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Transvenous lead extraction procedures in women based on ESC-EHRA EORP European Lead Extraction ConTRolled ELECTRa registry: is female sex a predictor of complications?

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Aims Female sex is considered an independent risk factor of transvenous leads extraction (TLE) procedure. The aim of the study was to evaluate the effectiveness of TLE in women compared with men.

Methods and results A *post hoc* analysis of risk factors and effectiveness of TLE in women and men included in the ESC-EHRA EORP ELECTRa registry was conducted. The rate of major complications was 1.96% in women vs. 0.71% in men; $P = 0.0025$. The number of leads was higher in men (mean 1.89 vs. 1.71; $P < 0.0001$) with higher number of abandoned leads in women (46.04% vs. 34.82%; $P < 0.0001$). Risk factors of TLE differed between the sexes, of which the major were: signs and symptoms of venous occlusion [odds ratio (OR) 3.730, confidence interval (CI) 1.401–9.934; $P = 0.0084$], cumulative leads dwell time (OR 1.044, CI 1.024–1.065; $P < 0.001$), number of generator replacements (OR 1.029, CI 1.005–1.054; $P = 0.0184$) in females and the number of leads (OR 6.053, CI 2.422–15.129; $P = 0.0001$), use of powered sheaths (OR 2.742, CI 1.404–5.355; $P = 0.0031$), and white blood cell count

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(OR 1.138, CI 1.069–1.212; $P < 0.001$) in males. Individual radiological and clinical success of TLE was 96.29% and 98.14% in women compared with 98.03% and 99.21% in men ($P = 0.0046$ and 0.0098).

Conclusion The efficacy of TLE was lower in females than males, with a higher rate of periprocedural major complications. The reasons for this difference are probably related to disparities in risk factors in women, including more pronounced leads adherence to the walls of the veins and myocardium. Lead management may be key to the effectiveness of TLE in females.

Keywords Transvenous lead extraction • Female sex • Complications • Registry

What's new?

- Transvenous leads extraction (TLE) in women is characterized by lower efficacy and a greater number of serious complications.
- For the first time, different risk factors for TLE in female and male sex have been documented.
- The main risk factors of TLE in women include: signs and symptoms of venous occlusion, cumulative leads dwell time, and number of generator replacements.
- The concept of the leading role of appropriate lead management in women has been presented.

Introduction

The progress in clinical pacing starting in the second half of the 20th century has led to a rise in the number of patients with cardiac implantable electronic devices (CIED). This rise in the device implantation rates translates into increased need for reoperation due to changes in pacing mode, device infection, or lead dysfunction. According to the report of 2017, there are over 9000 lead extractions performed annually in Europe, which corresponds to an average of 15 extraction procedures per million inhabitants.[1] Women and men undergoing transvenous lead extraction (TLE) differ in regard to indications for CIED implantation and referral for TLE. Electrophysiological observations show that sick sinus syndrome and atrial fibrillation, are the most common indications for device implant in women, whereas in men is atrioventricular block, which means that dual-chamber devices are more common in men.[2–4] It is also known that less women than men receive implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices despite their documented efficacy in both sexes.[5,6] Several studies show a higher rate of early periprocedural complications in female patients: pneumothorax, pocket haematomas, and lead perforation.[2,7,8] Similarly, some reports demonstrate that TLE procedure can be less effective in women.[9–12] Preliminary analysis of the European Cardiac Society (ESC) EURObservational Research Programme (EORP) ELECTRa registry showed that female sex is an independent risk factor for major complications during or immediately after TLE [odds ratio (OR) 2.11, 95% confidence interval 1.23–3.62; $P = 0.0067$].[13] The present study was undertaken to provide an in-depth analysis of the efficacy and safety of TLE in women and men and to evaluate risk factors for the procedure in females and males.

Methods

Study population

Clinical data for analysis were obtained from ESC EORP ELECTRa registry which encompassing included 76 centres from 19 European countries and including 3555 patients (72.2% men) undergoing TLE between November 2012 and May 2014. Leads characteristics were calculated on the population of 3510 patients: 971 (27.7%) women and 2539 (72.3%) men who underwent the intervention. The Executive Committee, in collaboration with the EURObservational Research Programme (EORP) provided the study design, protocol, and scientific leadership of the registry under the responsibility of the European Heart Rhythm Association (EHRA) Scientific Initiatives Committee (SIC). The study design has been discussed in greater detail elsewhere.[14]

The present investigation was undertaken to assess the efficacy and safety of TLE in women and men and to compare the clinical and procedure-related factors that were likely to affect the effectiveness of TLE in females and males. The following clinical factors were taken into account: left ventricular ejection fraction (LVEF) and the New York Heart Association (NYHA) functional class, the presence of arterial hypertension, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease (COPD), diabetes mellitus, malignancy, and renal failure. Of CIED related factors, we analysed type of implanted devices, indications for TLE, previous CIED procedures (system changes, revision, or upgrade), number and type of extracted leads, extraction of abandoned leads, signs and symptoms of venous occlusion, and tricuspid valve dysfunction before TLE and leads extraction techniques.

Definitions

Transvenous lead extraction, radiological success, clinical success, major and minor complications were defined according to the 2017 HRS (Heart Rhythm Society)[15] and 2018 EHRA guidelines.[16]

Lead extraction was defined as any lead removal procedure in which at least one lead requires the assistance of equipment not typically required during implantation or at least one lead was implanted for longer than 1 year.

Radiological success (complete procedural success considered for each lead) was defined as removal of all targeted leads and material with the absence of any permanently disabling complication or procedure-related death.

Clinical success was defined as lead extraction procedures with removal of all targeted leads and lead material from the vascular space or retention of a small portion of the lead (<4 cm) that does not negatively impact the outcome goals of the procedure.

