablation the use of an oesophageal temperature probe is a commonly  
11 accepted strategy. However, its usage during RF based ablation is less common, and one study  
12 showed that it could be a risk factor for the development of endoscopically detected esophageal  
13 lesions.<sup>20</sup> However, in general, the use of a temperature probe seems to be a potential way to  
14 reduce the risk of oesophageal overheating and cooling and therefore a potential strategy to  
15 prevent oesophageal injuries. In the POTTER-AF study, an oesophageal temperature probe was  
16 utilized in 24.6% of POTTER-AF patients, and the mean maximal measured temperature was  
17  $40.2 \pm 2.2^\circ\text{C}$ .

#### 18 19 Clinical presentation and diagnostics

20 Although the pathophysiology of OF development is not completely understood, there is  
21 agreement that ablation energy from any source delivered to the posterior LA wall leads to  
22 thermal damage to the oesophagus. Since lesion formation requires time to progress, the first

1 symptoms typically occur within 60 days after the procedure.<sup>21</sup> The symptoms are diverse and  
2 not specific, consisting primarily of fever and neurological abnormalities, sometimes mimicking a  
3 cerebral vascular accident.<sup>22</sup> The findings of POTTER-AF are in line with these observations since  
4 most patients reported fever (59.3%), chest pain/odynophagia (54.2%) and neurological signs  
5 (44.1%). With a median of 18 (7.75, 25) days (range 0-60) the observed time to symptoms was  
6 shorter than previously reported. Additionally, the time to diagnosis (median 21 (15, 29.5) days,  
7 range: 2-63 days) and time from first symptom onset to OF diagnosis (3 (1, 9) days (range: 0-42  
8 days)) were relatively short but showed a relatively wide range. This observation might reflect the  
9 possibility that some patients presented at hospitals where they had not received the catheter  
10 ablation procedure which might lead to a longer time to diagnosis compared to the patients who  
11 presented at experienced electrophysiological centers who are potentially more aware of OF. In  
12 order to plan rapid treatment of OF, it is essential to detect this complication early. In more than  
13 80% of patients, a chest CT was the most common diagnostic method, which has been previously  
14 recommended by other authors. In the CT scan, signs such as oesophageal opacification and air  
15 detected inside the left atrium are highly suggested to be associated with OF. It is important to  
16 state that endoscopy is discouraged that air should not be injected into the oesophagus due to  
17 the potential development of air embolism.

### 18 19 Treatment strategies and outcome

20 Since most patients reported fever and developed sepsis and/or septic shock, all patients were  
21 treated with antibiotics. The overall mortality was 65.8%, with significantly reduced mortality in  
22 patients undergoing surgical repair (51.9%) compared with endoscopic treatment only (56.5%)

1 and conservative management (89.5%), (OR 7.463 (2.414, 23.072)  $p < 0.001$ , compared with  
2 conservative treatment).

3 Although these observed improvements in mortality are highly significant, the reason for the  
4 different treatment strategies shows a selection bias, since patients who were not able to  
5 undergo any oesophageal surgery or endoscopic treatment and received conservative treatment  
6 due to critical illness had the worst outcome. In fact, the time to the earliest onset of symptoms  
7 and the time to OF diagnosis were the shortest in patients who received endoscopic treatment  
8 only followed by oesophageal surgery and conservative treatment. Patients with an early OF  
9 detection received an early treatment via endoscopy or oesophageal surgery with a lower  
10 mortality while patients with late detection more often received a conservative treatment with a  
11 higher mortality. This observation again underlines the importance of early diagnosis, detection  
12 and treatment of OF. The findings of the multivariable binary logistic regression analysis detected  
13 an intervention of OF patients via an oesophageal surgery as a factor that was associated with a  
14 lower mortality. Coronary artery disease, coma, and cardiac arrest were identified as the factors  
15 associated with a higher mortality. The use of an oesophageal thermal probe and the use of  
16 conscious sedation were also associated with better survival.

