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1 **Title: Assessing long term survival and hospitalisation following transvenous lead extraction in**
2 **patients with cardiac resynchronisation therapy devices: A propensity score matched analysis**

3

4 **Short Title: Survival following TLE in CRT patients**

5

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26

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44 Transvenous lead extraction; CRT; Cardiac Resynchronisation Therapy; Mortality; Hospitalisation;
45 Propensity Score Matching

46

47 **Abstract**

48

49 **Background:**

50 Longer term outcomes of patients post transvenous lead extraction (TLE) is poorly understood in
51 patients with cardiac resynchronisation therapy (CRT) devices.

52

53 **Objectives:**

54 A propensity score (PS) matched analysis evaluating outcomes post-TLE in CRT and non-CRT
55 populations was performed.

56

57 **Methods:**

58 Data from consecutive patients undergoing TLE between 2000 to 2019 were prospectively collected.
59 Patients surviving to discharge and re-implanted with the same device were included. The cohort was
60 split depending on presence of CRT device. Associations with all-cause mortality and hospitalisation
61 was assessed by Kaplan-Meier estimates. An exploratory endpoint was evaluated whether early (<7
62 days) or late (>7 days) reimplantation was associated with poorer outcomes.

63

64 **Results:**

65 Of 1005 patients included, 285 (25%) had a CRT device. Median follow-up was 57.00 [27.00-93.00]
66 months, age at explant was 67.7±12.1 years, 83.3% were male and 54.4% had an infective indication
67 for TLE. PS were calculated using 43 baseline characteristics. After matching, 192 CRT patients
68 were compared with 192 non-CRT patients. In the matched cohort, there was no significant
69 difference with respect to mortality (hazard ratio [HR]=1.01, 95% confidence interval [CI] [0.74-
70 1.39], p=0.093) or hospitalisation risk (HR=1.2[0.87-1.66], p=0.265) was observed. In the matched
71 CRT group, late reimplantation was associated with increased mortality (HR=1.64[1.04-2.57],
72 p=0.032) and hospitalisation risk (HR=1.57[1.00-2.46], p=0.049).

73

74 **Conclusion:**

75 Outcomes of CRT patients post-TLE is similarly poor to non-CRT patients in matched populations.
76 Reimplantation within 7 days was associated with better outcomes in a CRT population but was not
77 observed in a non-CRT population, suggesting prolonged periods without biventricular pacing should
78 be avoided.

79 **Key Findings:**

- 80 • This is the largest matched analysis of mortality and clinical outcomes of patients with and
81 without cardiac resynchronisation therapy (CRT) devices following transvenous lead extraction
82 (TLE).
- 83 • In an unmatched analysis, patients with CRT devices post TLE were more likely to die and be
84 readmitted to hospital for any cardiovascular cause
- 85 • In a matched analysis, patients with and without CRT devices post TLE had similar outcomes
86 with respect to mortality and hospitalisation.
- 87 • Delayed reimplantation following TLE in the CRT group was associated with greater risk of
88 mortality and hospitalisation. This was not observed in the non-CRT group. This suggests
89 minimising time without biventricular pacing following TLE in a CRT population is desirable.

90

91

92 **Introduction**

93

94 The rise in the use of intracardiac implantable electronic devices (CIEDs) has been paralleled by an
95 increase in the number of procedures required for the removal of such devices and their associated
96 leads¹. Transvenous lead extraction (TLE) forms the basis of the management of infected CIEDs,
97 malfunctioning and redundant leads². High procedural success rates with low rates of major in-
98 hospital complications as achieved in the European Lead Extraction ConTRolled Registry
99 (ELECTRa), demonstrate a complete clinical success at 96.7% and an in-hospital major complication
100 rate at 1.7%³. Overall hospital mortality was low at 1.4% with a procedural related mortality of 0.5%.
101 The outcomes for the subgroup of patients who have TLE procedures with cardiac resynchronization
102 therapy (CRT) devices is less well understood. CRT is an effective therapy to improve symptoms and
103 reduce mortality in patients with dyssynchronous heart failure, however these patients have a higher
104 morbidity and mortality rate related to poorer left ventricular ejection fraction (LVEF) and co-
105 morbidity burden. Similarly, the number of CRT devices implanted with left ventricular (LV) leads
106 has been paralleled by an increased requirement for CRT system extraction⁴. Current evidence
107 suggests that there is no significant difference in acute complications, or 30-day mortality associated
108 with CRT system extraction⁵. Less is understood regarding long term outcomes regarding mortality
109 and morbidity following TLE in this group. In addition, the impact of delayed reimplantation of a
110 CRT device following TLE is poorly understood, despite the theoretical risk of negative reverse
111 remodelling⁶ or acute haemodynamic compromise⁷ caused by the absence of biventricular pacing.
112 We hypothesised that patients had poorer outcomes who had a CRT device vs non-CRT device,
113 however it was unclear if matching the baseline characteristics would maintain this effect. In
114 addition, we hypothesised that delayed reimplantation post TLE in a CRT population would result in
115 poorer outcomes compared to non-CRT populations. We studied data from a single, high-volume
116 tertiary referral centre for TLE, regarding long-term outcomes in a CRT and non-CRT population.

