Details of the ENCOR Unipolar Atrial 'J' Leads

INTRODUCTION

On September 11, 1995, Telectronics Pacing Systems issued a letter regarding the voluntary withdrawal from the market of all atrial passive fixation leads containing a J wire, including the ENCOR Unipolar J Passive Fixation Models. These leads were withdrawn due to five reports of protrusion in the bipolar models ENCOR 330-854 and ENCOR DEC 033-856. While no ENCOR Unipolar clinical complaints of J wire protrusion or injury existed at the time of market withdrawal, an independent Physician Advisory Committee recommended a multi-center study (MCS) to estimate the prevalence of J wire protrusion in these leads using fluoroscopic screening. The MCS began September 1996 and ended January 1999. This report will provide a summary of the worldwide information presented to the PAC at the November 2004 meeting and the summary of the multi-center study.

ENCOR UNIPOLAR SUMMARY PRESENTED AT NOVEMBER 2004 PAC MEETING

Based on distribution records combined with patient registration records, it is estimated that 32,000 leads were implanted worldwide between 1981 and 1995 with less than 3,000 estimated patients currently alive with an ENCOR Unipolar J lead. Of the 13 model numbers distributed, only 2 of the models (ENCOR Unipolar Model 330-755 and ENCOR DEC Model 033-757) were distributed after 1992.

To date, Accufix Research Institute has received one report of a severed ENCOR Unipolar lead, a situation that could allow the J wire to migrate out of the lead but no reports of patient injury. The design differences between Accufix Bipolar leads, ENCOR Bipolar leads and ENCOR Unipolar leads may account for the differences in observed protrusion rates. The Accufix Bipolar lead has an estimated protrusion risk of 1.3% per year compared to ENCOR Bipolar protrusion risk of 0.2% per year, and the 0% estimated protrusion rate in the ENCOR Unipolar leads.

The J wire in the Accufix lead is located outside the outer conductor coil and just inside the outer polyurethane insulation. This designs contrasts the ENCOR Bipolar and ENCOR Unipolar leads where the J wire is contained within at least a single conductor coil for the entire length. All protrusions in the ENCOR Bipolar lead have occurred in the inter-electrode regions, which may be subjected to increased stresses due to motion and kinking.

As with other J wire models, suspected and actual ENCOR Unipolar fractures exist but in contrast to other models, no actual protrusions or injuries have been identified in multi-center studies or from reports to the worldwide registry. Fractures are clinically relevant where concern for injury exists. With the absence of identified protrusions, especially in an elderly patient population with long lead implant durations and an almost certainly greater extraction risk than leaving the lead in situ, fluoroscopic screenings to identify fractures is of doubtful clinical benefit. Based on the extremely low possibility of injury, the PAC still does not recommend fluoroscopic screening or extraction for ENCOR Unipolar leads.

ENCOR UNIPOLAR MULTI-CENTER STUDY (MCS) FINAL SUMMARY

The primary objective of the ENCOR Unipolar multi-center study, which began in 1996 and ended in 1999, was to estimate the prevalence of J wire protrusion. Secondary objectives were: (1) To estimate the prevalence of J wire fractures (2) To estimate the prevalence of kinks (3) To estimate the prevalence of severed leads (4) To determine the relationship of protrusion to variables such as shape of the lead at screening, location of lead tip in the atrium, implant duration and patient variables.

A sample size of 600 leads with a J wire classification was established. If no protrusions were observed out of 600 leads, this sample size would provide 95% confidence that the true protrusion prevalence was less than 0.5%.

The Telectronics Pacing System USA Implant Patient Registration database and the Rest of World distribution database was reviewed to identify centers with more than 100 implants or 100 leads distributed to a center. All

29 centers meeting the above criteria and an additional six centers were contacted to examine their interest in study participation as well as their ability to meet study requirements. Eight centers (six centers out of 29 centers with more than 100 leads and 2 centers out of the additional centers with less than 100 implants) indicated a willingness to participate and agreed to locate patients and gather the information required by the protocol. MCS study sites were located in the United States (n= 3), Europe (n=3) and Canada (n=2).