Major complications were defined as any of the outcomes related to the procedure, which is life-threatening or results in death (cardiac or non-cardiac) or any complication that causes persistent or significant disability or requires significant surgical intervention.

Minor complications were defined as any undesired event related to the procedure that requires medical intervention or minor procedural intervention to remedy and does not limit persistently or significantly the patient's function, nor does it threaten life or cause death.

The list of major and minor complications is provided in the Supplementary material online, *Tables S1* and *S2*.

Intra-procedural complications were defined as any event related to the performance of the procedure that occurred or became evident from the time the patient entered the operating room or catheterization laboratory until the time the patient left the operating room.[13]

Post-procedural complications were defined as any other such event occurring after the procedure until patient discharge.

Lead extraction procedure

Leads extraction techniques in ELECTRa population included use of manual traction, locking stylets and sheaths. The sheaths consisted of mechanical non-powered (polypropylene or similar plastic material made) or powered tools: laser, radio frequency electrosurgical, controlled-rotational with threaded tip. Other tools, dedicated to other procedures (pigtail catheters, deflectable wires, deflectable catheters, deflectable sheaths) were rarely used in this population. The most often approach was subclavian venous entry, an alternative methods with jugular and femoral access were rarely used.

Men and women were compared with respect to total procedure duration, fluoroscopy time, lead extraction technique, venue for lead extraction, total number and types of extracted leads, tricuspid valve function, presence of vegetations, and pericardial effusion. A comparative analysis of cumulative leads dwell time in females and males was also carried out. Cumulative leads dwell time was calculated as the sum of age of the extracted leads.

Efficacy and safety of lead extraction

We analysed radiological and clinical success of TLE in women and in men, and the presence of major and minor complications in both sexes.

Statistical analysis

The statistical analysis was performed using the SAS (tm) software. Continuous variables were expressed as mean ± standard deviation or as median and interquartile range (IQR), using the Mann–Whitney test to compute the *P*-value of women vs. men regiments. Categorical variables were expressed as percentages (without missing values if applicable) and the Fisher's exact test was used to compute the *P*-value. The analysis of relevant factors for major events in man and women was performed with a univariate logistic regression (SAS PROC LOGISTIC), see*Table 5*; only the factors having a *P*-value below 5% entered the multivariate analysis, with a stepwise selection at entry and stay levels of 5%.

Results

The women undergoing TLE were younger than men: 67.0 (IQR 54.0–76.0) vs. 68.0 (IQR 58.0–76.0) years; $P = 0.0425$. They also had lower body mass index (BMI): 25.92 ± 5.34 vs. 26.91 ± 4.49 kg/m^2; $P < 0.0001$ and higher LVEF: 55.0% (IQR 44.0–60.0) vs. 45.0% (IQR 30.0–56.0) and were more likely to be in NYHA Class I–II: 90.11% vs. 86.44; $P < 0.0001$. Men more often had additional diseases: arterial hypertension, diabetes mellitus, renal failure, COPD, and coronary artery disease, and they were more likely to receive antiplatelet agents, also in the periprocedural period. Hypertrophic cardiomyopathy and primary electrical disease were more often observed in women. Moreover, more women had a history of malignancy (*Table 1*).

Men more often received complex devices (ICD, CRT-defibrillator) and underwent generator replacement. Infectious complications were less common in women. In contrast, both pocket infection and systemic infection were more frequent in men, which were associated with a higher number of vegetations and elevated inflammatory parameters. Number of targeted leads was higher in men, whereas women were found to have more non-functional, abandoned leads: 46.0% vs. 34.8%; $P < 0.0001$. Cumulative leads dwell time was similar in both sexes, with a tendency in women towards extracting leads with implant duration of more than 10 years (21.42% vs. 18.79%; $P = 0.0865$). Women more often had tricuspid regurgitation (7.65% vs. 5.23%; $P = 0.0198$) and pericardial effusion (7.91% vs. 4.72%; $P = 0.0018$) before TLE. Venous complications related to the presence of leads were also more common in women: 5.97% vs. 4.33%; $P = 0.0514$ (*Table 2*).

Female sex was associated with a higher rate of procedure-related major complications (2.57% vs. 1.30%; $P = 0.012$). The higher frequency of major complications in women vs. men was mainly due to injury to the heart muscle and large vessels during the procedure, yielding notably lower rates of radiological and clinical success in women. The number of minor complications was similar in both sexes (*Table 3*, *Figure 1*).

The majority of leads extracted in women were pacing leads (84.85% vs. 79.20%; $P < 0.0001$). Defibrillation leads and left ventricular leads were extracted more often in males than in females (46.93% vs. 27.63% and 17.06% vs. 10.21%; $P < 0.0001$) (*Table 4*).

Regarding TLE techniques and approaches, mechanical, non-powered sheaths were more frequently used in women (49.9% vs. 41.73%; $P < 0.0001$), while in men the powered sheaths were more often (32.97% vs. 26.16%; $P < 0.0001$) with a predominance of laser sheaths (23.29% vs. 17.32%; $P < 0.0001$). The majority of patients required dilatation through the subclavian venous entry site, while alternative approaches like femoral or jugular were rarely used with a comparable frequency in women and men.

Significant tricuspid regurgitation and pericardial effusion after TLE were more common in women (7.03% vs. 4.65%; $P = 0.0280$ and 12.62% vs. 7.55%; $P = 0.0002$).

Analysis of procedure-related factors also showed that women more frequently underwent TLE in the cardiac surgery room or hybrid operating room than in an electrophysiology room as compared to men.