117

118 **Methods**

119

120 Data Collection

121

122 All consecutive patients undergoing TLE in a high-volume centre in the UK were prospectively
123 recorded onto a computer database between October 2000 and November 2019. Multiple parameters
124 were recorded, including demographics, extraction indication, device and lead type, comorbidities,
125 biochemistry and pathology results, procedural success, major complications, and technical extraction
126 information. Patients reimplemented with the same device and surviving to discharge following TLE
127 were included. Only the most recent entry for patients with multiple TLEs during the study period
128 were included. Mortality was recorded retrospectively by linking unique patient registration numbers
129 (National Health Service (NHS) numbers) and the Office for National Statistics (ONS) mortality data
130 updated as of February 2020⁸. Hospital readmission information was obtained from the source data
131 feeding directly to the Hospital Episodes Statistics (HES) national database, which records all NHS
132 hospital-based activity in England and has been validated as an accurate way of recording medical
133 activity and is used for allocating resources based on needs in the NHS⁹. Any cardiovascular cause of
134 inpatient admission was identified as the primary outcome measure of hospitalisation, as defined by
135 the World Health Organisation International Classification of Diseases (ICD-10-CM) coding system
136 (ICD-10-CM codes: Diseases of the circulatory system: ICD I00-199; Heart failure: I50;
137 Complications of cardiac and vascular prosthetic devices: ICD T82)¹⁰. The database collection and
138 analysis were approved by the Institutional Review Board of Guy's and St Thomas' Hospital.

139

140 Definitions

141

142 TLE was defined as per the EHRA and HRS guidelines¹¹. The 2018 EHRA guidelines defined the
143 extraction indication, procedural success and complication rate¹². The extraction procedure
144 undertaken at this centre has been described in detail elsewhere¹³. If there was more than one
145 indication for lead extraction or original implantation indication, this was counted independently.
146 Number of previous device interventions was defined as the number of CIED procedures undertaken
147 on the patient prior to the recorded lead extraction. Lead dwell time was calculated as the oldest

148 targeted lead in situ at time of extraction. Follow-up time and age were calculated from date of TLE.
149 Major cardiovascular co-morbidities were recorded. Glomerular filtration rate (GFR) was estimated
150 by the MDRD 4-variable equation¹⁴.

151

152 Statistical Analysis

153

154 Missing data for variables of interest were handled by multiple imputation with chained equations and
155 the multiple imputed data frames were merged into a single data frame by computing the mean or
156 selecting the most likely imputed value (R-packages mice and sjmisc; 10 imputed datasets)¹⁵. The
157 propensity score (PS) for the CRT group was calculated by a logistic regression model using 43
158 clinically relevant covariates. CRT patients were matched 1:1 to non-CRT patients by their PSs,
159 using the nearest neighbour method with a calliper of 0.10 and no replacements. Variables included
160 in either the multiple imputation models or considered for PS calculation are shown in table 1. The
161 ability of the matching to balance baseline characteristics in CRT versus non-CRT group was assessed
162 by absolute standard differences, with a value of <10% considered as not significant¹⁶.

163

164 Baseline variables of the matched cohort were compared by calculating standardised mean differences
165 and the chi-squared test, student's t-test or Mann Whitney U-test when appropriate. Primary
166 outcomes in this analysis were overall survival and time to first cardiovascular hospitalisation at
167 follow-up. Kaplan-Meier method was used to estimate survivor functions in the CRT vs non-CRT
168 group, with a secondary outcome analysis dependent on whether patients were reimplanted within or
169 after 7 days of initial TLE. A sub-analysis of the matched CRT and non-CRT groups was undertaken
170 with the same outcomes assessed as above. Univariable cox (proportional hazard) regression was
171 performed, and the results are presented as (Hazard Ratio (HR) [95% Confidence Interval (CI)], p-
172 value).

173

174 Results

175

176 Study Cohort

177 Between October 2000 and November 2019, 1171 consecutive patients underwent TLE at the
178 reference centre. After applying the inclusion criteria, 1005 patients were eligible. Of these, 285
179 (28.4%) patients had a CRT device. After PS matching, the analysis was restricted to 384 patients,
180 192 in both the CRT and non-CRT groups.

181

182 Baseline Characteristics (Table 1)

183 In the overall cohort, mean age was 65.1 ± 14.7 years, 72.7% were male and 51.9% had a TLE for an
184 infective indication. Median lead dwell time was 5.40 [1.80-9.80] years, 28.5% had an ICD, 43.2%
185 had a permanent pacemaker and the remainder had a CRT-D/P device at time of TLE. Most of the
186 baseline characteristics were differently distributed in the CRT versus non-CRT group. CRT patients
187 were older (68 ± 10.7 vs 64 ± 15.6 years, $p < 0.001$), had higher mean number of co-morbidities (3.18 vs
188 1.49, $p < 0.001$), poorer renal function (108.00 [86.00-136.00] vs 89.00 [75.00-110.00] mg/dL,
189 $p < 0.001$), and lower LVEF (35.5 ± 12.4 vs 47.4 ± 12.1 , $p < 0.001$). The CRT group also had shorter lead
190 dwell time (4.70 [1.80-8.10] vs 5.90 [1.80-10.50] years, $p = 0.01$), were less likely to have their device
191 reimplanted within 7 days of TLE procedure ($n = 159$, 55.8% vs $n = 470$, 65.3%, $p = 0.006$), longer time
192 to reimplantation ($p = 0.029$) and have had a previous device intervention ($p = 0.038$). After PS
193 matching, baseline characteristics considered for PS calculation were equally distributed between the
194 2 study groups, with well-matched PS in both groups (supplement figure 1).

195

196 Outcome analysis

197

198 All-Cause Mortality (Figure 1)

199

200 In the overall cohort, during long-term follow-up with a median of 57.00 [27.00-93.00] months, 345
201 (34.3%) patients died. Kaplan-Meier survival analysis demonstrated a survival probability of 93.4% at
202 1 year, 88.4% at 2 years, 73.1% at 5 years and 50.4% at 10 years. At follow-up a higher proportion of
203 patients died in the CRT vs non-CRT group (43.9% vs 30.6%, $P < 0.001$) with survival probability of

204 88.9% vs 97.1% at 1 year; 80.7% vs 91.4% at 2 years; 59.3% vs 78.3% at 5 years, and 27.6% vs
205 56.7% at 10 years. Overall unadjusted hazard ratio (HRs) for mortality and 95% CIs in the CRT
206 group were [HR = 2.16, 95% CI (1.72-2.70), p<0.001].