The multi-center study obtained data on 1423 patients in whom 1429 leads were implanted or fluoroscopically screened on or before April 30, 1998 at one of the eight study centers. The location and status of all implanted patients was investigated and available patients were asked to undergo cinefluoroscopic visualization of the lead containing the J wire.

The occurrence of injuries related to the J wire in the MCS patients before the initiation of the study was determined by review of medical records. In "Dear Doctor Letters", Accufix Research Institute requested any identified or presumed injury due to the J wire be reported to ARI as well as lead extraction data.

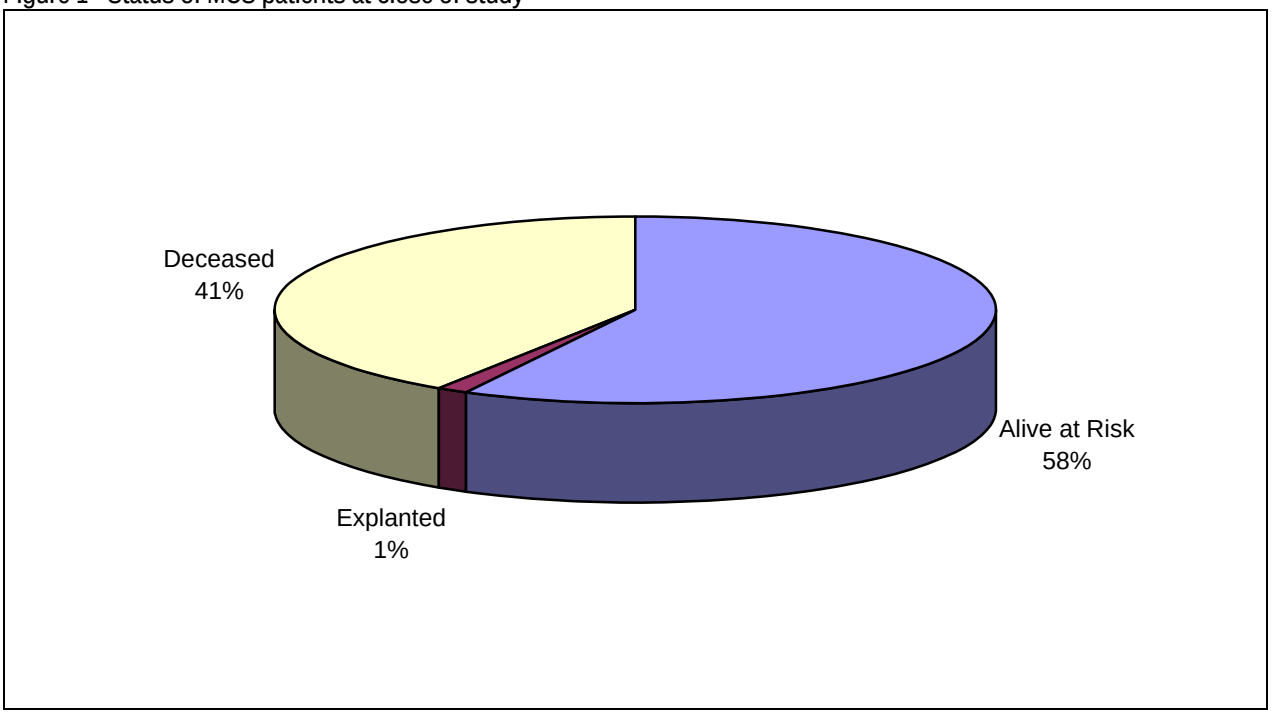
Lead extraction data was collected and extraction complication data was categorized as None, Fatal, Life-threatening, Other Major, Minor. Life-threatening complications were clinical events that require intensive care, result in cardiac arrest or require emergent surgical intervention. Other major complications were defined as clinical events that require surgical intervention, subsequent infection or a high degree of medical intervention.