17 These observations are in line with a large meta-analysis conducted in 2017 with 120 reported OF  
18 cases from a total of 85 studies. The overall mortality was reported to be 55%, with significantly  
19 reduced mortality in patients undergoing surgical repair (33%) compared to endoscopic  
20 treatment (65%) and conservative management (97%).<sup>21</sup>

21

22

## 1 Limitations

2 The POTTER-AF study has several limitations. First, the findings were based on a retrospective  
3 analysis. Nevertheless, the data were obtained from a large number of centers across the globe  
4 represent the largest database on OF up to date. Second, since only data from patients with  
5 periprocedural OF were collected, we were unable to assess predictors of its occurrence. Third,  
6 not all data were available and some patients were lost to follow-up. Fourth, because OF typically  
7 occurs relatively late after the procedure, the incidence may be underreported, and the true  
8 incidence remain unknown. Fifth, there were no data on how the temperature measured by the  
9 esophageal temperature probe was utilized in these patients, and no cut-off values were  
10 available. Sixth, no accurate data were available reporting on the specific ablation design for the  
11 participating centers. Seventh, no subgroup analysis on the incidence of the use of contact force  
12 catheters, ablation index and lesion size index was available. Eighth, the absence of data from a  
13 significant proportion of invited centers strongly limits the applicability of the present results to  
14 a general population and may result in underestimation of the true incidence of OF. Finally, our  
15 findings concerning different treatment strategies and outcomes show the above mentioned  
16 selection bias concerning critical illness and operability of the patients.

17

## 18 **Conclusions**

19 In this large worldwide registry, the incidence of OF was very low, in general the incidence was  
20 lower for cryoballoon- compared to radiofrequency-based procedures. The observed time to  
21 symptoms was shorter than previously reported. Additionally, the time to diagnosis and the time  
22 from first symptom onset to OF diagnosis were relatively short but showed a relatively wide



1 range. The overall prognosis was poor. Surgical or endoscopic intervention is mandatory for  
2 improving patient survival.

3

#### 4 **Acknowledgements**

5 We thank all the local investigators and assistant personnel for their great effort. Furthermore,  
6 we thank all the POTTER-AF collaborators listed in the Supplemental Table 2.

ACCEPTED MANUSCRIPT

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## 9 **Appendices**

10 Table 1: Baseline characteristics

11 Table 2: Procedural data

12 Table 3: Multivariable binary logistic regression

13

14

15

1 **Figure legends**

2 Graphical abstract:

3 Summary of the POTTER-AF study results. CI, confidence interval; OR, odds ratio.

4 Figure 1:

5 Flowchart of the POTTER-AF study

6 AF = atrial fibrillation, OF = oesophageal fistula, CT = computed tomography

7 Figure 2:

8 A: Endoscopic view of the oesophagus in a patient with an atrio-oesophageal fistula

9 B: Intraoperative situ during oesophageal surgery in a patient with an atrio-oesophageal fistula

10 Figure 3:

11 A: Time to first symptoms and time to diagnosis. Overview of the clinical presentation (B), utilized  
12 diagnostic modalities (C) and complications (D) of all patients with oesophageal fistula (n=118).