207

208 In the matched cohort, during long-term follow-up with a median of 46.00 [25.00-76.25] months, 159
209 (41.4%) patients died. At follow-up a similar proportion of patients died in the matched CRT vs non-
210 CRT group (40.1% vs 42.7%, P=0.68) with survival probability of 91.4% vs 91.5% at 1 year; 83.9%
211 vs 86.9% at 2 years; 65.0% vs 63.6% at 5 years, and 33.5% vs 34.9% at 10 years. Similar unadjusted
212 HR were observed for the matched CRT group [HR = 1.02, 95% CI (0.74-1.39), p=0.933].

213

214 Cardiovascular Hospitalisation (Figure 2)

215

216 In the overall cohort during long-term follow-up, 371 (36.9%) patients were hospitalised. Kaplan-
217 Meier survival analysis demonstrated a freedom from hospitalisation probability of 76.7% at 1 year,
218 71.0% at 2 years, 62.2% at 5 years and 50.1% at 10 years. At follow-up a higher proportion of
219 patients were hospitalised in the CRT vs non-CRT group (58.9% vs 44.9%, P<0.001) with survival
220 probability of 71.6% vs 78.7% at 1 year; 62.8% vs 74.0% at 2 years; 51.6% vs 65.9% at 5 years, and
221 42.8% vs 53.1% at 10 years. Overall unadjusted hazard ratio (HR) and 95% CIs for hospitalisation in
222 the CRT group were greater than in the non-CRT group [HR = 1.46, 95% CI (1.17-1.83), p<0.001].

223

224 In the matched cohort during long-term follow-up, 147 (38.3%) patients died. At follow-up a similar
225 proportion of patients were hospitalised in the matched CRT vs non-CRT group (41.1% vs 35.4%,
226 P=0.294), with hospitalisation probability of 72.2% vs 76.3% at 1 year; 63.3% vs 70.6% at 2 years;
227 54.0% vs 60.4% at 5 years, and 43.7% vs 46.5% at 10 years. Similar unadjusted HR were observed
228 for the matched CRT group for risk of hospitalisation [HR = 1.20, 95% CI (0.87-1.66), p=0.265].

229

230 Sub-group analysis

231

232 Re-implantation timing

233

234 In the sub-group analysis within the matched cohorts, an analysis of survival probability with respect
235 to mortality and hospitalisation following TLE was performed. There were similar baseline
236 characteristics between the late reimplantation groups in the matched CRT and non-CRT groups, with
237 similar infective indications for TLE (local: 64.1% vs 64.9%; systemic: 26.9% vs 27.0%; any
238 infection: 91.0 vs 91.9%), eGFR (61.6 vs 61.9 ml/min/m²), LVEF (38.4 vs 40.1%) and age at explant
239 (69.2 vs 70.0 years) (supplement table 1).

240

241 Within the matched non-CRT group, there was no significant difference with regards to risk if
242 reimplantation occurred late (i.e. 7 days after TLE procedure) with an unadjusted HR for death of [HR
243 = 1.33, 95% CI (0.86-2.05), p=0.208] and for hospitalisation [HR = 1.14, 95% CI (0.69-1.89),
244 p=0.601]. Within the matched CRT group, there was a significant difference with regards to risk
245 associated with late reimplantation with an unadjusted HR for death of [HR = 1.64, 95% CI (1.04-
246 2.57), p=0.032] and for hospitalisation [HR = 1.57, 95% CI (1.00-2.46), p=0.049]. There was no
247 evidence of differences in risk of mortality (p=0.576) or hospitalisation (p=0.911) between the early
248 reimplantation groups in the CRT and non-CRT groups. There was increased risk of hospitalisation in
249 the late reimplantation group in the CRT group vs non-CRT group [HR=1.71 95% CI (1.01-2.9),
250 p=0.048] (figures 3 and 4).

251

252 Risk depending on cause of hospitalisation

253

254 There was a greater risk of hospitalisation associated with TLE in the CRT group compared to the
255 non-CRT group with regards to any cardiovascular cause (ICD-10 I00-I99 codes) for hospitalisation
256 [Relative Risk (RR) 3.79, 95% CI (2.04-7.02), p<0.001], or heart failure decompensation (ICD I50-
257 I59 codes) [RR 1.45, 95% CI (1.14-1.86), p=0.004]. No significant difference was identified with
258 respect to risk of device related complications requiring hospitalisation [RR 1.13, 95% CI (0.79-1.64),
259 p=0.515] (figure 5).

260

261 **Discussion**

262 An understanding of mortality and morbidity at follow-up post TLE in the CRT population is
263 important to evaluate the longer-term implications of the procedure. To our knowledge, this analysis
264 is the largest registry analysis to date evaluating mortality and morbidity outcomes following TLE in
265 patients who survive to discharge and are reimplemented with the same device.

266

267 The main findings are that:

268

- 269 1. The baseline characteristics of patients undergoing TLE in the CRT group are significantly
270 different to the non-CRT group, and this is reflected in a higher risk of mortality and
271 cardiovascular hospitalisation following TLE.
- 272 2. In a matched cohort, CRT and non-CRT patients had similar outcomes with respect to
273 mortality and hospitalisation risk post TLE.
- 274 3. Following TLE, CRT patients had a higher risk of hospitalisation for any cardiovascular
275 cause or heart failure, however no increased risk of hospitalisation due to a device related
276 complication.
- 277 4. Reimplantation within 7 days was associated with better outcomes in a matched population in
278 patients with a CRT device compared to a non-CRT population.

