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Clinical impact of antithrombotic therapy in transvenous lead extraction complications: a sub-analysis from the ESC-EORP EHRA ELECTRa (European Lead Extraction ConTRolled) Registry

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Aims A sub-analysis of the ESC-EHRA European Lead Extraction ConTRolled (ELECTRa) Registry to evaluate the clinical impact of antithrombotic (AT) on transvenous lead extraction (TLE) safety and efficacy.

Methods and results ELECTRa outcomes were compared between patients without AT therapy (No AT Group) and with different pre-operative AT regimens, including antiplatelets (AP), anticoagulants (AC), or both (AP + AC). Out of 3510 pts, 2398 (68%) were under AT pre-operatively. AT patients were older with more comorbidities ($P < 0.0001$). AT subgroups, defined as AP, AC, or AP + AC, were 1096 (31.2%), 985 (28%), and 317 (9%), respectively. Regarding AP patients, 1413 (40%) were under AP, 1292 (91%) with a single AP, interrupted in 26% about 3.8 ± 3.7 days before TLE. In total, 1302 (37%) patients were under AC, 881 vitamin K antagonist (68%), 221 (17%) direct oral anticoagulants, 155 (12%) low weight molecular heparin, and 45 (3.5%) unfractionated heparin. AC was 'interrupted without bridging' in 696 (54%) and 'interrupted with bridging' in 504 (39%) about 3.3 ± 2.3 days before TLE, and 'continued' in 87 (7%). TLE success rate was high in all subgroups. Only overall in-hospital death (1.4%), but not the procedure-related one, was higher in the AT subgroups ($P = 0.0500$). Age >65 years and New York Heart Association Class III/IV, but not AT regimens, were independent predictors of death for any cause. Haematomas were more frequent in AT subgroups, especially in AC 'continued' ($P = 0.025$), whereas pulmonary embolism in the No-AT ($P < 0.01$).

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† A complete list of the ELECTRa Investigators is provided in the Supplementary material online, *Appendix S1*.

Conclusions AT minimization is safe in patients undergoing TLE. AT does not seem to predict death but identifies a subset of fragile patients with a worse in-hospital TLE outcome.

Keywords Transvenous lead extraction • Antithrombotic therapy • ELECTRa Registry

What's new?

- Management of antithrombotic (AT) therapy in the case of transvenous lead extraction (TLE) appears to be even more controversial, given the scanty availability of data.
- The ESC-EHRA European Lead Extraction ConTRolled (ELECTRa) Registry is a large multicentre study which evaluated the safety and efficacy of TLE in Europe.
- The aim of our sub-analysis was to evaluate the impact of AT on in-hospital complications and mortality in patients undergoing TLE in the ESC-EHRA ELECTRa Registry.
- Our analysis demonstrates, for the first time, that patients under chronic AT show a high TLE success rate, but with a higher overall mortality and more minor bleeding events compared to no ATs, especially in case of 'continued' anticoagulation.
- AT minimization is safe in patients undergoing TLE.
- AT does not seem to predict death but identifies a subset of fragile patients with a worse in-hospital TLE outcome.

Introduction

The complexity of candidates for transvenous lead extraction (TLE) has shown a parallel increase, both in terms of comorbidities, and of concomitant therapy, including antithrombotic (AT) therapy. Current data indicate that 50% of patients with pacemakers (PMs) and implantable cardiac defibrillators (ICDs) use single or dual antiplatelets,[1–3] and the rate of use of anticoagulant therapy ranges from 15% to 35%,[1,2] reaching almost 50% in patients with cardiac resynchronization therapies (CRTs).[3]

The management of candidates for low-risk cardiac implantable electronic device (CIED) procedures, like implantation or replacement, receiving concomitant AT is a debated issue, and only marginally the object of evidence-based recommendations in current guidelines.[4,5] Nevertheless, the management of AT in TLE procedures appears to be even more controversial, given the scanty availability of data.[6]

The ESC-EHRA European Lead Extraction ConTRolled (ELECTRa) Registry is a prospective registry of consecutive TLE procedures conducted by the European Heart Rhythm Association (EHRA) in order to identify the safety and efficacy of the current practice of TLE.[7]

The present study is a sub-analysis of the ESC-EHRA ELECTRa Registry conducted with the aim of evaluating the clinical impact of AT on TLE safety and efficacy.

Methods

For this study, we used individual patients' data from the ESC-EHRA ELECTRa Registry.[7] The ELECTRa Registry included 73 centres from 19 European countries that enrolled 3555 consecutive patients, of whom 3510 underwent TLE. 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 EHRA Scientific Initiatives Committee (SIC). All EHRA affiliated centres in Europe performing TLE (irrespective of volume) were identified and invited to participate by EHRA and the regional coordinators. Participating centres were required to recruit all consecutive patients with an indication for TLE (excluding those patients primarily requiring surgical extraction) in their institution. No specific protocol or recommendations regarding technique were made for the TLE procedure. Data were prospectively collected using a secure web-based database system. Dedicated data monitors were used to ensure the integrity of the data and to ensure that all consecutive patients were included. The study design comprised a baseline visit at the time of admission for TLE and at the time of hospital discharge and a clinical evaluation at 1-year follow-up. In this investigation, we only included patients with data from both the baseline and the pre-discharge follow-up visit. A detailed description of the study design and of the electronic case report form has been previously described.[8]

Definitions and endpoints

Study subgroups

For the purpose of this study, we specifically performed a population sub-analysis focused on the AT therapy. According to the AT therapy assumed before TLE, four groups were identified:

(1) No-AT Group: no AP or AC therapy.
(2) AP Group: at least 1 AP drug, from Aspirin, Clopidogrel, Prasugrel, and Ticagrelor.
(3) AC Group: at least 1 AC drug, from warfarin, low weight molecular heparin (LWMH), unfractionated heparin (UFH), and direct oral anticoagulants (DOAC).
(4) AP/AC Group: a combination of at least one AP and one AC.

According to the study design, AT management before a TLE procedure was at the discretion of Operators. In the database, AP or AC interruption, related interruption timing and eventual AC bridging should be clearly indicated. AC patients were further analysed according to the pre-procedural management strategy, as 'interrupted with bridging', 'interrupted without bridging', and 'continued'.