13 Multiple symptoms were possible.

14 Figure 4:

15 A: Overview of the different treatment strategies and outcome of patients

16 B: Outcome of all patients with oesophageal fistula

17

18

1 Table 1: Baseline characteristics

Characteristics	All patients	Survivors	Non-survivors	p-value
Number of patients	118	40	77	
Age, years	62.0 ± 11.4	58.8 ± 12.4	64 ± 10.5	<b>0.045</b>
Female sex	55 (47)	20/40 (50)	35/76 (46.1)	0.700
Body mass index, kg/m <sup>2</sup>	26.4 (23.6, 28.9)	26.6 (24.6, 29.1)	26.1 (23.1, 28.8)	0.772
Paroxysmal AF	49 (42)	19/40 (47.5)	30/77 (39)	0.432
Persistent AF	61 (52)	19/40 (47.5)	41/77 (53.2)	0.566
Long standing persistent AF	8 (7)	2/40 (5)	6/77 (7.8)	0.714
Structural heart disease	36 (31)	8/40 (20)	28/76 (36.8)	0.090
Coronary artery disease	20/112 (18)	2/38 (5.3)	18/73 (24.7)	<b>0.017</b>
Congestive heart failure	20/115 (17)	3/39 (7.7)	17/76 (22.4)	0.068
LA surface, cm <sup>2</sup>	25.5 ± 15.4	25.32 ± 8.3	34.5 ± 20.2	0.0830
LA volume, ml	132.6 ± 57.9	199 ± 31.5	125.2 ± 29.6	<b>0.0041</b>
LVEF, %	60 (50, 65)	60 (55, 65)	60 (50, 60)	<b>0.038</b>
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	2.1 ± 1.4	1.9 ± 1.3	2.3 ± 1.4	0.192
Arterial hypertension	70/117 (60)	23/40 (57.5)	47/76 (61.8)	0.692
Type II diabetes mellitus	17 (14)	5/40 (12.5)	12/76 (15.8)	0.785
Chronic kidney disease	10/91 (11)	1/29 (3.4)	9/61 (14.8)	0.158
History of oesogastric pathology	9/109 (8)	1/38 (2.6)	8/70 (11.4)	0.156
Preprocedural PPI therapy	25/110 (23)	6/38 (15.8)	19/71 (26.8)	0.237
OF after 1 <sup>st</sup> ablation procedure	105 (89)	37/40 (92.5)	67/77(87)	0.538
OF after >1 <sup>st</sup> ablation procedure	13 (11)	3/40 (7.5)	10/77 (13)	0.538

2

1 Values are counts, n (%), mean  $\pm$  SD or median (first quartile, third quartile). AF= atrial fibrillation,  
 2 LA = left atrium, LVEF = left ventricular ejection fraction, TIA = transitory ischemic attack, PPI =  
 3 proton pump inhibitors, OF = Oesophageal fistula

4 Table 2: Procedural data

5

Characteristics	All patients	Survivors	Non-survivors	p-value
Usage of general anesthesia	56 (47.5)	18/40 (45)	38/77 (49.4)	0.700
Usage of deep analgesedation	35 (29.7)	12/40 (30)	23/77 (29.9)	1.000
Procedure time, min	147 (108, 180)	135.5 (108.5, 177.5)	150 (110.3, 191.3)	0.124
RF energy	114 (96.6)	39/40 (97.5)	74/77 (96.1)	1.000
RF duration, min	38.5 (23.8, 52.6)	31 (22.5, 51)	43.5 (27, 53.9)	0.217
RF contact force catheter	52/113 (46.0)	17/39 (43.6)	35/73 (47.9)	0.695
RF power on LA posterior wall, Watts	30 (25, 30)	30 (25, 35)	30 (25, 30)	0.404
Circumferential PVI	102/109 (93.6)	33/36 (91.7)	68/72 (94.4)	0.684
Segmental ostial	2/109 (1.8)	0/36 (0)	2/72 (2.8)	0.551
Anatomical ostial	6/109 (5.5)	4/36 (11.1)	2/72 (2.8)	0.094
Additional LA line ablation	50/110 (45.5%)	20/37 (54.1)	30/72 (41.6)	0.231
Roof line	34/110 (30.9)	10/37 (27)	24/72 (33.3)	0.663
Posterior line	27/110 (24.5)	10/37 (27)	17/72 (23.6)	0.815
Anterior lines	8/110 (7.3)	0/37 (0)	8/72 (11.1)	<b>0.049</b>
Inferior Lines	2/110 (1.8)	1/37 (2.7)	1/72 (1.4)	1.000
Mitral isthmus line	4/110 (3.6)	1/37 (2.7)	3/72 (4.2)	1.000
CFAE ablation at the LA posterior wall	12/79 (15.2)	2/25 (8)	10/53 (18.9)	0.319
Cryoballoon	3 (2.5)	0/40 (0)	3/77 (3.9)	0.550
1 <sup>st</sup> generation cryoballoon	1/3 (33.3)	0	1/3 (33.3)	