The Social Security Death Index was utilized to investigate a deceased status for United States MCS patients whose last contact date was greater than one year earlier and who were not located by the primary investigator.

Patient and Lead Survival

In the MCS, there are 1429 ENCOR Unipolar J leads implanted in 1423 patients (55% male) with an observed cumulative implant duration of 6211 years of follow-up, i.e. from date of implant to date of death, lead extraction or last reported follow-up. The implants occurred between January 1982 and September 1995, with 62% occurring prior to 1990. The median patient implant age was 74 years (range 10-103).

Figure 1 - Status of MCS patients at close of study



Patients were considered at risk until reported deceased or explanted. Eight hundred twenty six (826) patients (51% male) were considered at risk as of February 2000. Figure 1 describes the patient and lead status of the MCS population. As of February 2000, the median age for the at risk MCS population was 83 years of age (range 24-109 years) The age distribution for the MCS at risk population is described in Table 1.

Table 1 - MCS Alive At Risk Patient Age Distribution at close of study

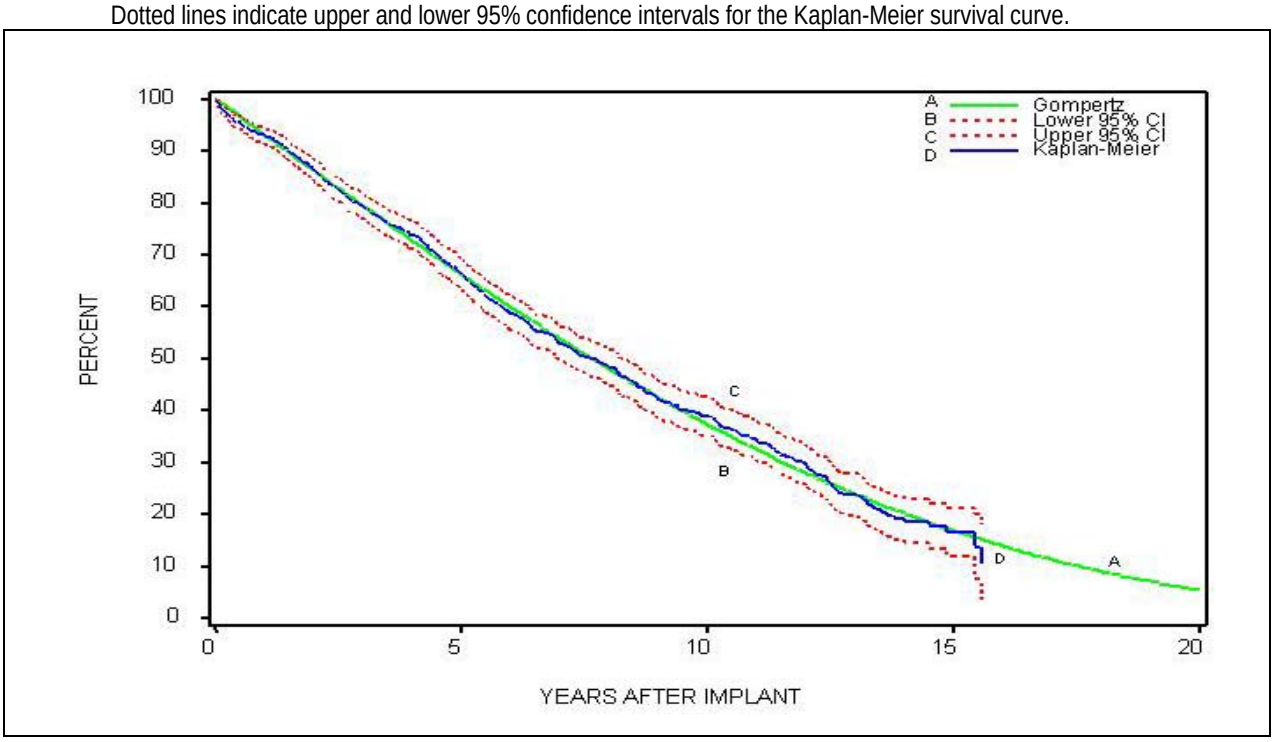
Age (years)	Number	Percent
21-30	3	0.4%
31-40	7	1.0%
41-50	8	1.1%
51-60	28	3.9%
61-70	80	11.1%
71-80	199	27.5%
81-90	243	33.6%
>90	155	21.4%

