# Details of the ENCOR Bipolar Atrial 'J' Leads

## INTRODUCTION

The ENCOR Bipolar J leads (models 033-856, 327-747, 327-754, 329-749, 329-754, 330-848, 330-854) were recalled on September 11, 1995 after 5 reports of protruding J wires (1 pericardial effusion, 1 cardiac tamponade, 2 chest pain, and 1 asymptomatic).

A prospective Multi-Center Study (MCS) began immediately, as recommended by an independent Physician Advisory Committee. The initial objective of the Phase I study was to estimate whether the prevalence of J wire protrusion was less than 0.5% based on a one-time fluoroscopic evaluation of the lead. An analysis of 523 patients was presented to the PAC on November 12, 1995. At that time, the point estimate for protrusion was 0.4% (95% confidence interval (0.05-1.4%). Based on the recommendation of the Physician Advisory Committee, Phase I of the ENCOR Bipolar J lead study was closed and Phase II was designed to continue exploration of an effective management approach through serial fluoroscopic screening with collection of potential predictor variables of protrusion and explant data. The Phase II study objectives were identified as follows: (1) To estimate the rate of J wire protrusion (2) To estimate the rate of injury (3) To estimate the rate of extraction complications (4) To determine the relationship of extraction complications to factors such as inter-electrode contour, fracture classification, implant duration and patient variables (5) To determine the relationship of J wire failure to factors such as lead variables, lead dynamics and patient variables.

In November 1999, the PAC reviewed the Phase II MCS data and elected to close the MCS and transition to an Injury Surveillance Program. This decision was based on the low observed risk of protrusion, the even lower risk of injury, and recognition that the achievable goals of the MCS were met.

The Injury Surveillance Program (ISP), initiated January 2000, monitors worldwide protrusion and injury reports to identify any potential increase in risk.

The following is a summary of the protrusion and injury data reviewed at the November 7, 2004 Physician Advisory Committee (PAC) meeting and the detail MCS data as of the close of the study in 1999.

Based on distribution records combined with patient registration records, it is estimated that 24,000 ENCOR Bipolar J leads were implanted worldwide between 1983 and 1995 with 6,200 estimated patients currently alive with an ENCOR Bipolar J lead.

## SUMMARY OF DATA REVIEWED AT THE NOVEMBER 2004 PAC MEETING

### Protrusions and Injuries associated with the ENCOR Bipolar J wire

As of November 2004, 54 protrusions have been reported worldwide with a protrusion risk of 0.2% per year. Only 6 protrusions have been reported since the last Dear Doctor letter in 2000.

Only 5 directly related J wire injuries have been reported representing 9.3% of the reported protrusions and 0.02% of the estimated 24,000 implants. The median time to injury is 14 months (range 5 to 29 months). Of the 4,908 deaths from all causes that have been reported to ARI, only one of the deaths was directly attributable to the J wire (0.02%). The risk of injury due to the ENCOR Bipolar lead is very low (0.02% per year) with no evidence of increasing risk. No new J wire injuries have been reported since 1996. The injury risk is higher in younger patients as injured patients were implanted at a younger age than patients with no reported injury ($p<0.01$). The median age at implant for injured patients = 54 years versus median age at implant for non-injured patients = 74 years.

Three out of five directly related injuries occurred prior to initiation of fluoroscopic screening. Of the 2 injuries occurring after fluoroscopic screening, one injury occurred 21 days after an interpretation of a severed inter-electrode contour and one injury occurred 5 months after fluoroscopic detection of

protrusion.

The very limited number of injuries makes it difficult to identify an optimal screening interval from an assessment of the existing injury data. The low protrusion and injury risk can support a longer screening interval than originally proposed. For these reasons, the general recommendation is for an annual screening interval. Shorter and or longer screening intervals should be based on individual patient factors including: (1) Patient informed decision regarding the risks (2) Risk of Fracture – Based on multivariate analyses, patients with closed J Shape, less than 10 degrees of inter-electrode motion and implant age greater than 50 are at lower risk of fracture (3) Risk of Injury- older patients are at lower risk of injury than younger patients ($p<0.01$) (4) Suitability of patient as an extraction candidate -The option of no further fluoroscopic screenings should be considered in patients who are not potential candidates for extraction.