Definitions

Definitions published in the guidance documents by HRS[6,9] and by EHRA[10] were used to define procedural approaches, techniques, and outcomes. Transvenous lead extraction safety and efficacy were calculated by evaluating the rate of procedure-related complications (major and minor) and success/failure (radiological and clinical).

- *Major complications* were defined as those related to the procedure that were life-threatening or resulted in death, or any unexpected event that caused persistent or significant disability, or any event that required significant surgical intervention to prevent any major outcomes[6,9]
- *Minor complications* were defined as any undesired event related to the procedure that required medical intervention or minor procedural intervention to remedy, and did not limit persistently or significantly the patient's function; nor did it threaten life or cause death.
- *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.
- *Post-procedural complications* were defined as any other such event occurring after the procedure until patient discharge. All-cause in-hospital major complications including deaths were all major complications including deaths, irrespective of their classified relation to the procedure.[7]

Endpoints

The *primary endpoint* was major complications and deaths observed during the hospitalization, in the non-AT and AT subgroups. Predictors of major complications were also evaluated. *Secondary endpoints* included procedural success rates of TLE among non-AT and AT groups, as well as baseline patient and lead characteristics, indications for TLE, techniques, and tools used.

Statistical analysis

Univariate analysis was applied to both continuous and categorical variables. Results were summarized by AT therapy (No-AT vs. AP vs. AC vs. AP/AC). Continuous variables were reported as mean ± standard deviation (SD) or as median and interquartile range (IQR). Among-group comparisons were made using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages (without missing values if applicable). Among-group comparisons were made using a χ^2 test or the Fisher's exact test (if any expected cell count was <5). A stepwise multiple Cox regression was used to determine the predictors of intra- and post-procedural major related complications (Model A) and all-cause mortality (Model B) including in the models all the candidate variables (variables with $P < 0.05$ in univariate, except those with a high number of missing data, and variables considered of relevant clinical interest). No interaction was tested. A two-sided *P*-value of 0.05 was considered as statistically significant. All the analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

From 1 November 2012 to 31 May 2014, 116 European centres across all regions of the European continent were invited to participate, of which 73 from 19 countries participated in the study. A total of 3555 consecutive patients were enrolled and 3510 (98.7%) underwent TLE.

Patient material

Among 3510 patients, 1112 (32%) were No-AT and 2398 (68%) were AT patients. Particularly, the number of AT patients, defined as AP, AC, or AP + AC, was 1096 (31.2%), 985 (28%), and 317 (9%), respectively. The overall cohort was 72.2% male, with a mean age of 64.8 ± 15.6 years. Comorbidities present were as follows: hypertension 54%, coronary artery disease 40%, primary electrical disease 27%, dilated cardiomyopathy 26%, diabetes 22%, chronic kidney disease 18%, and COPD 9%. Baseline characteristics were significantly different among groups (*Table 1*).

In particularly, AT patient subgroups (AP, AC, and AP + AC) were significantly older, with a higher prevalence of cardiac disease, heart failure, and comorbidities, as shown in *Table 1*.

Regarding AP, 1413 (40%) patients were under AP, 1292 (91%) with a single AP and 121 (9%) with a dual AP therapy. Among AP patients, 1288 (91%) were under acetyl salicylic acid, 204 (14%) under Clopidogrel, 12 (0.8%) under Prasugrel, and 7 (0.5%) under Ticagrelor. Antiplatelet was 'continued' in 1042 (74%) and 'interrupted' in 371 (26%) pts about 3.8 ± 3.7 days before the procedure (*Figure 1*).

Regarding AC, 1302 (37%) patients were under AC. Among AC patients, 881 were under vitamin K antagonist (68%), 221 (17%) under DOAC, 155 (12%) under LWMH, and 45 (3.5%) under UFH. AC pre-procedural management strategy included 'interruption without bridging' in 696 (54%), 'interruption with bridging' in 504 (39%) and a 'continued' strategy in 87 (7%) (*Figure 1*). AC was interrupted about 3.3 ± 2.3 days before TLE. The last dose of LWMH was usually administered the night before.

Patient demographics are shown in *Table 1*.

Cardiac implantable electronic device data and procedural data

Regarding devices, 52.9% of patients had a PM and 47.1% an ICD. A CRT device was found in 20.6% of patients. AT subgroups (AP, AC, and AP + AC) showed a high prevalence of CRT-D devices ($P < 0.0001$). Regarding procedural indications, in the overall population infection was the most frequent indication (53%). Infection and thrombosis were statistically more frequent in the AT subgroups ($P = 0.0005$ and $P = 0.0096$, respectively), whereas chronic pain and recalled leads were more frequent in the No-AT group ($P = 0.0354$ and $P = 0.0002$, respectively). Cardiac implantable electronic device characteristics and TLE indications are reported in *Table 2*.

Regarding TLE technique and approaches, locking stylets were frequently used (67%). Manual traction was effective in removing 27.3% of total leads and was more effective in the AT subgroups (25% vs. 28% vs. 28% vs. 32%, for No-AT, AP, AC, and AP/AC, respectively, $P = 0.0077$). Dilatation was required in 63% of leads and included mechanical not powered (36%), mechanical rotational (8%), and laser

Table 1 Comparison of baseline characteristics between patients not treated with AT, treated with AP, with AC and both AP + AC