279

280 Few studies have compared long term outcomes of patients following TLE specifically evaluating
281 patients with CRT and non-CRT devices. Larger registry analyses have not evaluated outcomes
282 beyond early complications and mortality in both CRT and non-CRT cohorts, including the
283 ELECTRa study¹⁷ and the Cleveland Clinic series of 5000 TLEs¹⁸. Data from the same reference
284 centre by Gould et al utilising a smaller cohort of patients, has demonstrated no significant difference
285 in 30-day mortality rates between CRT (3.0%, n=7) and non-CRT patients (2.0%, n=14) ($p=0.443$)⁵.
286 This study also evaluated outcomes using case-control matching, which also demonstrated no
287 significant difference in 30-day outcomes, however only 185 patients were included in each group,

288 and were matched only for 4 variables (lead dwell time, age, renal impairment, and systemic
289 infection), whereas the current analysis matched for 43 variables (table 1). Zuchelli et al,
290 demonstrated a 1-year mortality of 5.5% in a CRT population post TLE¹⁹, whereas our study
291 demonstrated higher incidence of mortality of 11.1%. In a more recent study, Nishii et al compared
292 the prognosis of patients who had severe LV systolic dysfunction (SLVD) compared to those who did
293 not. Whilst not looking specifically at patients with CRT devices, they demonstrated that those with
294 SLVD were not more likely to die at 30 days (97.2% vs 99.4%, p=0.215) or 1 year (80.6% vs 91.5%,
295 p=0.053) post TLE⁷. They also identified that patients with SLVD were more likely to require
296 additional hemodynamic support, such as temporary cardiac resynchronization therapy pacing (27.8%
297 vs 1.2%; p<0.001), which may attest to the findings in our study identifying poorer outcomes for
298 those who had delayed reimplantation. Of note, this study only included 36 patients with SVLD, out
299 of a total cohort of 200 patients, whereas our study utilises data from 1005 patients. Few studies have
300 evaluated cardiovascular hospitalisation as an endpoint in CRT patients post TLE. Regoli et al
301 identifying 37.0% requiring hospitalisation, and 23.9% dying at a median follow-up of 21 months
302 post TLE²⁰, which compared similarly to our study at the same follow-up time (hospitalisation:
303 34.9%; mortality: 16.5%).

304

305 Most published data involving PS matching in patients with cardiac resynchronisation therapy has
306 been to compare outcomes of CRT cohorts with and without defibrillator devices^{21,22}, with only one
307 study utilising PS matching in patients following TLE²³. This study is the first to match CRT and
308 non-CRT patients post TLE. Matching resulted in an increase in mean age at explant (64.0 to 67.8
309 years), total number of comorbidities (1.49 to 2.78 comorbidities), and reduction in LVEF (47.4 to
310 37.7%) and eGFR (70.5 to 63.9 ml/min/1.73m²) of the non-CRT group. In the unmatched cohort,
311 CRT patients were at significantly increased risk of any cardiovascular hospitalisation and mortality,
312 with an increased relative risk of heart failure hospitalisation, compared to a non-CRT population.
313 Matching resulted in similarly poor outcomes in the CRT and non-CRT group, which suggests that all
314 patients with a greater co-morbidity burden regardless of whether they have a CRT may benefit from

315 closer evaluation following TLE. This could confer significant cost savings for healthcare services,
316 which can tailor services to reduce risk of hospitalisation in these at-risk patients²⁴.
317
318 Notably, the exploratory endpoint demonstrated poorer outcomes in those who had delayed
319 implantation following CRT explant. It is possible that those with CRT devices explanted for an
320 infective indication may have a greater burden of infective material due to the presence of an LV lead,
321 which may contribute to the poorer outcomes associated with delayed reimplantation. It may also be
322 argued that an infective indication, whether this be systemic or local may be an unidentified
323 confounder. However, within each matched cohort there was not a survival difference depending on
324 whether there was an infective indication for TLE, and whether this was a systemic or local infection
325 (Supplement Figure 1). This suggests that the presence of infection was unlikely to be a confounder
326 influencing this observation within the matched cohorts. Additionally all patients had interrupted
327 biventricular pacing from time of TLE procedure to time of reimplantation. Most published work
328 evaluates the acute implications of interrupting continuous biventricular (BiV) pacing. These studies
329 have demonstrated that even brief interruptions in BiV pacing can result in worsening dyssynchrony
330 and mitral regurgitation (MR)²⁵, left atrium and left ventricular dimensions²⁶, and contractile
331 reserve²⁷. Changes in cardiac biomarkers have also been associated with 48 hours of BiV interruption
332 of CRT responders, with Rubaj et al identifying a significant increase in proinflammatory cytokines
333 and BNP concentrations²⁸. These findings may be a reason for the observed negative outcomes
334 observed in this study associated with delayed reimplantation seen in the matched CRT cohort, but
335 not observed in the matched non-CRT cohort.

336

337 **Limitations**

338

339 Although the database collects many variables and allowed us to perform adjustments by PS
340 matching, residual and unmeasured confounding within the matched and unmatched cohorts cannot
341 be ruled out. Although our PS models were fitted based on several variables to foster adequate
342 adjustments, we did not consider potential interactions among the covariates. The findings of our

343 study are limited by the inherent issues identified with observational studies. Associations with
344 mortality and hospitalisation for the groups were discussed, however the cause-and-effect relationship
345 remain associative. Causes of death in these patients is unknown. We opted to only include patients
346 who survived to discharge, which may have introduced survival and treatment bias. As our institution
347 is a tertiary care centre, referral bias could have affected the clinical data, thereby limiting
348 generalisation of these findings to other patient populations. The analysis on the impact of delayed
349 reimplantation was performed within the matched cohorts as the baseline characteristics of the CRT
350 and non-CRT groups were similar after matching was performed. Within these constrains, a PS
351 match analysis was considered an appropriate method of evaluating this hypothesis and potentially
352 form the basis of further investigation in the form of a randomised trial which could more effectively
353 reduce the potential number of unidentified confounders which are often unavoidable as part of
354 observational studies. As the baseline characteristics of the matched groups were very balanced,
355 particularly with respect to the proportion of systemic and local infective indications for TLE, we
356 believe there was justification for this comparison.