2 <sup>nd</sup> generation cryoballoon	2/3 (66.6)	0	2/3 (66.6)	
Range minimal temperature, C°	-69 - -47		-69 - -47	
Laserballoon	1 (0.8)	1/40 (2.5)	0/77 (0)	0.342
Maximal laser energy, Watts	10	10		
Usage of oesophageal temperature probe	29 (24.6)	14/40 (35)	15/77 (19.5)	0.075
Maximal temperature, C°	40.2 ± 2.2	39.9 ± 2.6	40.7 ± 1.6	0.481
Post procedure prescription of PPI	85/114 (74.6)	29/39 (74.4)	56/75 (74.7)	1.000

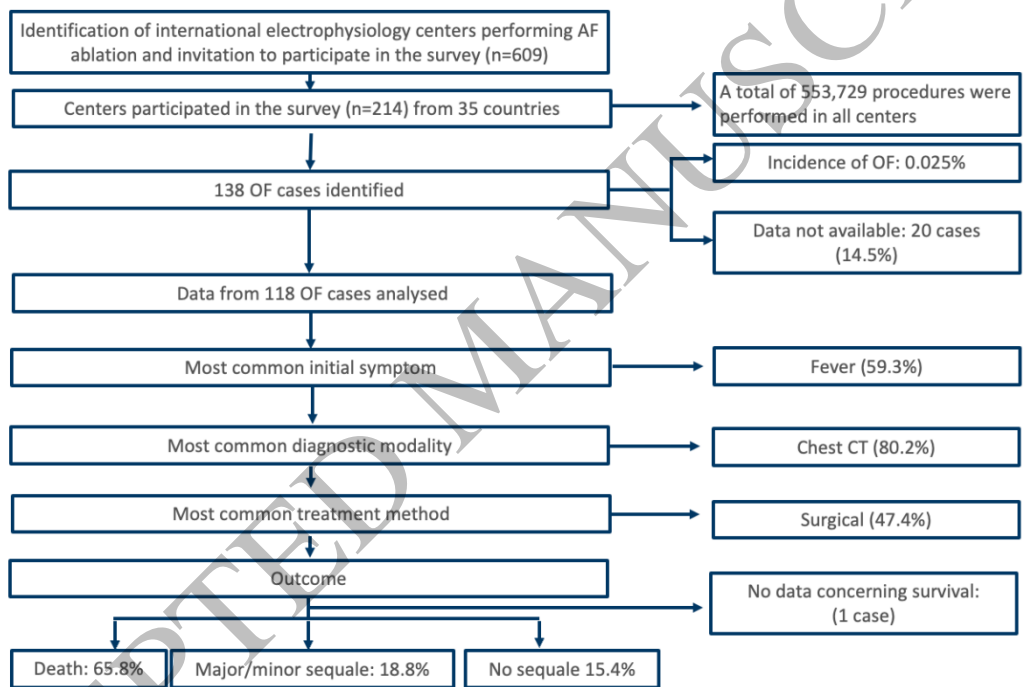
1  
2 Values are counts, n (%), mean ± SD or median (first quartile, third quartile). RF = radiofrequency,  
3 LA = left atrium, PVI = pulmonary vein isolation, CFAE = complex fractionated atrial electrograms,  
4 PPI = proton pump inhibitors.