Variable	Total (*N* = 3510)	No AT (*N* = 1112)	AP (*N* = 1096)	AC (*N* = 985)	AP + AC (*N* = 317)	*P*-value
Characteristics, *n*/*N* (%)						
Age (years)	64.9 ± 15.6	58.7 ± 19.5	68.3 ± 11.4	68.9 ± 12.3	68.9 ± 11.0	<0.0001
Male gender	2539/3510 (72)	704/1112 (63)	883/1096 (81)	684/985 (69)	268/317 (85)	<0.0001
BMI (kg/m^2), mean ± SD	26.6 ± 4.8)	25.6 ± 4.5	27.4 ± 4.8	27.0 ± 4.8	26.7 ± 4.8	<0.0001
Comorbidities, *n*/*N* (%)						
Hypertension	1888/3478 (54)	387/1107 (35)	711/1081 (66)	584/976 (60)	206/314 (66)	<0.0001
Coronary artery disease	1375/3482 (40)	152/1104 (14)	658/1088 (61)	320/974 (33)	245/316 (78)	<0.0001
Primary electrical disease	950/3483 (27)	411/1102 (37)	240/1088 (22)	243/978 (25)	56/315 (18)	<0.0001
Dilated cardiomyopathy	917/3492 (26)	197/1109 (18)	320/1090 (29)	297/977 (30)	103/316 (33)	<0.0001
Hypertrophic cardiomyopathy	158/3502 (5)	70/1109 (6)	27/1094 (3)	50/983 (5)	11/316 (4)	0.0001
Valvular heart disease	514/3500 (15)	75/1109 (6.8)	98/1093 (9)	266/981 (27)	75/317 (24)	<0.0001
Chronic heart failure	1557/3488 (45)	243/1103 (22)	584/1090 (54)	528/979 (54)	202/316 (64)	<0.0001
NYHA, Class III/IV	486/3472 (14)	72/1101 (6)	147/1086 (13)	188/975 (19)	79/310 (25)	<0.0001
LVEF (%), mean ± SD	45.5 ± 14.7	52.5 ± 12.9	42.9 ± 14.2	43.4 ± 14.2	38.3 ± 14.1	<0.0001
Diabetes mellitus	781/3487 (22)	156/1108 (14)	285/1084 (26)	233/980 (24)	107/315 (34)	<0.0001
Chronic kidney disease	613/3493 (18)	89/1108 (8)	219/1086 (20)	221/983 (22)	84/316 (27)	<0.0001
COPD	297/3483 (9)	54/1108 (5)	104/1080 (10)	100/980 (10)	39/315 (12)	<0.0001
Medical therapy, *n*/*N* (%)						
Antipatelets						
ASA	1288/1413 (91)	NA	1004/1096 (92)	NA	284/317 (90)	0.2656
Clopidogrel	204/1413 (14)	NA	153/1096 (14)	NA	51/317 (16)	0.3423
Prasugrel	12/1413 (0.85)	NA	10/1096 (0.91)	NA	2/317 (0.63)	0.6305
Ticagrelor	7/1413 (0.50)	NA	6/1096 (0.55)	NA	1/317 (0.32)	0.6043
Dual antiplatelets	121/1413 (8.5)	NA	97/1096 (8.8)	NA	24/317 (7.56)	0.5137
Antiplatelets interruption	371/1413 (26)	NA	290/1096 (27)	NA	81/317 (26)	0.7463
Interruption of AP (days)	3.8 ± 3.7	NA	3.9 ± 3.7	NA	3.7 ± 3.7	0.6383
Anticoagulants						
Treatments						0.0028
VKA	881/1302 (68)	NA	NA	690/985 (70)	191/317 (60)	
LMWH	155/1302 (12)	NA	NA	103/985 (11)	52/317 (16)	
UFH	45/1302 (4)	NA	NA	29/985 (3)	16/317 (5)	
DOAC	221/1302 (17)	NA	NA	163/985 (17)	58/317 (18)	
Interruption						0.8493
Interrupted AC without bridging	696/1287 (54)	NA	NA	523/985 (53.1)	173/317 (54.6)	
Interrupted AC with bridging	504/1287 (39)	NA	NA	385/985 (39)	119/317 (37.5)	
Continued AC	87/1287 (7)	NA	NA	67/985 (6.8)	20/317 (6.3)	
Interruption of AC (days)	3.3 ± 2.3	NA	NA	3.3 ± 2.2	3.28 ± 2.6	0.4890
Other therapy						
Antibiotics	1587/3510 (45)	459/1112 (41)	474/1096 (43)	493/985 (50)	161/317 (51)	<0.0001
Digoxin	277/2842 (10)	35/617 (6)	47/1000 (5)	156/920 (17)	39/305 (13)	<0.0001
Diuretics	1648/2842 (58)	246/617 (40)	574/1000 (57)	615/920 (67)	213/305 (70)	<0.0001
Ace/ATII-inhibitors	1981/2842 (70)	364/617 (59)	781/1000 (78)	628/920 (68)	208/305 (68)	<0.0001
Calcium antagonists	360/2842 (13)	68/617 (11)	147/1000 (15)	108/920 (12)	37/305 (12)	0.1095

Patients characteristics were calculated on the population of 3555 consecutive patients enrolled. Leads characteristics were calculated on the population of 3510 consecutive patients enrolled who underwent the intervention (TLE). In the calculations all values unknown were excluded.

AC, anticoagulants; AP, antiplatelets; ASA, acetyl salicylic acid; AT, antithrombotic; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; LVEF, left ventricular ejection fraction; LWMH, low molecular weight heparin; NYHA, New York Heart Association; UFH, unfractionated heparin; VKA, vitamin K antagonists.