Age missing in 103 patients

Figure 2 shows survival estimates based on the MCS study leads using both Kaplan-Meier and Gompertz methods. This plot shows good agreement between the non-parametric Kaplan-Meier estimates and the parametric Gompertz estimates, allowing the Gompertz estimates to be used to predict the number of worldwide ENCOR Unipolar leads that would be implanted in living patients at the beginning of each calendar year (Figure 3). Based on the Kaplan-Meier curve, the observed probability of patient survival was 66.5% at 5 years post implant (95% CI: 63.4%-69.3%), 38.9% at 10 years post implant (95% CI: 35.3%-42.6%) and 16.6% (95% CI: 11.9%-21.2%) at 15 years post implant.

Figure 2 –Survival in ENCOR Unipolar MCS patients

A plot overlying the Kaplan-Meier and Gompertz estimates of survival shows good agreement between the non-parametric Kaplan-Meier estimates and the parametric Gompertz estimates. The observed probability of patient survival was 66.5% at 5 years after implant, 38.9% at 10 years after implant and 16.6% at 15 years after implant. Dotted lines indicate upper and lower 95% confidence intervals for the Kaplan-Meier survival curve.



Risk of ENCOR unipolar 'J' wire fracture and Protrusion (MCS)

The J wire fracture classification was determined by combined cinefluoroscopic examination, visual analysis post explant and analysis of returned leads. J wire classification data were available for 378 leads with a median time to fracture identification of 59 months post implant (range 17-178 months). The J wire classification of these 378 leads is displayed in Table 2. The median implant duration for these 378 leads is 5.9 years range 1.5-17.4 years (time from implant to last J wire classification).