The future probability of J wire injury during a patient's remaining lifetime was estimated using the same methodology described in the Accufix section, using the overall J wire injury rates combined with the Gompertz survival curve to derive a cumulative incidence curve. With only 5 worldwide reported injuries, it is not reasonable to generate age and gender specific cumulative incidence curves although we do know the probability of an injury anytime after implant is lower for patients who are older at implant for two reasons: older patients have an intrinsically lower risk of injury and older patients have a lower expected lifetime in which to experience the risk than younger patients.

The cumulative incidence curves describe a patient's probability of injury over time from implant (Figure 1). This curve will level out when there is almost zero chance that the patient is still alive (although the intrinsic risk of injury is still continuing at an assumed constant rate). The value of the cumulative incidence curve at that plateau point is the probability the patient will ever experience injury before dying.

The risk of interest to an ENCOR Bipolar patient, who is now at least 9 years post-implant, is the cumulative risk during his or her remaining expected lifetime. Figure 2 shows the remaining probability of J-wire injury as a function of time post-implant. Beginning at time zero, the risk of injury at implant is equal to the height of the plateau from the cumulative incidence. But that risk decreases over time, as the risk of death from other causes depletes the population at risk, and finally reaches zero "expected remaining risk" by the time all patients are expected to be deceased.

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.

Figure 1 - Cumulative Incidence of ENCOR Bipolar 'J' Wire Injury

Based on 5 directly related injuries. The cumulative risk of injury taking into account the probability of patient survival is displayed by years post implant. The MCS Gompertz survival curve and the worldwide injury rate are used to calculate the cumulative incidence of J wire injury.

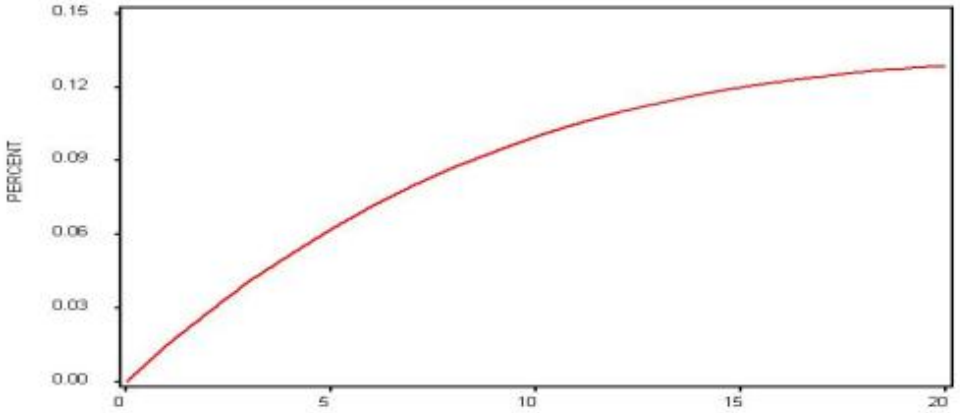
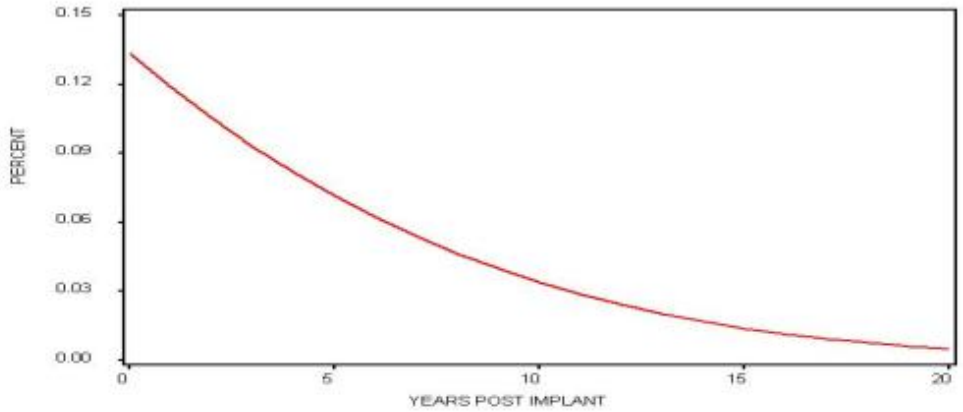



Figure 2 - Probability of Future ENCOR Bipolar 'J' wire Injury

The probability of J wire injury depends upon the cumulative incidence of J wire injury and decreases over time, as the risk of death from other causes deplete the population at risk.