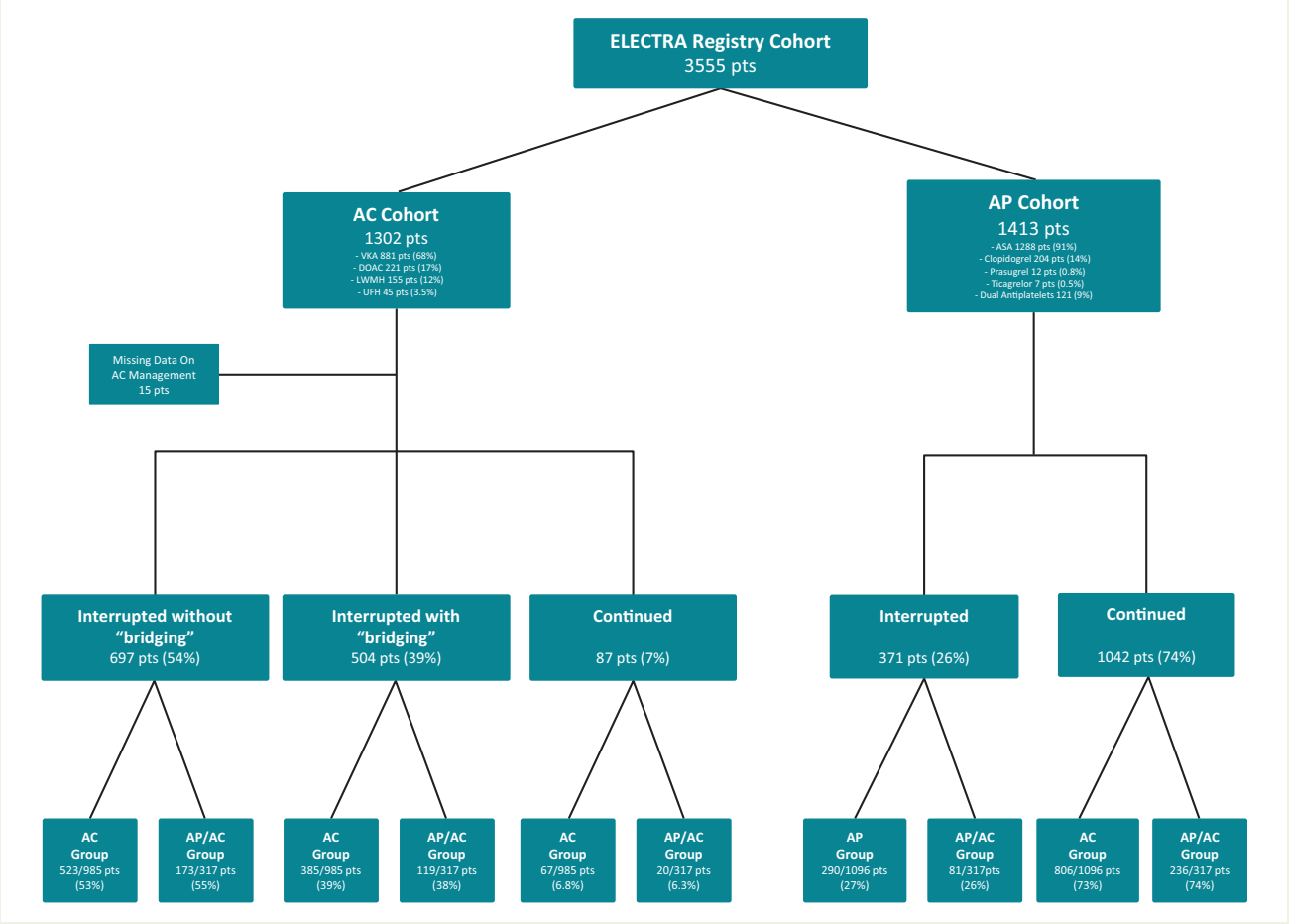

Figure 1 ELECTRa registry patient flow diagram presenting the proportion of patients of the total enrolled patient cohort of the registry under chronic anticoagulation (AC) and antiplatelet (AP) therapy. Details are provided on the AC and AP agent chronically prescribed as well as the pre-operative strategies. ASA, acetyl salicylic acid; DOAC, direct oral anticoagulants; LMWH, low-molecular weight heparin; VKA, vitamin K antagonist.

sheath (19%). Mechanical not powered and mechanical rotational sheaths were more frequently used in the No-AT patients ($P < 0.0001$), while no differences were observed in the use of laser sheaths ($P = 0.3547$) among groups. The majority of patients in all groups required dilatation through the subclavian venous entry site, while alternative approaches like femoral (4.7%) or jugular (5.4%) were rarely used, without differences among groups ($P = 0.2483$).

Regarding leads extracted, 75.7% were PM leads and 24.3% ICD leads. Leads extracted were ventricular (55%), atrial (34%), and LV (8.4%). Among groups, the majority of leads extracted in the No-AT group were pacing leads, while ICD and LV ventricular leads were mainly removed in the AT subgroups ($P < 0.0001$). The average implantation time was 6.4 ± 5.4 years and was statistically significantly different between groups, with a longer implantation time in the No-AT group ($P < 0.0001$).

Procedural data are shown in *Table 3*.

Procedural outcomes

The radiological procedural success rate was 96%, and was a bit higher in the AT subgroups (94% vs. 97% vs. 96% vs. 98%, for No-AT, AP, AC, and AP/AC, respectively, $P < 0.0001$). Regarding *major complications*, the overall incidence (2.7%) was not statistically different among groups (*Figure 2*). Nevertheless, the incidence of in-hospital death for any cause was 1.4% and resulted statistically higher in the AT subgroups (0.7% vs. 1.5% vs. 1.8% vs. 2.5%, for No-AT, AP, AC, and AP/AC, respectively, $P = 0.0500$), while no statistically significant differences in procedure-related death were observed among groups (0.3% vs. 0.6% vs. 0.6% vs. 0.6%, for No-AT, AP, AC, and AP/AC, respectively, $P = 0.0656$) (*Figure 3*).

Regarding *minor complications*, the overall incidence (5%) was not statistically different among groups (*Figure 2*). Of note, the sub-analysis showed a statistically significant difference in the occurrence of haematoma requiring reintervention, which were more frequent in the AT subgroups (0.5% vs. 1% vs. 1.8% vs. 1.9%, for No-AT, AP, AC, and AP/AC, respectively, $P = 0.0140$), and of pulmonary embolism not requiring surgery, which was more often observed in the No-AT group (1% vs. 0.1% vs. 0.2% vs. 0.6%, for No-AT, AP, AC, and AP/AC, respectively, $P = 0.0081$) (*Figure 4*).

At the sub-analysis of AC patients according to the pre-procedural AC management strategy, no differences were observed in terms of

Table 2 Comparison of CIED, lead characteristics, and procedural indications between patients not treated with AT, treated with AP, with AC, and both AP + AC