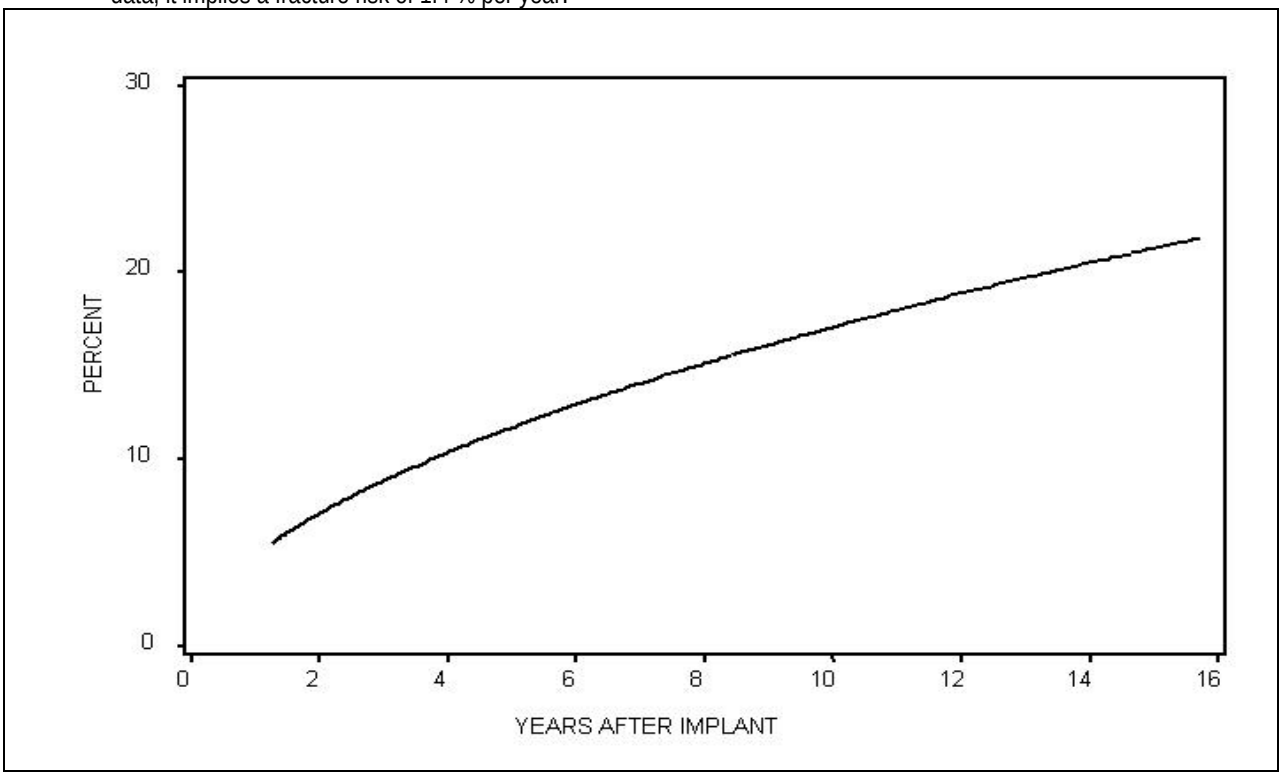
Due to the nature of the mechanism of J wire failure i.e. stress fatigue; it is important to examine a time-based risk of fracture. The cumulative risk of fracture at 5 years after implant is 12% and appears to be constant over time based on a Weibull shape parameter (1.84) which is not significantly greater than one (p=0.1). If a constant risk is applied to the data, it implies a fracture risk of 1.4 % per year.

Table 2 - ENCOR Unipolar 'J' wire classification

J Wire Classification	***Number***	***Percent (95% Confidence Interval)***
Class A: Fracture of the J wire not suspected,	333	88% (84%-91%)
Class B: Fracture of J wire suspected but not visualized e.g. marked kink, or Class C: Fracture of the J wire visualized without protrusion,	45	12% (9%-16%)
Class D: J wire protrudes from the lead,	0	0% (0%-0.79%)
Class E: Fragment of the J wire has migrated away from the lead	0	0% (0%-0.79%)
Total	378	

Figure 4 - Cumulative Risk of Fracture for MCS ENCOR Unipolar 'J' leads

The cumulative risk of fracture at 5 years after implant is 12% and appears to be constant over time based on a Weibull shape parameter (1.84) which is not significantly greater than one (p=0.1). If a constant risk is applied to the data, it implies a fracture risk of 1.4 % per year.



Closure of ENCOR Unipolar MCS

The ENCOR Unipolar multi-center study primary investigators encountered considerable difficulty in locating patients and obtaining fluoroscopic screenings due to the elderly patient population and the length of time since the implant of the lead. Extensive efforts were made to locate patients and determine patient status by the study sites and by using the social security death index. After a review of the data, the independent Physician Advisory Committee concluded that the protocol objective of 600 fluoroscopically screened leads could not be met with the existing population and the study goals were met to the extent possible. Further center recruitment was not a viable option since all centers with implant numbers greater than 100 implants were previously determined to be uninterested or unable to participate. The sample size of 600 fluoroscopically screened leads was originally established to demonstrate that if 0 protrusions out of 600 leads were found to be protruded in the MCS sample, then with 95% confidence the true protrusion prevalence in the population will be less than 0.5%. With J wire classification on 378 leads and no protrusions, there is 95% confidence the true protrusion prevalence in the population is less than 0.8%.