357

358 **Conclusions**

359

360 The prognosis of patients with CRT who undergo TLE demonstrates similar mortality and
361 hospitalisation risk to non-CRT patients in a matched population. In an unmatched population, CRT
362 patients had notably poorer outcomes and merit close follow-up post TLE procedures. There was
363 increased risk of adverse outcomes associated with delayed reimplantation of CRT devices compared
364 to other devices. This may be due to prolonged periods without continuous BiV pacing following
365 TLE in patients with CRT devices, and this should be avoided where possible.

366

367

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469 **Figures**

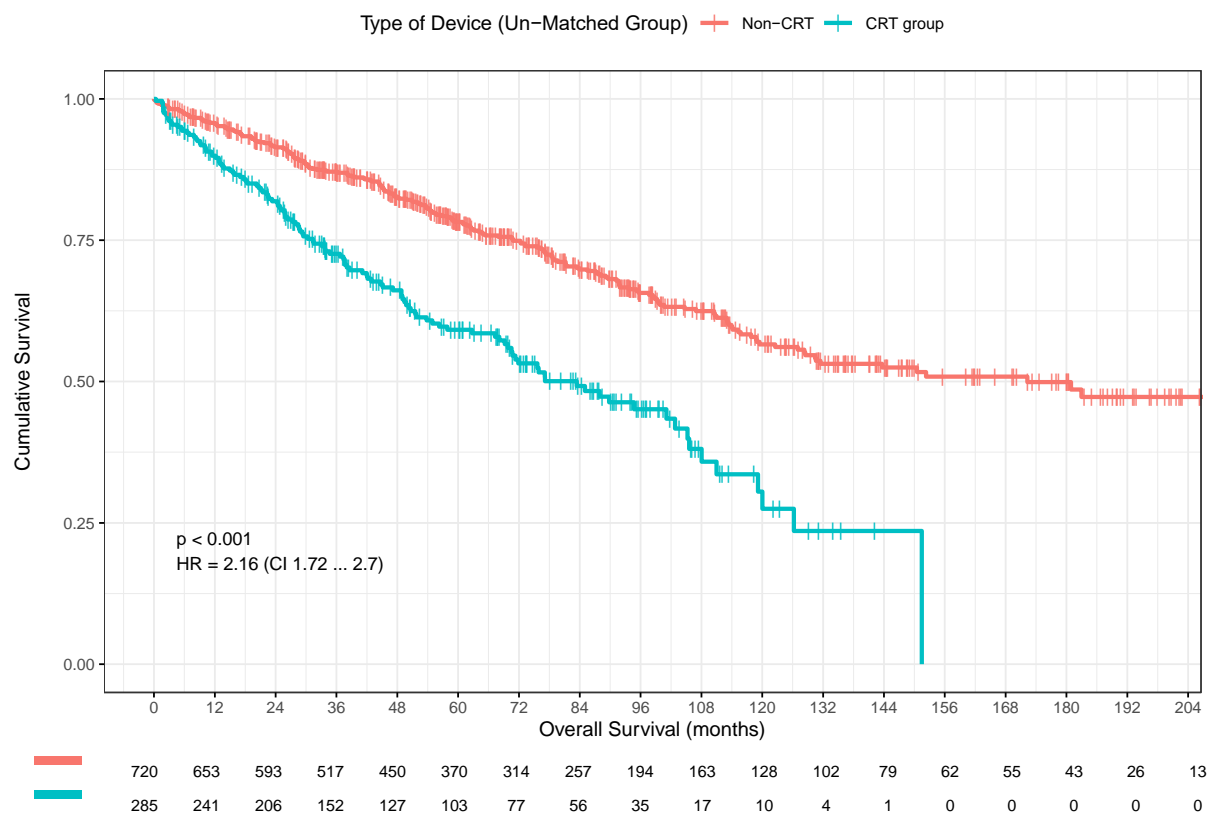
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471 **Figure 1**

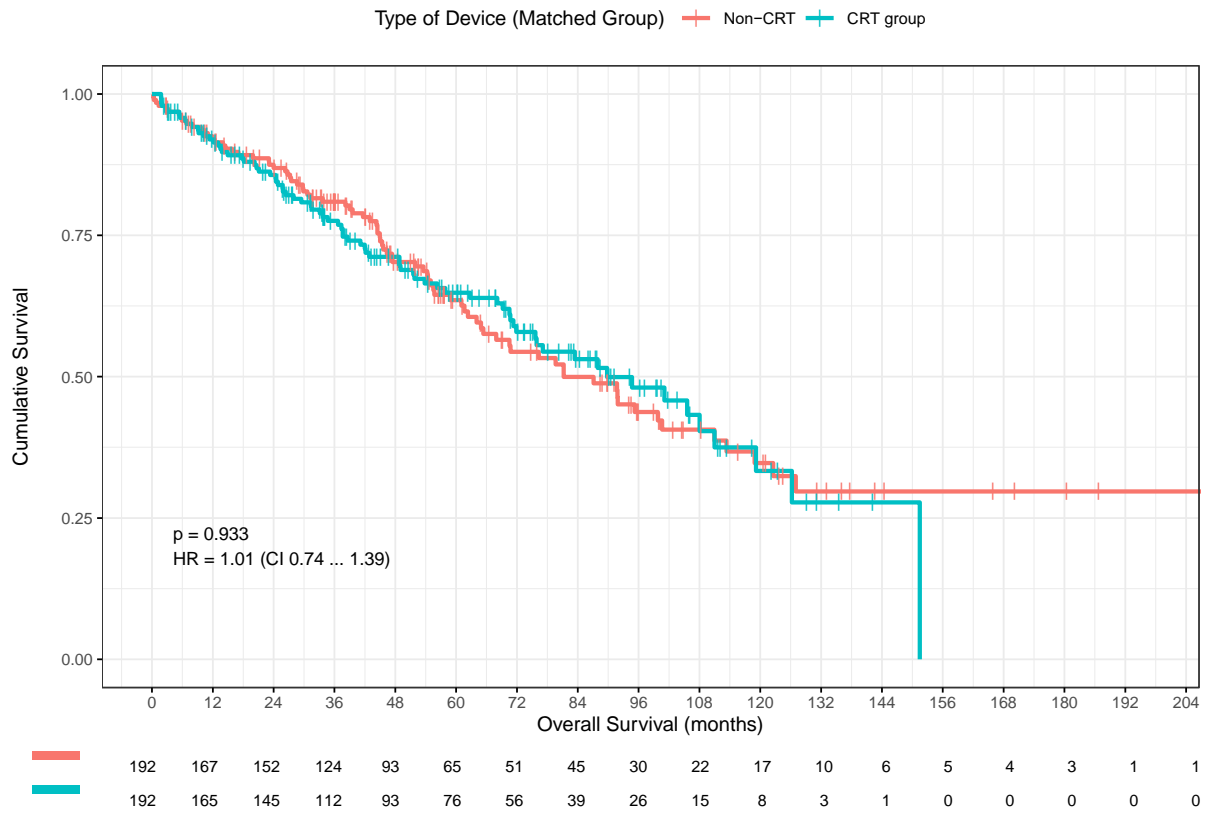
472 Kaplan-Meier survival probability for mortality in patients depending on type of device explanted.