Variable	Total (*N* = 3510)	No AT (*N* = 1112)	AP (*N* = 1096)	AC (*N* = 985)	AP + AC (*N* = 317)	*P*-value
Device type, *n*/*N* (%)						
CRT-pacemaker	127/3510 (3.6)	37/1112 (3.3)	32/1096 (2.9)	47/985 (4.8)	11/317 (3.5)	0.1339
CRT-defibrillator	607/3510 (17)	104/1112 (9.3)	233/1096 (21)	189/985 (19)	81/317 (26)	<0.0001
Lead type extracted, *n*/*N* (%)[a]						
PM	4584/6493 (71)	1547/1987 (78)	1339/2056 (65)	1322/1843 (72)	376/607 (62)	<0.0001
ICD	1576/6493 (24)	388/1987 (20)	613/2056 (30)	392/1843 (21)	183/607 (30)	
LV	333/6493 (5)	52/1987 (3)	104/2056 (5)	129/1843 (7)	48/607 (8)	
Lead extracted tip location, *n*/*N* (%)[a]						
Right atrium	2219/6493 (34)	708/1987 (36)	707/2056 (34)	598/1843 (32)	206/607 (34)	<0.0001
Right ventricle	3587/6493 (55)	1125/1987 (57)	1130/2056 (55)	1016/1843 (55)	316/607 (52)	
Coronary sinus	547/6493 (8)	89/1987 (5)	185/2056 (9)	197/1843 (11)	76/607 (13)	
Other	140/6493 (2)	65/1987 (3)	34/2056 (2)	32/1843 (2)	9/607 (2)	
Lead dwelling time (years)	6.4 ± 5.4	7.2 ± 5.8	5.8 ± 5.1	6.6 ± 5.5	5.3 ± 4.4	
Indication for TLE, *n*/*N* (%)						
Infections	1865/3499 (53)	550/1110 (50)	570/1092 (52)	553/981 (56)	192/316 (61)	0.0005
Chronic pain	180/3510 (5.1)	74/1112 (6.7)	53/1096 (4.9)	41/985 (4.2)	12/317 (3.8)	0.0354
Thrombosis or venous stenosis	160/3510 (4.6)	34/1112 (3.1)	49/1096 (4.5)	57/985 (5.8)	20/317 (6.3)	0.0096
Functional leads	2023/3510 (58)	620/1112 (56)	634/1096 (58)	593/985 (60)	176/317 (56)	0.1815
Non-functional leads	1331/3510 (38)	448/1112 (40)	443/1096 (40)	341/985 (35)	99/317 (31)	0.0010
Recalled leads (updated)	440/3510 (13)	139/1112 (13)	173/1096 (16)	94/985 (10)	34/317 (11)	0.0002
Upgrading indication	248/3510 (7)	43/1112 (4)	78/1096 (7)	98/985 (10)	29/317 (9)	<0.0001
MRI indication	26/3510 (0.7)	15/1112 (1.3)	6/1096 (0.5)	4/985 (0.4)	1/317 (0.3)	0.0378
Other	54/3510 (1.5)	22/1112 (2.0)	10/1096 (0.9)	16/985 (1.6)	6/317 (1.9)	0.2063
Previous attempt of lead extraction	171/3510 (5)	67/1112 (6)	48/1096 (4)	42/985 (4)	14/317 (4)	0.1957

AC, anticoagulants; AP, antiplatelets; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; MRI, magnetic resonance imaging; PM, pacemaker; TLE, transvenous lead extraction.
[a]Data are expressed per leads.

major complications, including death. Only AC 'continued' showed a more frequent pocket haematoma requiring reintervention (4.6%, $P = 0.0253$).

Procedural outcomes are shown in *Table 3*.

Predictors of transvenous lead extraction complications

Predictors of overall major and minor complications were also investigated. Several clinical and procedural variables were tested in the analysis, including AT regimen type (No-AT, AP, AC, and AP/AC) and AC management (interruption < or > 3 days, with or without bridging). Low (<30 TLE procedures/year) volume centre [hazard ratio (HR) 2.56, 95% confidence interval (CI) 1.16–5.5; $P = 0.02$], lead implantation time > 5 years (HR 2.69, 95% CI 1.14–6.37, $P = 0.02$), and use of laser sheath (HR 2.64, 95% CI 1.29–5.59, $P = 0.01$) resulted independent predictors of overall in-hospital complications in the uni- and multi-variate analyses. Regarding in-hospital death for any cause, only age >65 years (HR 2.85, 95% CI 1.16–7.14; $P = 0.02$) and New York Heart Association (NYHA) Class III/IV (NYHA III: HR 2.82, 95% CI 1.16–6.82; $P = 0.02$; NYHA IV: HR 6.59, 95% CI 1.78–24.46; $P > 0.005$) were independent predictors in the uni- and multivariate analyses.

Discussion

Although, PM or ICD implantation are classified as interventions with low bleeding risk,[11,12] lead extraction differs significantly from other CIED procedures and peri-procedural management of AT therapy in candidates for TLE deserves separate discussion.

Data from registries and RCTs document a cumulative rate of complications >10%. Although rare (2%), major complications are mainly represented by haemorrhagic events from direct and/or indirect trauma on the vascular and cardiac wall, such as venous laceration, cardiac perforation, tamponade, and haemothorax, which can be fatal in 0.3–0.7% of cases.[13–18] Similar data were confirmed in the ELECTRa Registry.[7] Our sub-analysis showed that, AT subgroups, (AP, AC, AP/AC) had an high success rate, also higher than No-AT (97% vs. 96% vs. 98% vs. 94% respectively, $P < 0.0001$). With the prevalent AT management observed in the registry (i.e. AP continued in 74% and AC interrupted in 93% of patients about 3 days before TLE) complication rate was low, with a non-statistically different incidence of overall major (2.7% vs. 2.6% vs. 2.6% vs. 3.5% for No-AT, AP, AC, and AP/AC, respectively, $P = 0.845$) and minor events (4.5% vs. 4.8% vs. 5.4% vs. 5.7% for No-AT, AP, AC, and AP/AC, respectively, $P = 0.738$), even if a negative trend cannot be completely

Table 3 TLE outcomes: technique, success and complications between patients not treated with AT, treated with AP, with AC, and both AP + AC