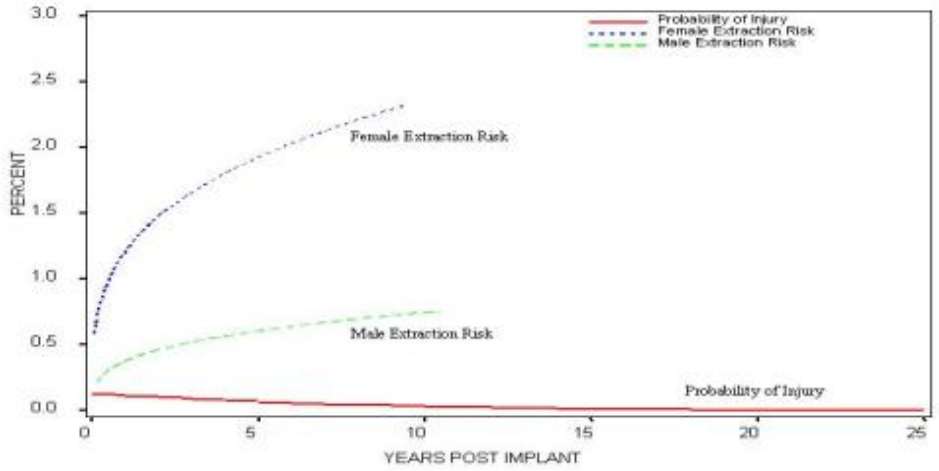
The cumulative risk of Fatal/Life-threatening extraction complication is determined by fitting a logistic regression model to the ACCUFIX post-recall intravascular extraction data, using the extraction complication risk factors of gender and the logarithm of time post implant. The cumulative risk of Fatal/Life-threatening extraction complication can then be compared to the probability of future J wire injury curve to determine when the risks are equal (Figure 3). The reported extraction attempts with known outcome for the ENCOR Bipolar extraction data is limited, especially when compared to the ACCUFIX experience with over 4,800 intravascular extraction attempts. The risk of Fatal/Life-threatening extraction is greater in Encor Bipolar than Accufix (2.8% vs. 1.1%) and the risk of J wire injury is less than Accufix (0.02%/year vs. 0.05%/year). Due to the limited ENCOR Bipolar extraction data, which results in a large extraction risk variability, the more extensive extraction experience obtained from the ACCUFIX lead is utilized as a comparison against the future probability of ENCOR Bipolar J wire injury.

Based on the current implant duration of these leads with a minimum implant duration of 9 years, the extremely low injury rate (0.02%/year) and the considerably higher extraction risk at 9 years implant duration, consideration for extraction is probably best reserved for patients with a protruding J wire. Despite the high extraction complication risk, extraction should be strongly considered in patients with a straight J wire protrusion in the inter-electrode region due to the injury potential from this type of protrusion.

At all times, attention should be focused on the emotional and psychological impact on the patient when assisting him/her in the decision-making process, especially in light of the low risk of J wire injury compared to extraction risk. In some patients, if management of the emotional and psychological impact might eventually require extraction, it would be better to extract earlier rather than later.

Figure 3 - Probability of Future ENCOR Bipolar 'J' Wire Injury compared to Fatal/ Life-threatening Extraction Complication Risk

The Fatal/Life-threatening extraction risk is displayed by gender and time from implant. The Fatal/ Life-threatening extraction risk can be compared to the probability of future J wire injury to determine the balance of risks between the probability of J wire injury in the patient's remaining lifetime and the one-time extraction risk.



### Unique Extraction Considerations

The location of the J wire within the inner conductor coil of the ENCOR Bipolar lead may cause difficulties during intravascular extraction of a fractured lead. Physicians have reported cases where the fractured J wire obstructed the central lumen making it difficult to pass a locking stylet sized in the usual way to the distal tip of the lead. It may require an undersized locking stylet in order to reach the distal tip of the lead. Experienced extractors have reported concerns regarding the locking stylet pushing a protruding segment of J wire further out of the lead causing atrial perforation or migration of the J wire away from the lead. Furthermore, the stylet itself could pass out of the central lumen at the point of fracture leading directly to damage or perforation of the right atrial wall. Members of the Physician Advisory Committee have suggested closely observing the passage of the locking stylet using high-resolution fluoroscopy.