473 Figure 1A – unmatched cohort. Figure 1B – Matched group. CRT - Cardiac Resynchronisation

474 Therapy



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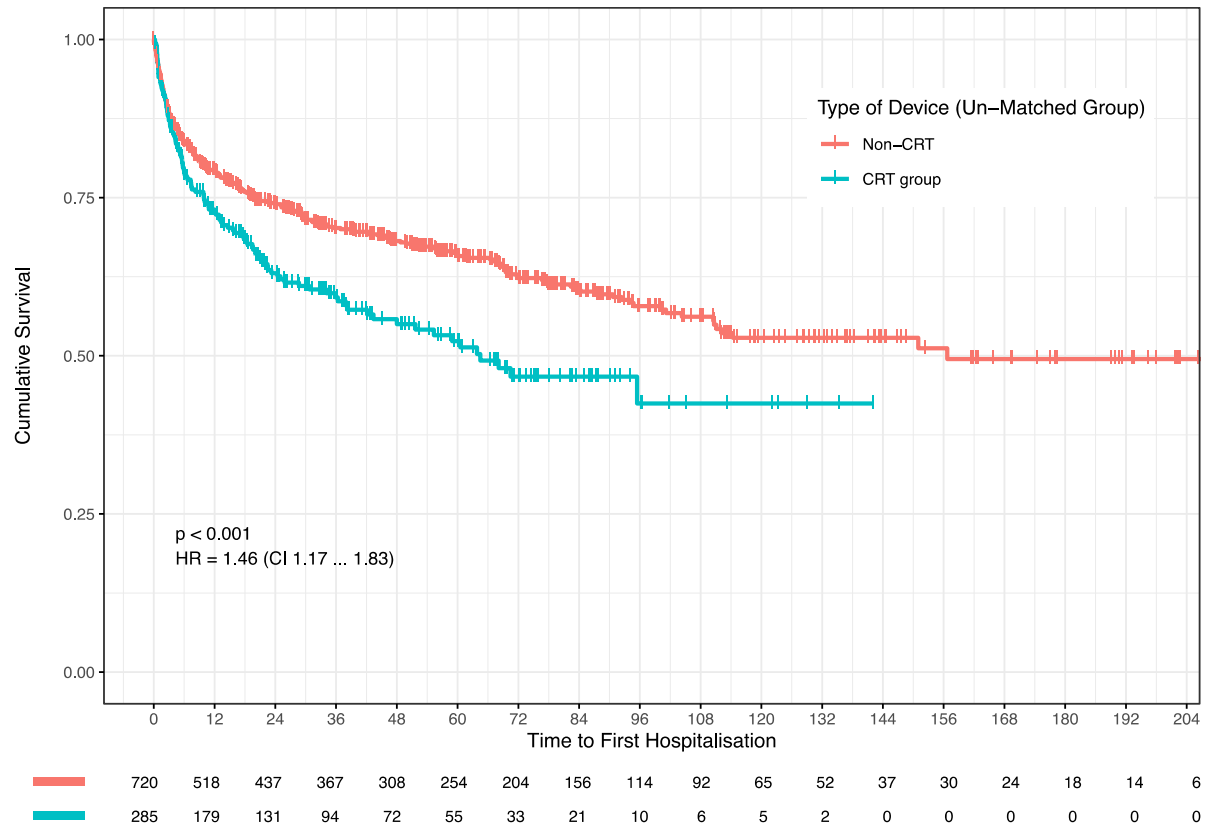
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479 **Figure 2**