Variables	Total (*N* = 3510)	No AT (*N* = 1112)	AP (*N* = 1096)	AC (*N* = 985)	AP + AC (*N* = 317)	*P*-value
TLE technique, *n*/*N* (%)[a]						
Locking stylets	4360/6493 (67.15)	1403/1987 (70.61)	1335/2056 (64.93)	1245/1843 (67.55)	377/607 (62.11)	<0.0001
Lead removed with traction alone	1741/6376 (27)	479/1925 (25)	574/2036 (28)	498/1812 (28)	190/603 (32)	0.0077
Sheaths used, *n*/*N* (%)[a]						
Mechanical not powered sheaths	2359/6492 (36)	721/1986 (36)	796/2056 (39)	669/1843 (36)	173/607 (29)	<0.0001
Mechanical rotational sheaths	500/6492 (8)	254/1986 (13)	111/2056 (5)	106/1843 (6)	29/607 (5)	<0.0001
Laser sheaths	1250/6492 (19)	372/1986 (19)	380/2056 (19)	370/1843 (20)	128/607 (21)	0.3547
Alternative TLE approach, *n*/*N* (%)[a]						
Femoral	308/6492 (4.74)	89/1986 (4.48)	97/2056 (4.72)	83/1843 (4.50)	39/607 (6.43)	0.2483
Jugular	352/6492 (5.4)	110/1986 (5.5)	97/2056 (5.3)	94/1843 (5.1)	39/607 (6.43)	0.2483
Procedural success, *n*/*N* (%)[a]						
Complete radiological success	6212/6493 (96)	1863/1987 (94)	1991/2056 (97)	1764/1843 (96)	594/607 (98)	<0.0001
Partial radiological success	184/6493 (2.83)	81/1987 (4.08)	39/2056 (1.90)	52/1843 (2.82)	12/607 (1.98)	<0.0001
Failure	97/6493 (1.49)	43/1987 (2.16)	26/2056 (1.26)	27/1843 (1.47)	1/607 (0.16)	<0.0001
Acute and post-procedural complications						
Major, *n*/*N* (%)	95/3510 (2.7)	30/1112 (2.7)	28/1096 (2.6)	26/985 (2.6)	11/317 (3.5)	0.8459
Intra-procedural	37/3510 (1.1)	17/1112 (1.5)	10/1096 (0.9)	8/985 (0.8)	2/317 (0.6)	0.2945
Post-procedural	21/3510 (0.6)	6/1112 (0.5)	7/1096 (0.6)	6/985 (0.6)	2/317 (0.6)	0.9915
Procedure-related deaths	17/3510 (0.5)	3/1112 (0.3)	6/1096 (0.6)	6/985 (0.6)	2/317 (0.6)	0.6566
In-hospital-death	50/3510 (1.4)	8/1112 (0.7)	16/1096 (1.5)	18/985 (1.8)	8/317 (2.5)	0.0500
Cardiovascular	28/50 (56)	2/8 (25)	11/16 (69)	10/18 (56)	5/8 (63)	0.2294
Not cardiovascular	22/50 (44)	6/8 (75)	5/16 (31)	8/18 (44)	3/8 (37)	
Minor, *n*/*N* (%)	174/3510 (5)	50/1112 (4.5)	53/1096 (4.8)	53/985 (5.4)	18/317 (5.7)	0.7386
Intra-procedural	34/3510 (1)	13/1112 (1.2)	11/1096 (1.0)	7/985 (0.7)	3/317 (0.9)	0.7614
Post-procedural	131/3510 (3.7)	32/1112 (2.9)	40/1096 (3.7)	44/985 (4.5)	15/317 (4.7)	0.1999
Haematoma at surgical site[b]	40/3510 (1.1)	5/1112 (0.5)	11/1096 (1.0)	18/985 (1.8)	6/317 (1.9)	0.0140
Pulmonary embolism[c]	16/3510 (0.5)	11/1112 (1)	1/1096 (0.1)	2/985 (0.2)	2/317 (0.6)	0.0081
Pneumothorax[d]	12/3510 (0.3)	6/1112 (0.5)	6/1096 (0.6)	0/985 (0.0)	0/317 (0.0)	0.0687

AC, anticoagulants; AP, antiplatelets; TLE, transvenous lead extraction.
[a]Data are expressed per leads.
[b]Requiring intervention.
[c]Not Requiring surgery.
[d]Requiring chest tube.

excluded (*Figure 1*). At the analysis of predictors, overall complications were predicted by technical/procedural factors, as old leads removed with laser sheaths in low-volume centres, but neither by clinical factors or AT regimens. Among TLE *major complications*, only in-hospital mortality (but not intra-procedural death, which was comparable among groups), resulted higher in AT patients, especially in the subgroup under combined AP/AC therapy (*Figure 2*). Of note, in-hospital mortality was predicted only by clinical factors, as old age and low NYHA class, but, also in this case, not by AT regimens. This finding seems to support the concept that, also minimizing pre-procedural AP and AC therapy, patient complexity and fragility, often observed in patients under AT, are likely to be responsible for the poor in-hospital outcome.

Regarding TLE *minor complications*, they usually include both bleeding or thrombotic complications, such as pocket haematoma, low-risk pulmonary thromboembolism, and post-extraction deep vein thrombosis at the venous entry site.[19] In our sub-analysis, the incidence of minor complications was comparable (5%) among groups. Of note, a high rate of minor bleedings (i.e. pocket haematoma requiring surgery), but with a lower incidence of pulmonary thromboembolism, were observed in AT subgroups (*Table 3*), especially in AP/AC subgroup (*Figure 3*), and when AC was 'continued' (*Table 4*). We could argue that AP with/without continued or bridged AC increases the bleeding risk, but potentially reducing the embolic one, invariably associated with any surgery.

To date, there are no controlled clinical data on AT therapy management associated with extraction procedures and recommendations about AT management remain poor.[19] The role of AT therapy was not included as primary or secondary endpoint in the ELECTRa Registry and recommendation on the optimal management of AT therapy would be beyond the purpose of the sub-analysis. Nevertheless, some considerations are due. Management of AT

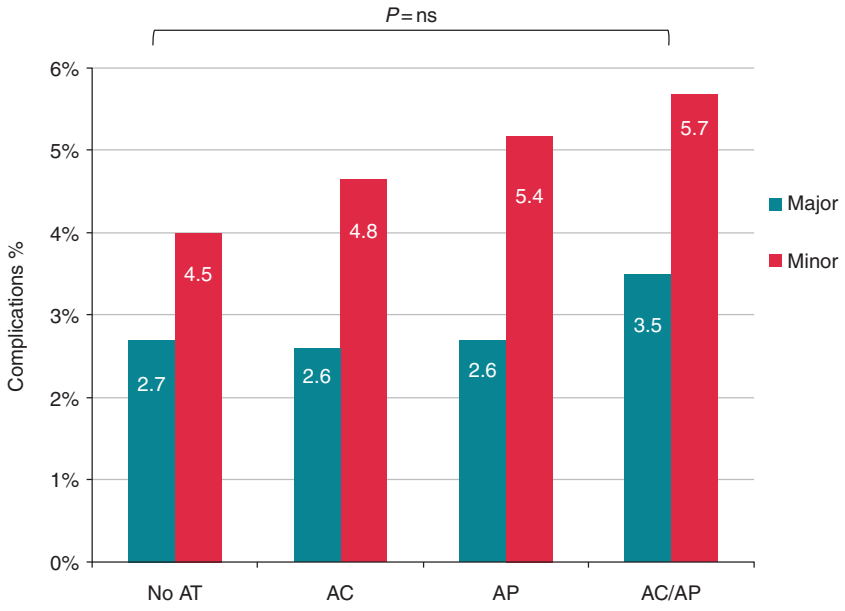

Figure 2 Comparison of major and minor complication rate between patients not treated with AT, treated with AP, with AC, and both AP + AC. AC, anticoagulants; AP, antiplatelets.