In the univariate analysis men and women differed in factors predicting major complications. In men, the clinical factors such as age, lower BMI, arterial hypertension, heart failure, and chronic renal failure were more prevalent. Device infection was another important risk factor for major complications for men. In women, only high levels of creatinine were confirmed as an important predictor of adverse outcomes. Of procedure-related factors, a higher number of previous CIED procedures and more leads with long implant duration in both sexes, and the oldest target lead dwelling time (>10 years) in women were identified as predictors of major complications: OR

Table 1 Clinical characteristics of women and men undergoing TLE

Variables	Women (*N* = 971)	Men (*N* = 2539)	*P*-value
Number, *n* (%)	971 (27.66%)	2539 (72.33%)	
Age (years)			
Mean (SD)	63.29 (17.73)	65.49 (14.69)	
Median (IQR)	67.00 (54.00–76.00)	68.00 (58.00–76.00)	0.0425
Age ≥65 years, *n/N* (%)	541/971 (55.72%)	1513/2539 (59.59%)	0.0387
Race (Caucasian), *n/N* (%)	821/848 (96.82%)	2067/2136 (96.77%)	1.0000
Mean BMI (kg/m^2), *n*	952	2480	
Mean (SD)	25.92 (5.34)	26.91 (4.49)	
Median (IQR)	25.30 (22.45–28.85)	26.30 (24.10–29.40)	<0.0001
LVEF, *n*	913	2389	
Mean (SD)	51.00 (13.11)	43.43 (14.72)	
Median (IQR)	55.00 (44.00–60.00)	45.00 (30.00–56.00)	<0.0001
LVEF ≤35%, *n/N* (%)	162/913 (17.74%)	899/2389 (37.63%)	<0.0001
NYHA Class I and II, *n/N* (%)	875/971 (90.11%)	2149/2539 (84.64%)	<0.0001
NYHA Class III and IV, *n/N* (%)	96/971 (9.89%)	390/2539 (15.36%)	<0.0001
Sinus node disease, *n/N* (%)	282/659 (42.79%)	431/1189 (36.25%)	0.0061
A-V block, *n/N* (%)	344/659 (52.20%)	686/1189 (57.70%)	0.0245
CAD, *n/N* (%)	216/967 (22.34%)	1159/2515 (46.08%)	<0.0001
VHD, *n/N* (%)	159/971 (16.37%)	355/2529 (14.04%)	0.0878
DCM, *n/N* (%)	173/967 (17.89%)	744/2525 (29.47%)	<0.0001
HCM, *n/N* (%)	60/969 (6.19%)	98/2533 (3.87%)	0.0046
CHD, *n/N* (%)	58/971 (5.97%)	68/2530 (2.69%)	<0.0001
Previous sternotomy, *n/N* (%)	125/971 (12.87%)	471/2533 (18.59%)	<0.0001
Primary electrical disease, *n/N* (%)	295/965 (30.57%)	655/2518 (26.01%)	0.0074
Hypertension, *n/N* (%)	502/966 (51.97%)	1386/2512 (55.18%)	0.0945
DM, *n/N* (%)	176/968 (18.18%)	605/2519 (24.02%)	0.0002
Chronic kidney disease, *n/N* (%)	123/967 (12.72%)	490/2526 (19.40%)	<0.0001
COPD, *n/N* (%)	60/968 (6.20%)	237/2515 (9.42%)	0.0022
Malignancy treatment, *n/N* (%)	13/971 (1.34%)	4/2539 (0.16%)	<0.0001
Anticoagulation preoperatively, *n*	971	2539	
Mean (SD)	0.36 (0.48)	0.37 (0.48)	
Median (IQR)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.4265
Antiplatelet therapy preoperatively, *n/N* (%)	262/971 (26.98%)	1151/2539 (45.33%)	<0.0001
ASA, *n/N* (%)	246/971 (25.33%)	1042/2539 (41.04%)	<0.0001
Clopidogrel, *n/N* (%)	27/971 (2.78%)	177/2539 (6.97%)	<0.0001
ASA + Clopidogrel, *n/N* (%)	15/971 (1.54%)	90/2539 (3.54%)	0.0012
Laboratory tests: WBC count, *n*	889	2307	
Mean (SD)	7.71 (2.96)	7.77 (2.90)	
Median (IQR)	7.00 (5.80–8.78)	7.29 (6.00–8.90)	0.0980
Laboratory tests: CRP, *n*	764	1960	
Mean (SD)	16.71 (41.86)	17.96 (43.51)	
Median (IQR)	3.06 [(1.00–10.45)	4.00 (1.04–12.80)	0.0234

ASA, Aspirin; BMI, body mass index; CAD, coronary artery disease; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation; VHD, valvular heart disease; WBC, white blood cell.

4.458 (2.139–9.294); $P < 0.0001$. Moreover, signs and symptoms of venous occlusion identified women at increased risk of adverse outcomes: OR 4.275 (1.674–10.913); $P = 0.0024$, whereas in men it was tricuspid regurgitation before TLE: OR 3.410 (1.564–7.434); $P = 0.0020$, use of powered sheaths: OR 2.593 (1.579–4.259); $P = 0.0002$, and technical problems during TLE: OR 2.152 (1.267–3.655); $P = 0.0046$, notably the use of alternative access techniques: 2.543 (1.273–5.081); $P = 0.0082$ (Supplementary material online, *Table S3*).