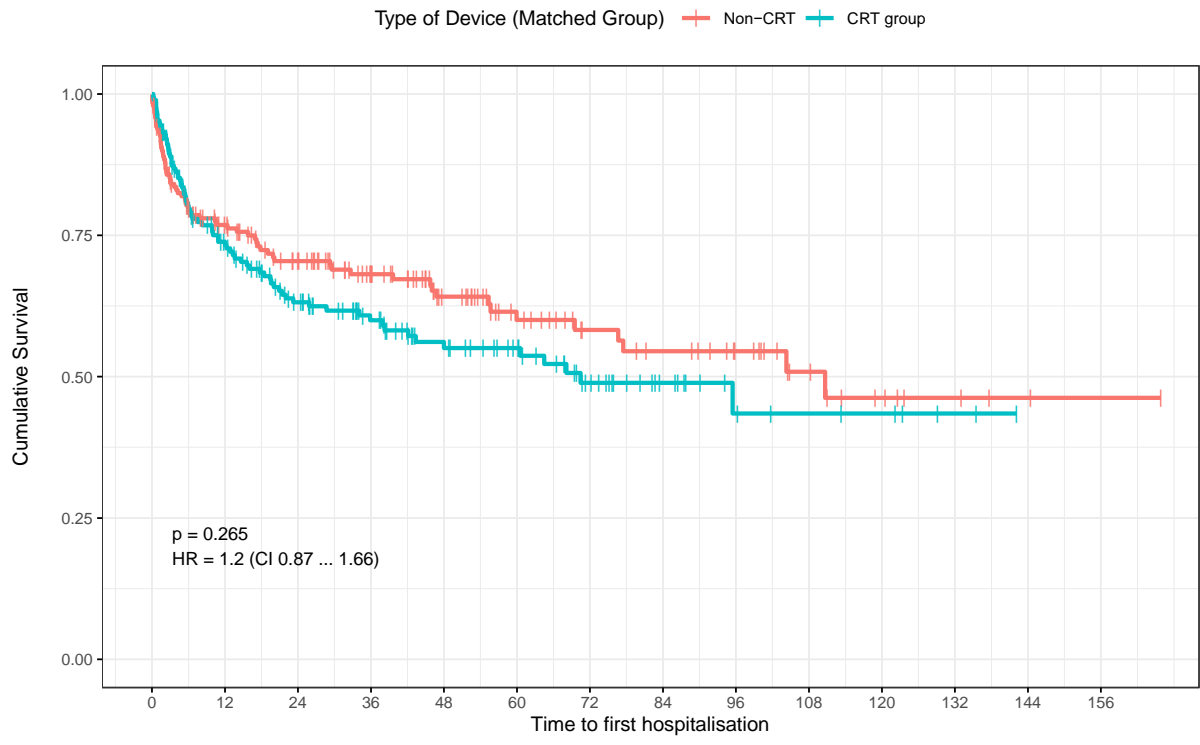
480 Kaplan-Meier survival probability for hospitalisation in patients depending on type of device

481 explanted. Figure 2A – unmatched cohort. Figure 2B – Matched group.



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	192	127	104	81	58	41	31	26	20	12	7	4	2	1
	192	125	92	70	53	42	26	15	8	6	5	2	0	0

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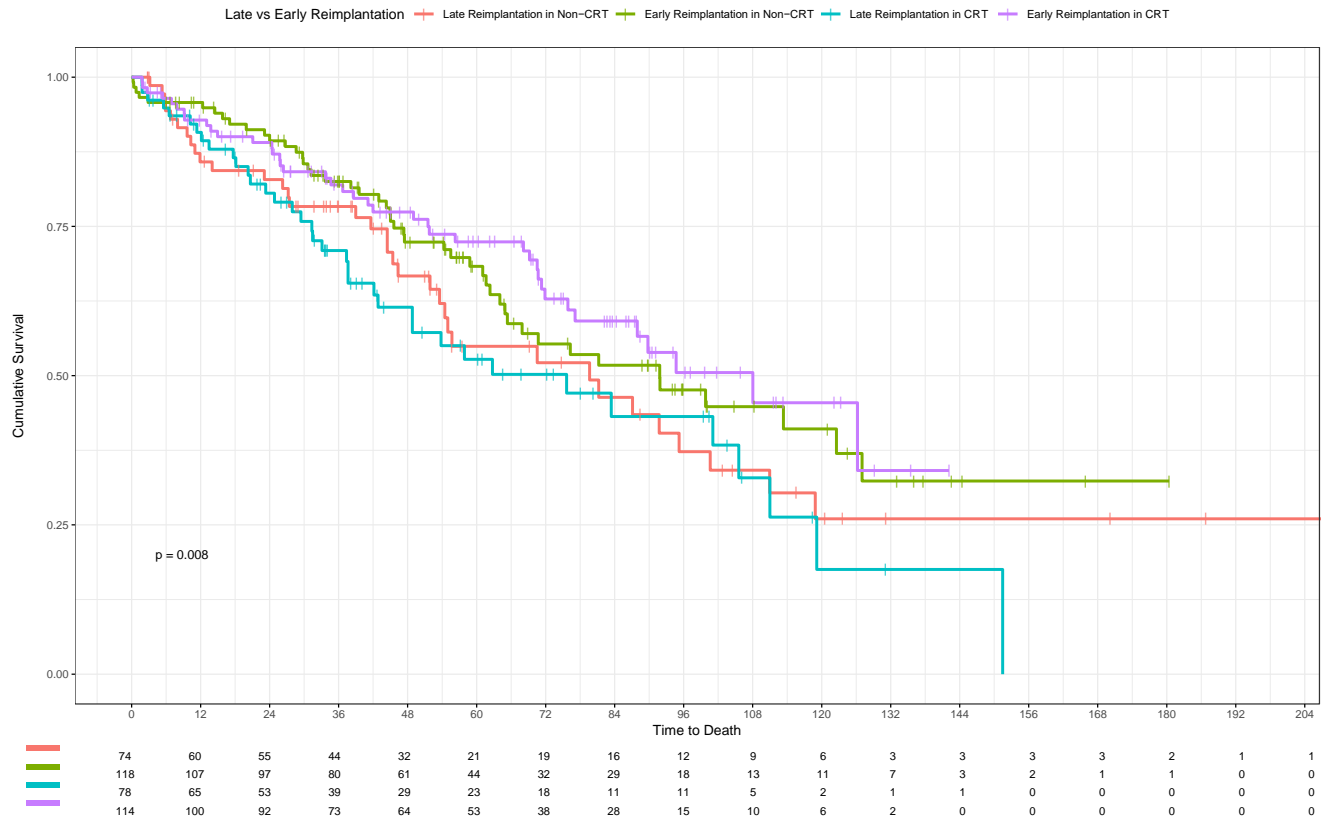
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487 **Figure 3**

488 Kaplan-Meier survival probability for mortality in patients depending on timing for reimplantation

489 post TLE in subgroup analysis of matched groups.