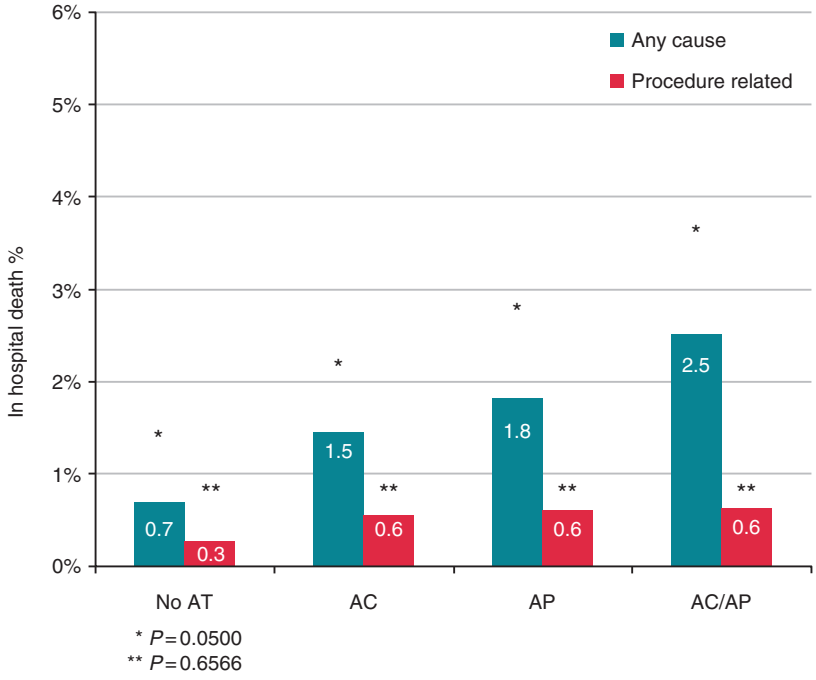

Figure 3 Comparison of all-cause and procedure-related death rates between patients not treated with AT, treated with AP, with AC, and both AP + AC. AC, anticoagulants; AP, antiplatelets.

therapy in candidates for any surgery should be based on the concept of balancing the thrombotic risk with the bleeding risk. The potential risk of injury to cardiovascular structures with fatal or disabling complications, and the possible need for emergency percutaneous or surgical procedures, are legitimate reasons to consider such procedures as interventions with a high haemorrhagic risk.[20] Nevertheless, the thrombo-embolic risk should not be underestimated. Post-procedural embolic risk remains invariably associated with the patient

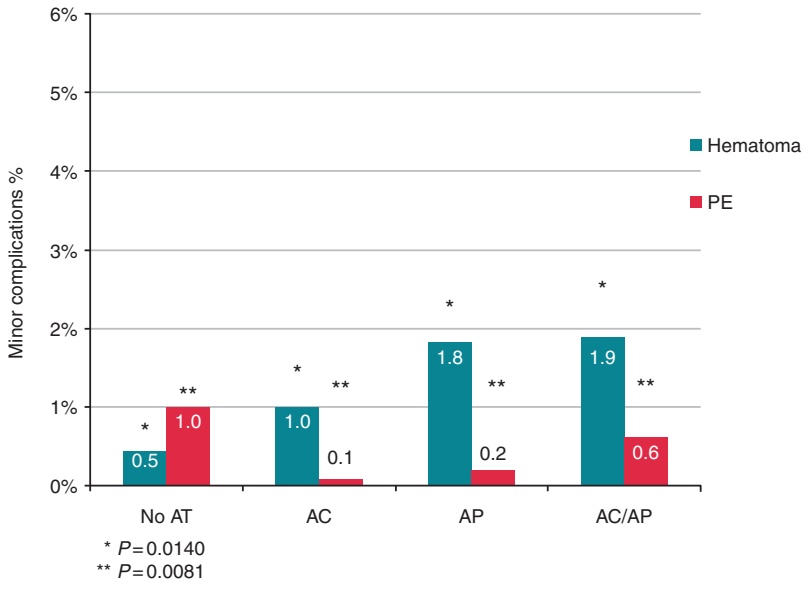

Figure 4 Comparison of haematoma (requiring revision) and pulmonary embolism (PE) not requiring surgery rates between patients not treated with AT, treated with AP, with AC, and both AP + AC. AC, anticoagulants; AP, antiplatelets.

Table 4 Comparison of complications and deaths between AC patients according to the pre-procedural management AC strategy

Complications	Total AC Pts (*N* = 1287)	Interrupted AC 'with bridging' (*N* = 504)	Interrupted AC 'without bridging' (*N* = 696)	Continued AC (*N* = 87)	*P*-value
Major, *n*/*N* (%)	36/1287 (2.80)	16/504 (3.17)	18/696 (2.59)	2/87 (2.30)	0.7955
Intra-procedural death	5/1287 (0.39)	2/504 (0.40)	3/696 (0.43)	0/87 (0.00)	0.8299
Post-procedural death	3/1287 (0.23)	2/504 (0.40)	0/696 (0.00)	1/87 (1.15)	0.0689
Minor, *n*/*N* (%)	70/1287 (5.44)	31/504 (6.15)	35/696 (5.03)	4/87 (4.60)	0.6557
Intra-procedural	10/1287 (0.78)	0/504 (0.00)	10/696 (1.44)[a]	0/87 (0.00)	0.0138
Post-procedural	60/1287 (4.66)	30/504 (5.95)	26/696 (3.74)	4/87 (4.60)	0.1986
Haematoma at surgical site req. reintervention	23/1287 (1.79)	12/504 (2.38)	7/696 (1.01)	4/87 (4.60)[b]	0.0253
Blood transfusion	9/1287 (0.70)	7/504 (1.39)	2/696 (0.29)	0/87 (0.00)	0.0559
Pulmonary embolism not req. surgery	3/1287 (0.23)	2/504 (0.40)	1/696 (0.14)	0/87 (0.00)	0.5994
Vascular repair near the implant site	1/1287 (0.08)	1/504 (0.20)	0/696 (0.00)	0/87 (0.00)	0.4596
Haemotorax without chest tube	1/1287 (0.08)	0/504 (0.00)	1/696 (0.14)	0/87 (0.00)	0.6538

AC, anticoagulants.
[a]Comparison between 'interrupted with bridging' vs. 'without' (*P* = 0.018).
[b]Comparison between 'interrupted without bridging' vs. 'continued' (*P* = 0.028).

profile, the traumatic nature of the procedure, and the duration of confinement to bed. In the registry, No-AT patients showed an high rate of thrombo-embolic events. It could be argued that a strategy of an AT therapy minimization, including AP dose reduction and AC interruption with or without bridging, could be beneficial, improving the peri-surgical TLE outcome. Regarding DOAC patients, no recommendations may be given at the present. The favourable pharmacokinetics of DOAC and the emerging possibility to rapidly reverse their effects, may further optimize peri-procedural AT management. A potential pre-procedural AT management strategy was summarized in the Supplementary material online, *Appendix S1* (Supplementary material online, *Table S1*).