## MULTI-CENTER STUDY CONCLUSIONS-STUDY CLOSED NOVEMBER 1999

### Risk of Fracture and Protrusion (MCS)

Eleven centers participated in Phase II of the MCS study and were asked to identify their implanted ENCOR Bipolar J lead population, to determine the patients available to them for monitoring, and to fluoroscopically evaluate these patients' leads every 6 or 12 months dependant on the inter-electrode contour Patients with a kinked inter-electrode contour were to be screened every 6 months. In addition, data were collected on patient survival, patient demographics, lead variables, and lead explant.

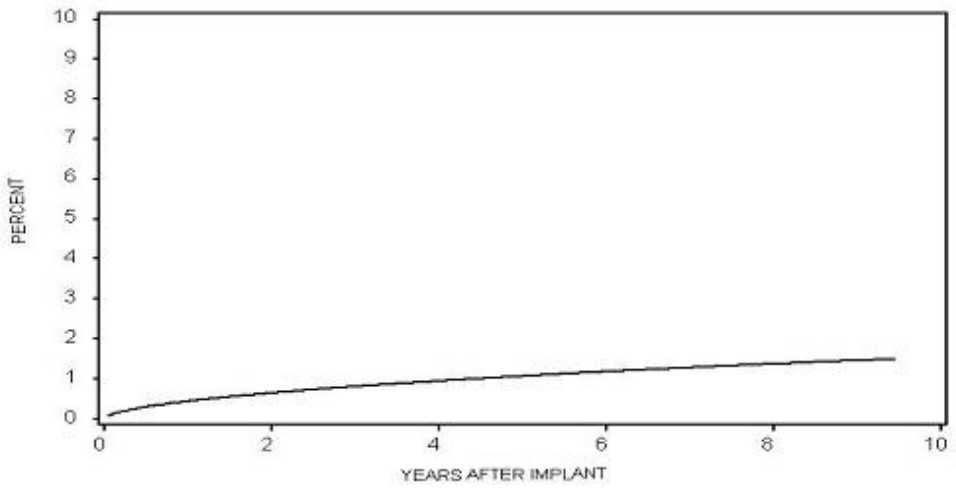
Due to the time related mechanism of metal fatigue leading to J wire fracture, the most appropriate method of examining risk is one that incorporates implant duration of the lead. The cumulative hazard function measures the risk over time for an event such as J wire fracture, protrusion or injury. The cumulative hazard function can also be used to assess the constancy of risk, in which case the cumulative hazard function is a straight line, and it's slope equals the risk per implant year. Because the exact time of fracture or protrusion of the J wire is not known (for example, a lead implanted in 1990 may show a protruded J wire at the time of the first fluoroscopic screening in 1994, or a lead with no J wire protrusion evident on a fluoroscopy in 1994 might show a protruded J wire on a later screening), the time to fracture or protrusion has to be estimated. A Weibull distribution of time to event was utilized for these time related analyses.

In November 1999, the PAC reviewed J wire classification data on 959 leads which combined data from cinefluoroscopic imaging, post explant observations and returned device analysis. The cumulative risk of fracture (Combined Group II, III, IV) appeared constant over time with an annual fracture risk estimated at 3.3% per year.

Figure 4 shows the MCS cumulative risk of protrusion. The Weibull shape parameter (1.83) is not statistically different from one (p=0.2) indicating a constant risk. The annual protrusion risk was estimated at 0.2% per year. At 10 years implant duration; there is a 2.0% probability of protrusion. There is a corresponding 98% probability of remaining free of protrusion at 10 years implant duration.

Figure 4 – Cumulative risk of protrusion in MCS ENCOR Bipolar 'J' leads

The risk of protrusion appears constant over time based on a shape parameter which in not statistically different from one p=0.2. Assuming a constant risk, the annual protrusion risk is estimated at 0.2% per year based on 9 Group III, IV leads out of 959 MCS leads with a J wire classification and implant date.




## PREDICTORS OF ENCOR BIPOLAR 'J' WIRE FRACTURE AND PROTRUSION (MCS)

The multi-center study (Phase II) evaluated the relationship of J wire failure and potential factors such as lead variables (implant approach, J Shape, implant inter-electrode contour), lead dynamics (inter-electrode motion), and patient variables (gender, age at implant).