In the multivariate analysis signs and symptoms of venous occlusion, cumulative leads dwell time and the number of generator replacements were the main risk factors for major complications in

Table 2 Comparison of CIED, lead characteristics, and procedural indications to TLE between women and men

Variables	Women (*N* = 971)	Men (*N* = 2539)	*P*-value
PM, *n*/*N* (%)	659/971 (67.87%)	1189/2539 (46.83%)	<0.0001
ICD, *n*/*N* (%)	310/971 (31.93%)	1345/2539 (52.97%)	<0.0001
CRT-P, *n*/*N* (%)	34/971 (3.50%)	93/2539 (3.66%)	0.9195
CRT-D, *n*/*N* (%)	98/971 (10.09%)	508/2539 (20.01%)	<0.0001
Number of previous system revisions, *n*	971	2539	
Mean (SD)	1.07 (7.79)	1.71 (10.86)	
Median (IQR)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.0550
Number of generator replacements, *n*	971	2539	
Mean (SD)	1.01 (6.38)	1.41 (8.74)	
median (IQR)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.0053
Infective indications for TLE, *n*/*N* (%)	413/969 (42.62%)	1452/2530 (57.39%)	<0.0001
Local, pocket infection, *n*/*N* (%)	248/969 (25.59%)	922/2530 (36.44%)	<0.0001
Systemic infection, *n*/*N* (%)	160/969 (16.51%)	520/2530 (20.55%)	0.0065
Non-infective indications for TLE, *n*/*N* (%)	558/971 (57.47%)	1087/2539 (42.81%)	<0.0001
Presence of vegetations, *n*/*N* (%)	136/408 (33.33%)	442/1036 (42.66%)	0.0013
Tricuspid valve regurgitation before TLE, *n*/*N* (%)	60/784 (7.65%)	104/1990 (5.23%)	0.0198
Pericardial fluid before TLE, *n*/*N* (%)	62/784 (7.91%)	94/1990 (4.72%)	0.0018
Number of targeted leads, *n*	971	2539	
Mean (SD)	1.71 (0.77)	1.89 (0.90)	
Median (IQR)	2.00 (1.00–2.00)	2.00 (1.00–2.00)	<0.0001
Leads dwell time (months), *n*	965	2522	
Mean (SD)	7.30 (6.35)	6.71 (5.32)	
Median (IQR)	6.00 (3.00–9.00)	6.00 (3.00–9.00)	0.2787
Oldest target lead dwell time >10 years, *n*/*N* (%)	208/971 (21.42%)	477/2539 (18.79%)	0.0865
Cumulative leads dwell time, *n*	964	2521	
Mean (SD)	11.88 (11.97)	11.86 (11.18)	
Median (IQR)	8.00 (4.00–16.00)	8.00 (4.00–16.00)	0.4300
Patients with target ICD lead, *n*/*N* (%)	268/970 (27.63%)	1189/2538 (46.85%)	<0.0001
Presence of non-functional leads, *n*/*N* (%)	447/971 (46.04%)	884/2539 (34.82%)	<0.0001
Presence of thrombosis or venous stenosis, *n*/*N* (%)	54/971 (5.56%)	106/2539 (4.17%)	0.0855
Signs and symptoms of venous occlusion, *n*/*N* (%)	58/971 (5.97%)	110/2539 (4.33%)	0.0514

CIED, cardiac implantable electronic devices; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; PM, pacemaker; SD, standard deviation; TLE, transvenous leads extraction.

women (*Figure 2*, *Table 5*). In men, the number of leads, use of powered sheaths, lower BMI, and high white blood cell count were identified as predictors of adverse outcomes (*Figure 3*, *Table 5*).

Discussion

Several investigations, including preliminary analysis of the ELECTRa Registry show that female sex is an independent predictor of periprocedural complications of TLEs,[9,11–13,17] however, a few studies found no difference in risk of adverse outcomes of TLE in women vs. men.[18,19] This discrepancy can result from differences in the treated population and lead extraction techniques. The present study confirmed that major complications associated with injury to the myocardium and large veins, and tricuspid dysfunction were more common in women. Previous reports have not investigated specific risk factors for TLE in female and male sexes. The current analysis of a large population of the ELECTRa registry (971 women) showed the difference in the factors determining the effectiveness and safety of TLE in women and men. The main risk factors for the complications of TLE in women were: signs and symptoms of venous occlusion, cumulative leads dwell time, and the number of generator replacements. More frequent occurrence of venous occlusion in the female sex together with a large impact of this factor on the risk of TLE confirms earlier hypotheses regarding the reasons of worse effects of procedures in women. According to previous studies, potential causes of increased procedure-related risk in women include lower BMI, small sizes of the vessels, and thinner walls of the myocardium and veins.[20] More vigorous lead ingrowth has also been suggested in women.[21] Venous occlusion is strictly connected with the next risks factors demonstrated in the present study. Lead dwell time is commonly known factor affecting the possibility of complications during TLE.[18,22–25] Similarly, the number of previous generator exchanges