At present, our sub-analysis shows that AT does not seem to predict death before TLE but identifies a subset of fragile patients with a worse in-hospital TLE outcome. Antiplatelet and/or AC treatment, alone or in combination, should alert physicians to the potentially high-risk TLE profile of this population. Considering the elective nature of TLE, AT therapy minimization, including partial or complete discontinuation depending on the thrombo-embolic risk, seems to be a reasonable approach.

Conclusions

In the ESC-EHRA ELECTRa Registry, AT patients showed a high TLE success rate. Not intra-procedural, but only in-hospital overall mortality, was increased in AT subgroups and it was predicted by clinical factors, such as age and NYHA class. Minor complications, such as pocket bleeding, were also more frequent in AT, whereas pulmonary thromboembolism appeared reduced in comparison with no-AT patients. Therefore, in patients under chronic AT therapy who undergo TLE, AT therapy should be minimized. Further data are warranted from prospectively designed studies.

Supplementary material

Supplementary material is available at *Europace* online.

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References

1. Nielsen JC, Thomsen PE, Højberg S, Møller M, Vesterlund T, Dalsgaard D *et al*; DANPACE Investigators. A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. *Eur Heart J* 2011;**32**:686–96.
2. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R *et al*. Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–37.
3. Bogale N, Witte K, Priori S, Cleland J, Auricchio A, Gadler F *et al*.; Scientific Committee, National Coordinators and the Investigators. The European cardiac resynchronization therapy survey: comparison of outcomes between de novo cardiac resynchronization therapy implantations and upgrades. *Eur J Heart Fail* 2011;**13**:974–83.
4. Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF *et al*. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. *Europace* 2012;**14**:1236–86.
5. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA *et al*. ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology ESC Developed in Collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;**15**:1070–118.
6. 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.
7. Bongiorni MG, Kennergren C, Butter C, Deharo JC, Kutarski A, Rinaldi CA *et al*.; ELECTRa Investigators. 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.
8. 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. *Herzschr Elektrophys* 2013;**24**:171–5.
9. Wilkoff BL, Love CJ, Byrd CL, Bongiorni MG, Carrillo RG, Crossley GH, 3rd *et al*.; Heart Rhythm Society, American Heart Association. Transvenous lead extraction: Heart Rhythm Society expert consensus on facilities, training, indications, and patient management. *Heart Rhythm* 2009;**6**:1085–104.
10. Rozkovec A, Bracke F, Defaye P, Fernandez-Lozano I, Golzio PG, Hansky B *et al*; European Heart Rhythm Association. Pathways for training and accreditation for transvenous lead extraction: a European Heart Rhythm Association position paper. *Europace* 2012;**14**:124–34.
11. Dubner S, Auricchio A, Steinberg JS, Vardas P, Stone P, Brugada J *et al*. ISHNE/EHRA expert consensus on remote monitoring of cardiovascular implantable electronic devices (CIEDs). *Europace* 2012;**14**:278–93.
12. Bongiorni MG, Di Cori A, Soldati E, Zucchelli G, Segreti L, Solarino G *et al*. Iatrogenic risk of permanent pacemaker and defibrillator implantation. *G Ital Cardiol* 2009;**10**:395–406.
13. Smith HJ, Fearnot NE, Byrd CL, Wilkoff BL, Love CJ, Sellers TD. Five-years experience with intravascular lead extraction. U.S. Lead Extraction Database. *Pacing Clin Electrophysiol* 1994;**17**:2016–20.
14. Byrd CL, Wilkoff BL, Love CJ, Sellers TD, Turk KT, Reeves R *et al*. Intravascular extraction of problematic or infected permanent pacemaker leads: 1994–1996. U.S. Extraction Database, MED Institute. *Pacing Clin Electrophysiol* 1999;**22**:1348–57.
15. Wilkoff BL, Byrd CL, Love CJ, Sellers TD, Hj V. Trends in intravascular lea extraction: analysis of data from 5339 procedures in 10 years. XIth World Symposium on Cardiac Pacing and Electrophysiology. *Pacing Clin Electrophysiol* 1999;**22**:A207.
16. Deckx S, Marynissen T, Rega F, Ector J, Nuyens D, Heidbuchel H *et al*. Predictors of 30-day and 1-year mortality after transvenous lead extraction: a single-centre experience. *Europace* 2014;**16**:1218–25.
17. Gomes S, Cranney G, Bennett M, Li A, Giles R. Twenty-year experience of transvenous lead extraction at a single centre. *Europace* 2014;**16**:1350–5.
18. Bongiorni MG, Soldati E, Zucchelli G, Di Cori A, Segreti L, De Lucia R *et al*. Transvenous removal of pacing and implantable cardiac defibrillating leads using single sheath mechanical dilatation and multiple venous approaches: high success rate and safety in more than 2000 leads. *Eur Heart J* 2008;**29**:2886–93.
19. Zacà V, Marcucci R, Parodi G, Limbruno U, Notarstefano P, Pieragnoli P *et al*. Management of antithrombotic therapy in patients undergoing electrophysiological device surgery. *Europace* 2015;**17**:840–54.
20. Zucchelli G, Di Cori A, Segreti L, Laroche C, Blomstrom-Lundqvist C, Kutarski A *et al*. Major cardiac and vascular complications after transvenous lead extraction: acute outcome and predictive factors from the ESC-EHRA ELECTRa (European Lead Extraction ConTRolled) registry. *Europace* 2019;**21**:771–80.