Throughout multiple MCS data analyses as well as in Accufix multi-center studies of J wire fracture, open J shape was a consistent predictor of J wire failure[1]. The final Phase II MCS analyses completed in November 1999 demonstrated that J-shape, implant approach, inter-electrode contour, and inter-electrode motion were predictive of J wire fracture by univariate analysis. Patients with true J shape, cephalic implant approach, straight inter-electrode contour, and inter-electrode motion less than 10 degrees were at lower risk of fracture. In earlier multivariate analysis, J-shape ($p<0.001$), inter-electrode motion ($p<0.001$) and implant age ($p=0.02$) were independent predictors of fracture, with patients having a true J-shape, inter-electrode motion less than 10 degrees and implant age greater than 50 years at lower risk of fracture.

J shape was also predictive of J wire protrusion by univariate analysis. In part due to the low event rate, there were no significant multivariate predictors of protrusion.

[1]Telectronics Pacing System, Dear Doctor Letter mailed to implanting and following physicians of Accufix patients, August 25, 1995 pg 2.

Table 1 – Univariate Predictors of ENCOR Bipolar 'J' Wire Fracture and Protrusion (MCS)

| Variable | Fracture Univariate | Protrusion Univariate |
|---|---|---|
| Gender | NS | NS |
| Implant Approach (Cephalic or Subclavian) | <0.01 | NS |
| J Shape (Closed J or Open J) | <0.001 | 0.05 |
| Inter-electrode Motion (<10 degrees motion, >10 degrees motion) | <0.001 | 0.08 |
| Implant Inter-electrode Contour (Straight, Curved, Kinked) | <0.001 | NS |
| Age at Implant (0-50, >50) | NS | 0.08 |

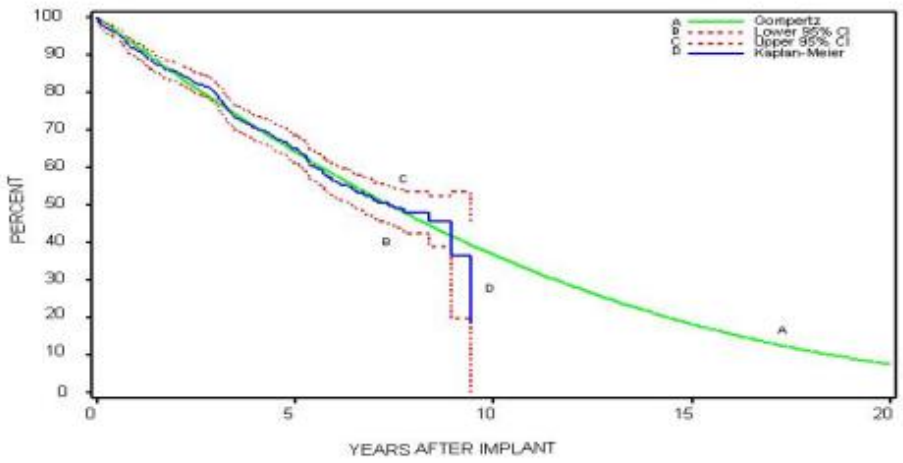
Values greater than 0.05 are considered not significant (NS). However, actual p-values are presented when if between 0.05 and 0.1. Lower risk variable listed first where significant differences exist.

## MCS Patient and Lead Survival

The Kaplan-Meier and Gompertz survival distributions for the MCS population are provided in Figure 5.[2] Based on the Kaplan-Meier curve, the observed probability of patient survival was 64.9% at 5 years post implant (95% CI: 61.2%-68.6%), with a projected survival of 36.7% at 10 years post implant (95% CI: 36.6%-36.8%) and 18.3% (95% CI: 18.2%-18.4%) at 15 years post implant based on the Gompertz survival curve.

Figure 5 - Survival in ENCOR Bipolar 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. Dotted lines indicate the 95% confidence intervals for the Kaplan-Meier survival curves.




[2] Gompertz B. On the nature of the function expressive of the low of human mortality, and on the new mode of determining the value of life contingencies. PhilosTrans R Soc Lond A Biol Sci 1825;115:513-580.