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6 Table 3. Multivariable binary logistic regression

Characteristics	OR	95% CI	p-value
Age (years)	1.039	0.995, 1.084	0.081
LVEF (%)	0.992	0.942, 1.044	0.748
Coronary artery disease	3.096	0.555, 17.259	0.197
Congestive heart failure	2.625	0.555, 12.411	0.223
Conscious sedation	0.229	0.060, 0.865	<b>0.030</b>
Use of thermal probe	0.231	0.074, 0.724	<b>0.012</b>
Diagnostic: CT	0.371	0.093, 1.481	0.160
Oesophageal surgery	0.329	0.123, 0.881	<b>0.027</b>

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1 The continuous variables have the unit of measurement in brackets. All other variables are  
 2 categorical variables. CI = confidence interval, OR = odds ratio, LVEF = left ventricular ejection  
 3 fraction, CT = computed tomography.



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 Figure 1  
 160x90 mm (x DPI)

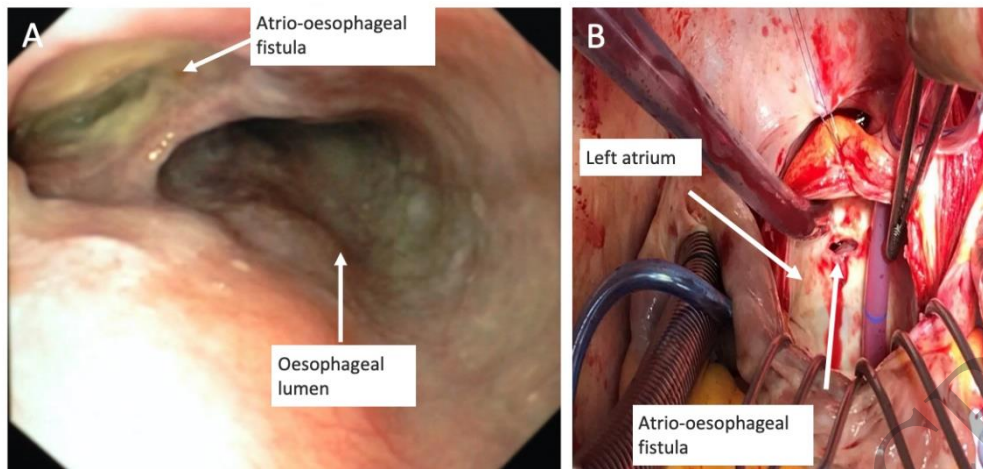


Figure 2  
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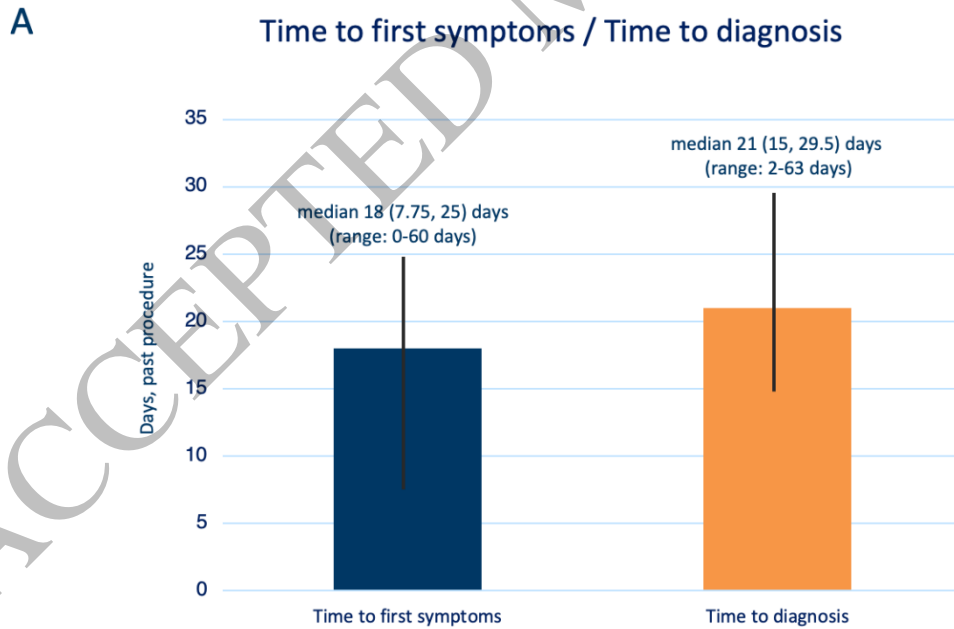
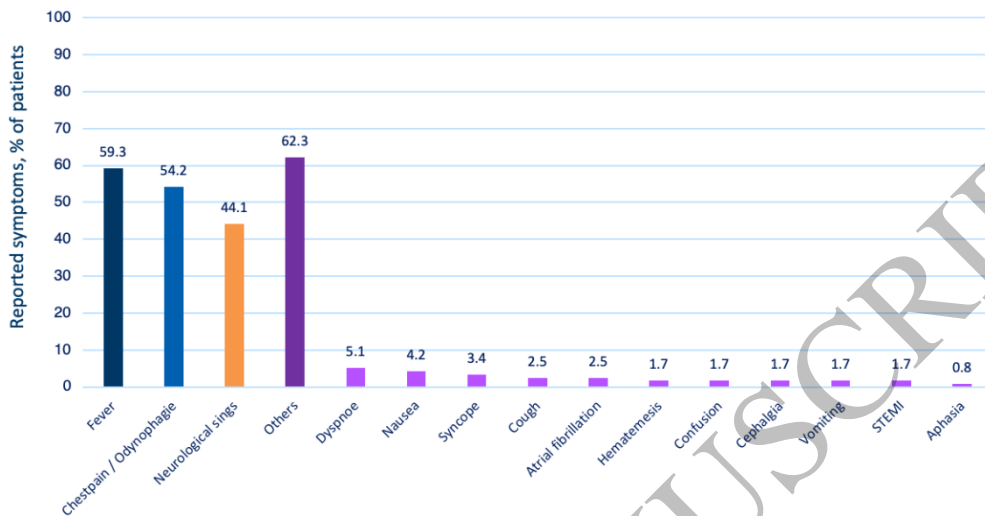


Figure 3A  
160x90 mm (x DPI)

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B

### Clinical presentation

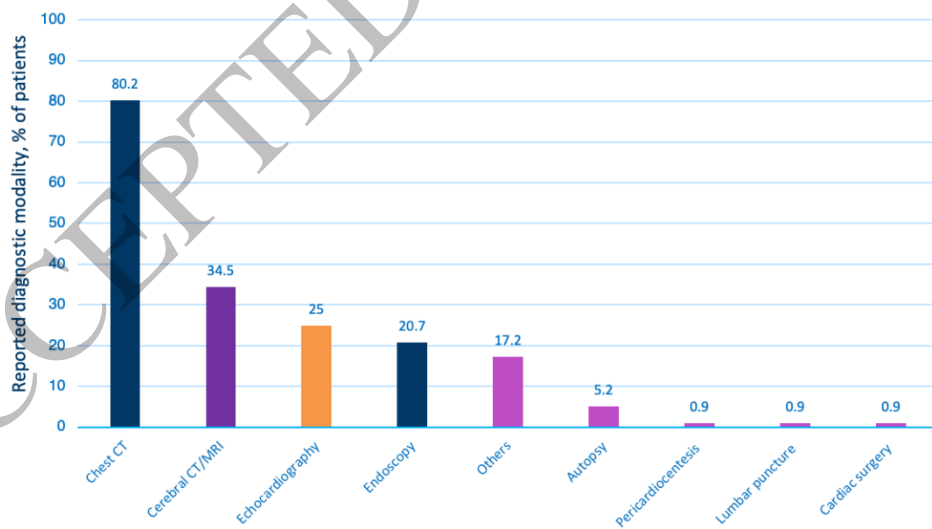


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Figure 3B  
160x90 mm (x DPI)