Table 3 Safety and efficacy of TLE in women and men

Variables	Women (*N* = 971)	Men (*N* = 2539)	*P*-value
MAJOR complications related to TLE, *n/N* (%)	25/971 (2.57%)	33/2539 (1.30%)	0.012
Intra procedural MAJOR complications, *n/N* (%)	19/971 (1.96%)	18/2539 (0.71%)	0.0025
Post-procedural MAJOR complication, *n/N* (%)	11/971 (1.13%)	47/2539 (1.85%)	0.1817
MAJOR complication death, *n/N* (%)	11/28 (39.29%)	39/60 (65.00%)	0.0368
Cause of death cardio or vascular, *n/N* (%)	5/971 (0.51%)	23/2539 (0.91%)	0.2940
Cardiac avulsion or tear requiring sternotomy, thoracotomy, pericardiocentesis, chest tube, or surgical repair, *n/N* (%)	15/971 (1.54%)	15/2539 (0.59%)	0.0120
Vascular avulsion or tear, *n/N* (%)	10/971 (1.03%)	11/2539 (0.43%)	0.0500
Pulmonary embolism requiring surgical intervention, *n/N* (%)	0/971 (0.00%)	0/2539 (0.00%)	
Respiratory arrest or anaesthesia related complications leading to prolongation of hospitalization, *n/N* (%)	2/971 (0.21%)	7/2539 (0.28%)	1.0000
Pacing system related infection of a previously non-infected site, *n/N* (%)	0/28 (0.00%)	0/61 (0.00%)	
Stroke, *n/N* (%)	0/28 (0.00%)	4/61 (6.56%)	0.3040
MINOR complications, *n/N* (%)	46/74 (62.16%)	134/192 (69.79%)	0.2447
Intra-procedural MINOR complications, *n/N* (%)	11/971 (1.13%)	24/2539 (0.95%)	0.5751
Post-procedural MINOR complications, *n/N* (%)	11/971 (1.13%)	24/2539 (0.95%)	0.5751
Pericardial effusion not requiring pericardiocentesis or surgical intervention, *n/N* (%)	6/46 (13.04%)	23/128 (17.97%)	0.4988
Hemothorax not requiring a chest tube, *n/N* (%)	0/46 (0.00%)	3/128 (2.34%)	0.5667
Haematoma at the surgical site requiring reoperation for drainage, *n/N* (%)	10/46 (21.74%)	30/128 (23.44%)	1.0000
Arm swelling or thrombosis of implant veins resulting in medical interventions, *n/N* (%)	9/46 (19.57%)	20/128 (15.63%)	0.6448
Vascular repair near the implant site or venous entry site, *n/N* (%)	0/46 (0.00%)	3/128 (2.34%)	0.5667
Haemodynamically significant air embolism, *n/N* (%)	0/46 (0.00%)	0/128 (0.00%)	
Migrated lead fragment without sequelae, *n/N* (%)	1/46 (2.17%)	4/128 (3.13%)	1.0000
Blood transfusion related to blood loss during surgery, *n/N* (%)	10/46 (21.74%)	16/128 (12.50%)	0.1504
Pneumothorax requiring a chest tube, *n/N* (%)	5/46 (10.87%)	7/128 (5.47%)	0.3056
Pulmonary embolism not requiring surgical intervention, *n/N* (%)	6/46 (13.04%)	10/128 (7.81%)	0.3711
Tip of the lead remained, *n/N* (%)	52/970 (5.36%)	110/2538 (4.33%)	0.2079
Fragment of the lead (less than 4 cm remained), *n/N* (%)	25/970 (2.58%)	47/2538 (1.85%)	0.1837
Radiological success of TLE, *n/N* (%)	934/970 (96.29%)	2488/2538 (98.03%)	0.0046
Clinical success of TLE, *n/N* (%)	952/970 (98.14%)	2518/2538 (99.21%)	0.0098

TLE, transvenous leads extraction.

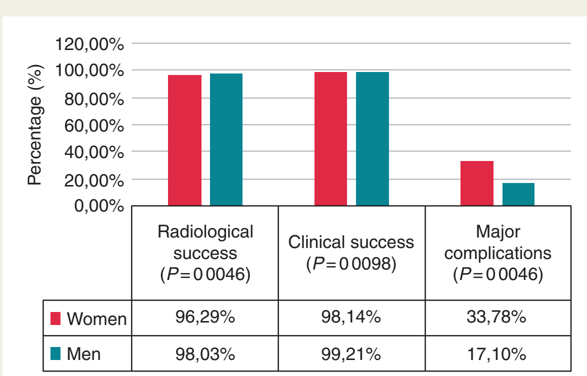

Figure 1 Individual radiological and clinical success and major complications in men and women.

is directly related to the age of the leads. The present findings documenting increased risk associated with cumulative leads dwell time and venous occlusion seem to confirm the concept of the smaller sizes of the vessels with stronger adhesion of the oldest leads to the walls of the thinner veins in females.

Generally, the population of women undergoing TLE is definitely lower than men, ranging from 15% to 39.3% in the available reports,[12,26] being 27.66% in the ELECTRa Registry. Probably, the next reason of worse efficacy of TLE with greater number of periprocedural complications could be a different lead management strategy in female patients with tendency to abandonment of the leads.[2,7] Presence of more non-functional abandoned leads (46.04% vs. 34.82%; $P < 0.001$) together with a tendency for extracting leads that have been implanted for more than 10 years (21.42% vs. 19.79%; $P = 0.0865$) indicates that female patients were referred for TLE at a later time, after choosing first a lead abandonment strategy. For this reason, leads with the longest dwell times (above 10 years) were