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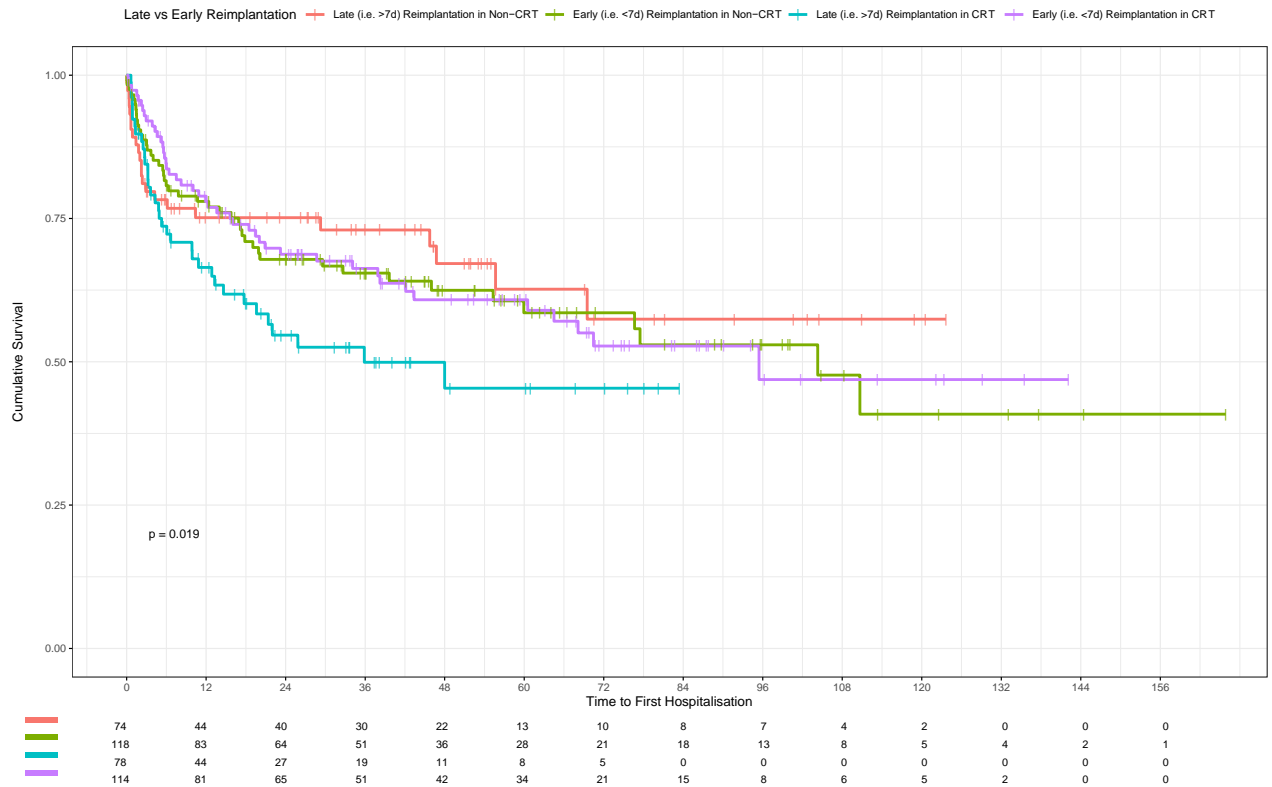
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496 **Figure 4**

497 Kaplan-Meier survival probability for hospitalisation in patients depending on timing for

498 reimplantation post TLE in subgroup analysis of matched group.



499

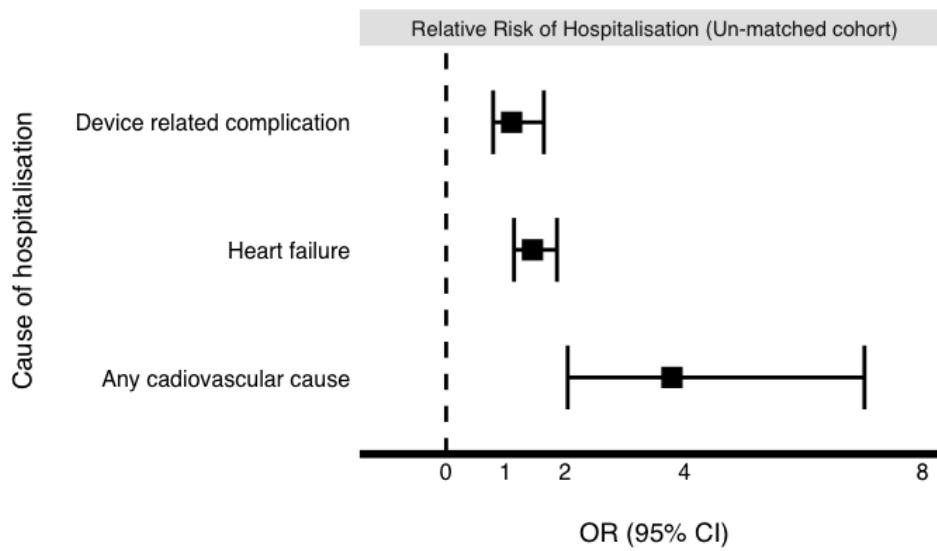
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503 **Figure 5**

504 Cause of hospitalisation analysis.



505

506 Forest plot assessing relative risk of hospitalisation for a specified cause following TLE in patients

507 with cardiac resynchronisation therapy (CRT) devices compared to non-CRT devices in the un-

508 matched cohorts.