C

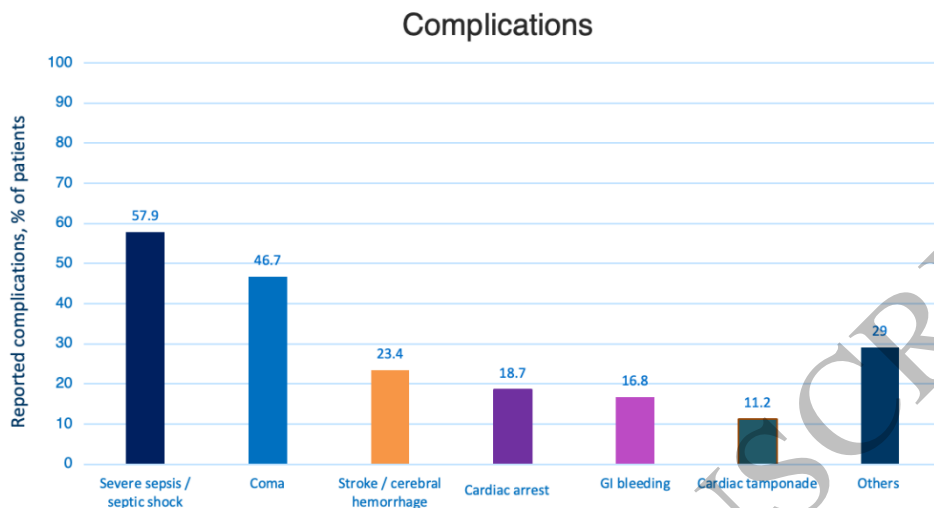
### Diagnostic modality



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Figure 3C  
160x90 mm (x DPI)

D

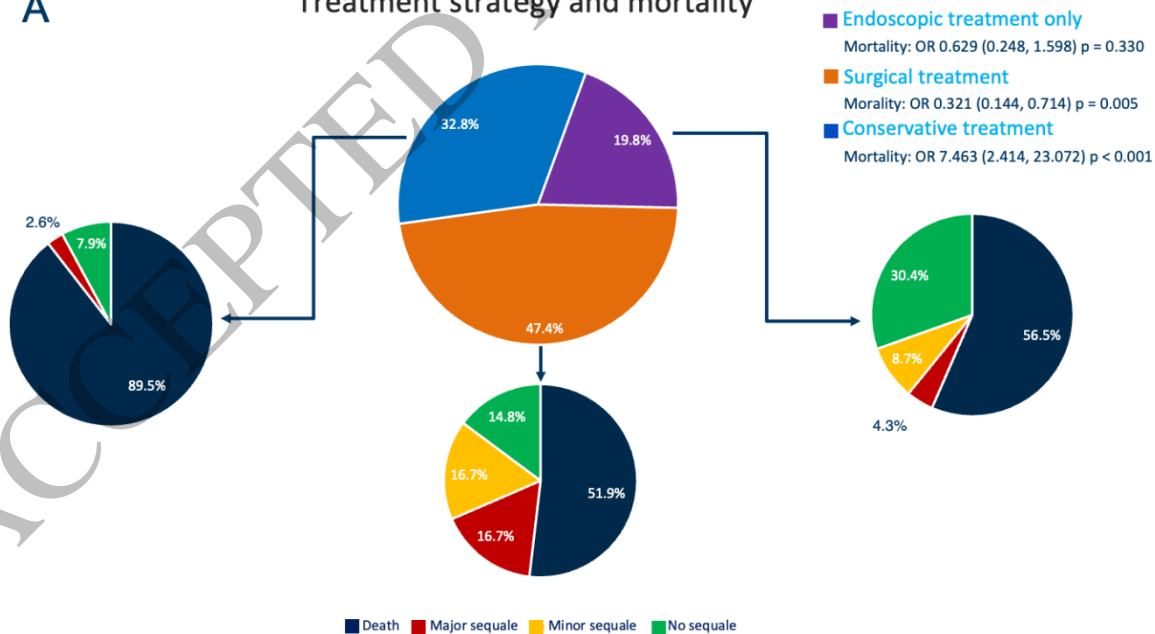


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Figure 3D  
160x90 mm (x DPI)