Table 4 TLE-procedure and post-procedure information

Variables	Women (*N* = 971)	Men (*N* = 2539)	*P*-value
Total leads removed, *n*	971	2539	
Mean (SD)	1.70 (0.79)	1.88 (0.90)	
Median (IQR)	2.00 (1.00–2.00)	2.00 (1.00–2.00)	<0.0001
Pacing (PM) leads extracted, *n/N* (%)	823/970 (84.85%)	2010/2538 (79.20%)	0.0001
PM atrial leads extracted, *n/N* (%)	577/970 (59.48%)	1542/2538 (60.76%)	0.5118
PM ventricular leads extracted, *n/N* (%)	832/970 (85.77%)	2349/2538 (92.55%)	<0.0001
High voltage (HV) leads extracted, *n/N* (%)	268/970 (27.63%)	1191/2538 (46.93%)	<0.0001
Coronary sinus (CS) leads extracted, *n/N* (%)	99/970 (10.21%)	433/2538 (17.06%)	<0.0001
Total procedure time (min), *n*	946	2457	
Mean (SD)	96.40 (62.71)	96.36 (61.68)	
Median (IQR)	80.00 (55.00–120.00)	83.00 (58.00–120.00)	0.7187
Total fluoroscopic time (min), *n*	933	2368	
Mean (SD)	13.41 (16.17)	13.81 (17.12)	
Median (IQR)	9.00 (4.09–16.00)	9.00 (4.00–17.46)	0.9343
Locking stylets used, *n/N* (%)	688/970 (70.93%)	1863/2538 (73.40%)	0.1496
Sheaths used, *n/N* (%)	363/970 (37.42%)	1107/2538 (43.62%)	0.0009
Mechanical non-powered sheath used, *n/N* (%)	484/970 (49.90%)	1059/2538 (41.73%)	<0.0001
Powered sheath used, *n/N* (%)	254/971 (26.16%)	837/2539 (32.97%)	<0.0001
Laser sheath used, *n/N* (%)	168/970 (17.32%)	591/2538 (23.29%)	0.0001
Evolution® mechanical dilator sheath used, *n/N* (%)	87/970 (8.97%)	245/2538 (9.65%)	0.5621
Electrosurgical dissection sheath used, *n/N* (%)	0/970 (0.00%)	5/2538 (0.20%)	0.3313
Other tools used, *n/N* (%)	4/970 (0.41%)	5/2538 (0.20%)	0.2725
Lead removed with traction alone, *n/N* (%)	309/960 (32.19%)	882/2503 (35.24%)	0.0934
Alternate approach required, *n/N* (%)	57/970 (5.88%)	175/2538 (6.90%)	0.2887
Technical issues during extraction, *n/N* (%)	177/970 (18.25%)	470/2538 (18.52%)	0.8840
TLE in operating room, *n/N* (%)	546/971 (56.23%)	1278/2539 (50.33%)	0.0020
TLE in hybrid room, *n/N* (%)	110/971 (11.33%)	225/2539 (8.86%)	0.0289
Tricuspid valve regurgitation grade III-IV after TLE, *n/N* (%)	44/626 (7.03%)	80/1722 (4.65%)	0.0280
Pericardial fluid after TLE, *n/N* (%)	79/626 (12.62%)	130/1722 (7.55%)	0.0002

IQR, interquartile range; SD, standard deviation; TLE, transvenous leads extraction.

Table 5 Multivariate logistic regression after stepwise algorithm selection—events: major complications in women and men

Covariables	Reference level	Class level	OR	95% CI	*P*-value
Major complications in women					
Number of generator replacements	No	Yes	1.029	1.005–1.054	0.0184
Signs and symptoms of venous occlusion	No	Yes	3.730	1.401–9.934	0.0084
Cumulative leads dwell time	–	–	1.044	1.024–1.065	<0.0001
Major complications in men					
Mean BMI (kg/m^2)	No	Yes	0.891	0.818–0.970	0.0077
Laboratory tests: WBC count	No	Yes	1.178	1.102–1.259	<0.0001
Number of targeted leads	No	Yes	6.053	2.422–15.129	0.0001
Total leads removed	No	Yes	0.287	0.118–0.695	0.0057
Powered sheath used	No	Yes	2.742	1.404–5.355	0.0031

CI, confidence interval; OR, odds ratio; WBC, white blood cell.

found in the female population, and the underlying causes of fewer extraction procedures and related complications were more complex. This theory is confirmed by the strong influence of cumulative leads dwell time on the occurrence of major complications of TLE in women.

The analysis of TLE risk factors in men has demonstrated that in males, the number of leads and use of powered sheaths appeared to increase the risk of developing major complications during or after TLE. Evidence shows that the use of more aggressive extraction techniques, especially laser technique may be the cause of more complications, especially associated with large vessel injury.[18,26] It should be emphasized that the present study demonstrated lower efficacy and more major complications in women despite less frequent use of powered sheaths, extracting fewer leads, and better protection during the procedure under the direct supervision of cardiac surgeons. It means that the impact of sex-specific risk factors is strong and always should be taken into consideration when choosing the appropriate lead management strategy in women.

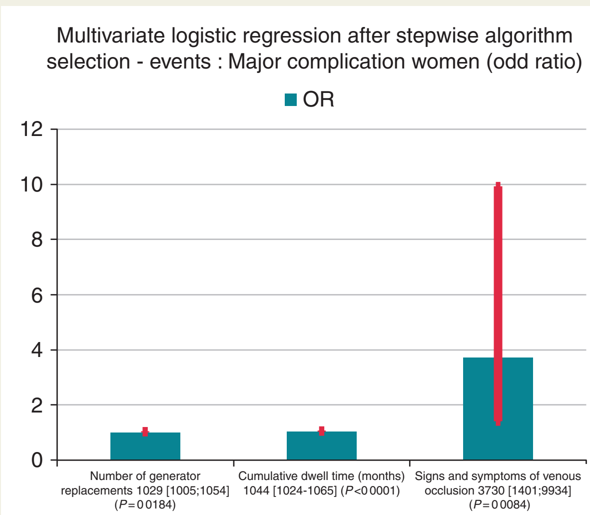

Figure 2 Significant risk factors of major complications in women—multivariate logistic regression.

The risk of TLE in men from the ELECTRa population was also associated with elevated white blood cells counts. The effect of this factor has already been identified in previous reports[10,22] and is related to the severe course of infection The problem of CIED related infections in women and men is complex, because this complications are more likely to occur in the male sex,[8,17,27–31] however, some studies documented worse clinical course of infections in women with more often presence of vegetations and higher mortality of females.[32,33] Furthermore, more frequent infectious indications for TLE in male sex contribute to more effective removal of younger leads in men. Current analysis seems to confirm these considerations.

In summary, the reasons for less effective TLE in women are complex and involve different risk factors for the procedure. Due to worse anatomical conditions (smaller size of the vessels, thinner heart walls) and documented impact of cumulative leads dwell time on the risk of TLE in females, the proper leads management is very important and the procedures in women should be performed in high-volume centres, in the hybrid room and by the most experienced operators.

Limitations

ELECTRa is an international registry whose results are developed *post hoc*, which is associated with some limitations. Despite monitoring the data reliability and database quality control there was a possibility of unknown confounders and bias in management strategy.

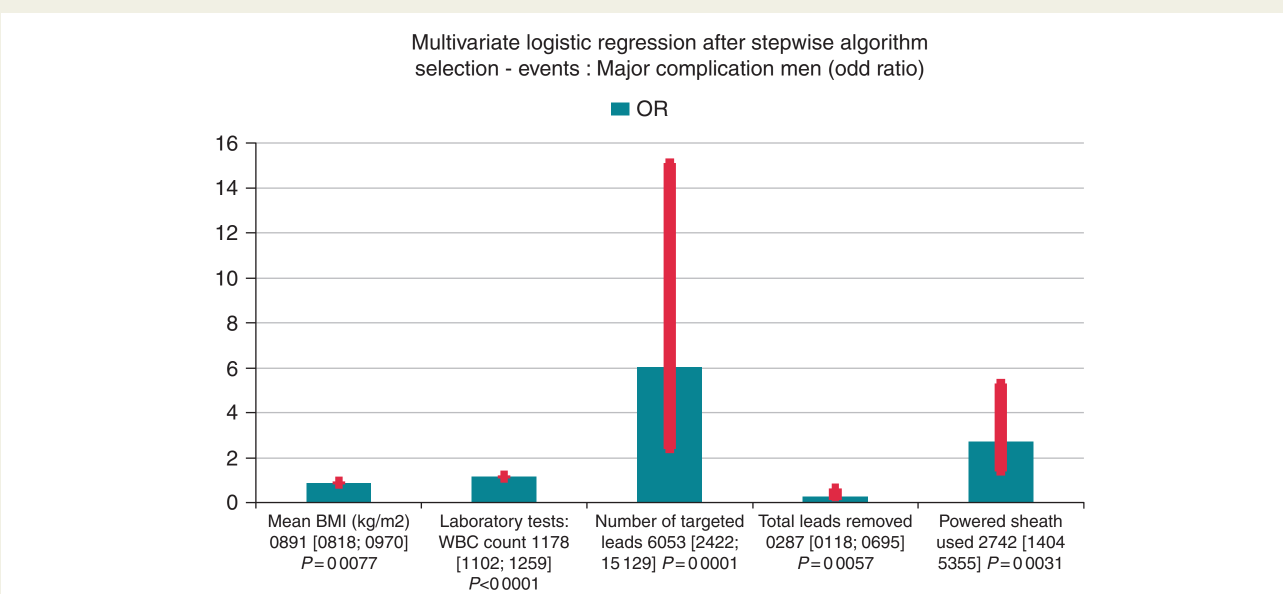

Figure 3 Significant risk factors of major complications in men—multivariate logistic regression.

The data collected in the register concern only patients who have completed the TLE procedure. There is no possibility to compare the patients' data with the indications for TLE in which the procedure was not performed.

Conclusions

The effectiveness of TLE in women was lower than in men, and the risk of complications was associated with other factors in the female and male sex. The main predictors of increased risk of major complications in women are factors influenced on strongly ingrown of the leads to the walls of the veins and myocardium. The initial management strategy with lead abandonment may increase the risk of the later leads extraction in women.

Supplementary material

Supplementary material is available at *Europace* online.

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Appendix 1

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References

1. Raatikainen MJP, Arnar DO, Merkely B, Nielsen JC, Hindricks G, Heidbuchel H. A decade of information on the use of cardiac implantable electronic devices and interventional electrophysiological procedures in the European Society of Cardiology Countries: 2017 report from the European Heart Rhythm Association. *Europace* 2017;**1**:19.
2. Nowak B, Misselwitz B, Erdogan A, Funck R, Irnich W, Israel CW *et al*. Do gender differences exist in pacemaker implantation? Results of an obligatory external quality control program. *Europace* 2010;**12**:210–5.
3. Guha A, Xiang X, Haddad D, Buck B, Gao X, Dunleavy M *et al*. Eleven-year trends of inpatient pacemaker implantation in patients diagnosed with sick sinus syndrome. *J Cardiovasc Electrophysiol* 2017;**28**:933–43.
4. Toff WD, Camm AJ, Skehan JD. Single-chamber versus dual-chamber pacing for high-grade atrioventricular block. *N Engl J Med* 2005;**353**:145–55.
5. Varma N, Mittal S, Prillinger JB, Snell J, Dalal N, Piccini JP. Survival in women versus men following implantation of pacemakers, defibrillators, and cardiac resynchronization therapy devices in a large, nationwide cohort. *J Am Heart Assoc* 2017;**6**:e005031.
6. Linde C, Bongiorni MG, Birgersdotter-Green U, Curtis AB, Deisenhofer I, Furokawa T *et al*. Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society. *Europace* 2018;**20**:1565–1565a.
7. Veerareddy S, Arora N, Caldito G, Reddy PC. Gender differences in selection of pacemakers: a single-center study. *Gend Med* 2007;**4**:367–73.
8. Kirkfeldt RE, Johansen JB, Nohr EA, Jorgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J* 2014;**35**:1186–94.
9. Sood N, Martin DT, Lampert R, Curtis JP, Parzynski C, Clancy J. Incidence and predictors of perioperative complications with transvenous lead extractions: real-world experience with National Cardiovascular Data Registry. *Circ Arrhythm Electrophysiol* 2018;**11**:e004768.
10. Byrd CL, Wilkoff BL, Love CJ, Sellers TD, Reiser C. Clinical study of the laser sheath for lead extraction: the total experience in the United States. *Pacing Clin Electrophysiol* 2002;**25**:804–8.
11. Maytin M, Epstein LM. The challenges of transvenous lead extraction. *Heart* 2011;**97**:425–34.
12. Kutarski A, Czajkowski M, Pietura R, Obszanski B, Polewczyk A, Jachec W *et al*. Effectiveness, safety, and long-term outcomes of non-powered mechanical sheaths for transvenous lead extraction. *Europace* 2017;**8**:1324–33.
13. Bongiorni MG, Kennergren C, Butter C, Deharo JC, Kutarski A, Rinaldi CA *et al*. The European Lead Extraction ConTRolled (ELECTRa) study: a European Heart Rhythm Association (EHRA) Registry of transvenous lead extraction outcomes. *Eur Heart J* 2017;**38**:2995–3005.
14. Bongiorni MG, Romano SL, Kennergren BC, Deharo JC, Kutarsky A, Rinaldi CA *et al*. ELECTRa (European Lead Extraction ConTRolled) Registry—shedding light on transvenous lead extraction real-world practice in Europe. *Herzschrittmacherther Elektrophysiol* 2013;**24**:171–5.
15. Kusumoto FM, Schoenfeld MH, Wilkoff BL, Berul CI, Birgersdotter-Green UM, Carrillo R *et al*. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. *Heart Rhythm* 2017;**14**:e503–51.
16. Bongiorni MG, Burri H, Deharo JC, Stark C, Kennergren C, Saghy L *et al*. 2018 EHRA expert consensus statement on lead extraction: recommendations on definitions, endpoints, research trial design, and data collection requirements for clinical scientific studies and registries: endorsed by APHRS/HRS/LAHRS. *Europace* 2018;**20**:1217.
17. Johansen JB, Jørgensen OD, Møller M, Arnsbo P, Mortensen PT, Nielsen JC. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. *Eur Heart J* 2011;**32**:991–8.