A

### Treatment strategy and mortality



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Figure 4A  
160x90 mm (x DPI)

B

Outcome, all patients

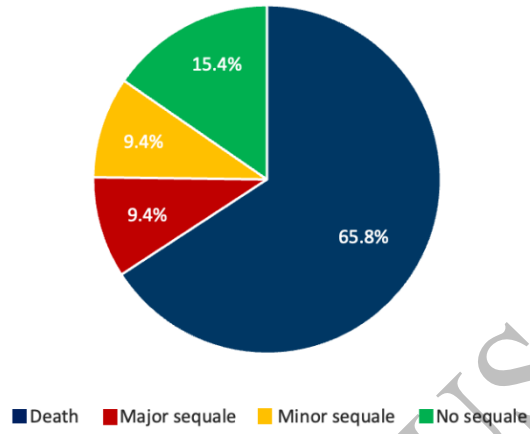


Figure 4B  
160x90 mm (x DPI)

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### Key question

Oesophageal fistula represents a rare but dreadful complication of atrial fibrillation catheter ablation. The POTTER-AF study aimed to investigate the characteristics of oesophageal fistulae after treatment of atrial fibrillation by catheter ablation in a large multinational registry.

### Key finding

Oesophageal fistula after catheter ablation of atrial fibrillation is rare (incidence: 0.025%) and occurs mostly with the use of radiofrequency energy (0.038%) rather than cryoenergy (0.0015%,  $p < 0.0001$ ). The mortality without surgical or endoscopic intervention is exceedingly high (89.5%).

### Take-home message

The overall mortality of oesophageal fistula after catheter ablation for atrial fibrillation treatment was 65.8%. The mortality following surgical (51.9%) or endoscopic treatment (56.5%) was significantly lower as compared with conservative management (89.5%), ( $p < 0.001$ ).

## Prognosis following oesophageal fistula formation in patients undergoing catheter ablation for AF – The POTTER AF Study

**553,729** procedures performed in **214** centers from **35** countries

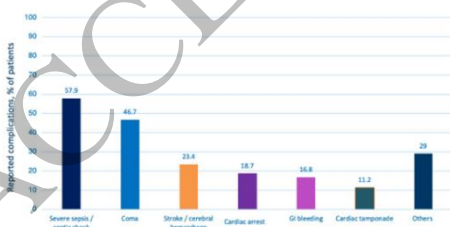


**138 oesophageal fistulae**

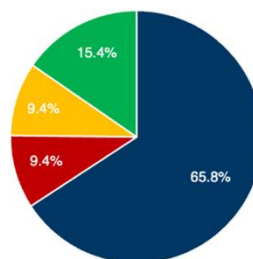
Total Incidence: **0.025%**  
 Radiofrequency: **0.038%**  
 Cryoballoon: **0.0015%** }  $p < 0.001$



### Complications



### Outcome



### Factors associated with survival

Use of an oesophageal temperature probe:  
 OR: 0.231 (95% CI: 0.074, 0.724),  $p = 0.012$

Treatment by oesophageal surgery:  
 OR: 0.329 (95% CI: 0.123, 0.881),  $p = 0.027$

Type of anesthesia: conscious sedation:  
 OR: 0.229 (95% CI: 0.060, 0.865),  $p = 0.030$

■ Death ■ Major sequelae ■ Minor sequelae ■ No sequelae

Structured Graphical Abstract  
 160x199 mm (x DPI)

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