18. Brunner MP, Cronin EM, Duarte VE, Yu C, Tarakji KG, Martin DO *et al*. Clinical predictors of adverse patient outcomes in an experience of more than 5000 chronic endovascular pacemaker and defibrillator lead extractions. *Heart Rhythm* 2014;**11**:799–805.
19. Jones SO 4th, Eckart RE, Albert CM, Epstein LM. Large, single-center, single-operator experience with transvenous lead extraction: outcomes and changing indications. *Heart Rhythm* 2008;**5**:520–5.
20. Deharo JC, Bongiorni MG, Rozkovec A, Bracke F, Defaye P, Fernandez-Lozano I *et al*. Pathways for training and accreditation for transvenous lead extraction: a European Heart Rhythm Association position paper. *Europace* 2012; **14**:124–34.
21. Novak M, Dvorak P, Kamaryt P, Slana B, Lipoldova J. Autopsy and clinical context in deceased patients with implanted pacemakers and defibrillators: intracardiac findings near their leads and electrodes. *Europace* 2009;**11**:1510–6.
22. Agarwal SK, Kamireddy S, Nemec JAN, Voigt A, Saba S. Predictors of complications of endovascular chronic lead extractions from pacemakers and defibrillators: a single-operator experience. *J Cardiovasc Electrophysiol* 2009;**20**:171–5.
23. Wazni O, Epstein LM, Carrillo RG, Love C, Adler SW, Riggio DW *et al*. Lead extraction in the contemporary setting: the LExICon study: an observational retrospective study of consecutive laser lead extractions. *J Am Coll Cardiol* 2010;**55**: 579–86.
24. Brunner MP, Cronin EM, Wazni O, Baranowski B, Saliba WI, Sabik JF *et al*. Outcomes of patients requiring emergent surgical or endovascular intervention for catastrophic complications during transvenous lead extraction. *Heart Rhythm* 2014;**11**:419–25.
25. Jacheć W, Polewczyk A, Polewczyk M, Tomasik A, Janion M, Kutarski A. Risk factors predicting complications of transvenous lead extraction. *Biomed Res Int* 2018;**2018**:8796704.
26. Segreti L, Di Cori A, Soldati E, Zucchelli G, Viani S, Paperini L *et al*. Major predictors of fibrous adherences in transvenous implantable cardioverter-defibrillator lead extraction. *Heart Rhythm* 2014;**12**:2196–201.
27. Nery PB, Fernandes R, Nair GM, Sumner GL, Ribas CS, Menon SM *et al*. Device-related infection among patients with pacemakers and implantable defibrillators: incidence, risk factors, and consequences. *J Cardiovasc Electrophysiol* 2010;**21**:786–90.
28. Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N *et al*. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation* 2007;**116**:1349–55.
29. Catanchin A, Murdock CJ, Athan E. Pacemaker infections: a 10-year experience. *Heart Lung Circ* 2007;**16**:434–9.
30. Cohen B, Choi YJ, Hyman S, Furuya EY, Neidell M, Larson E. Gender differences in risk of bloodstream and surgical site infections. *J Gen Intern Med* 2013;**28**:1318–25.
31. Olsen T, Jørgensen OD, Nielsen JC, Thøgersen AM, Philbert BT, Johansen JB. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982-2018). *Eur Heart J* 2019;**40**:1862–9.
32. Sohail MR, Henrikson CA, Braid-Forbes MJ, Forbes KF, Lerner DJ. Comparison of mortality in women versus men with infections involving cardiovascular implantable electronic device. *Am J Cardiol* 2013;**112**:1403–9.
33. Polewczyk A, Jachec W, Tomaszewski A, Brzozowski W, Czajkowski M, Polewczyk AM *et al*. Lead-related infective endocarditis: factors influencing the formation of large vegetations. *Europace* 2017;**19**:1022–30.