Università degli Studi di Ferrara

DOCTORAL COURSE IN
"Advanced Therapies and Experimental Pharmacology"

CYCLE XXXVI

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Ultrasound-guided venous axillary access vs standard fluoroscopic technique for cardiac lead implantation: ZEROFLUOROAXI RANDOMIZED TRIAL.

Scientific/Disciplinary Sector (SDS) _____/_____

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Year 2020/2023

INTRODUCTION

Pacemaker (PM) and implantable cardioverter defibrillator (ICD) implantations have increased noticeably over time [1]. Cephalic vein cut-down (CVC), axillary vein puncture (AVP), or intra/extra thoracic subclavian vein puncture are viable options for lead insertion [2]. Current guidelines emphasize the importance of implanters being proficient in all vascular access techniques, including CVC, AVP, and subclavian vein puncture [2]. While subclavian venous access is widely used due to its high success rate and short procedural time [3], evidence supporting fluoroscopy-guided AVP and CVC has been accumulating over the past two decades [4; 5]. AVP and CVC are considered safer in terms of periprocedural serious complications such as pneumothorax, hemothorax, and brachial plexus injuries, while exhibiting similar success rates and, importantly, lower rates of lead failure during follow-up [6; 7]. However, both CVC and AVP are more time-consuming and carry a slightly higher risk of pocket hematoma [6]. Despite the reported high success rate of fluoroscopic AVP with or without contrast venography [8; 9], the risk of accidental arterial puncture leading to axillary vein compression and troubleshooting venous access remains unresolved. Additionally, inadvertent arterial puncture could increase the risk of pocket hematoma and subsequent CIED infection [10]. Nonetheless, AVP still carries similar bleeding risks as CVC but offers a higher success rate [6]. Retrospective studies and registry data suggest that ultrasound-guided AVP may serve as an alternative to the fluoroscopic approach, yielding favorable results [11; 12]. This approach reduces X-ray exposure for both patients and operators and may mitigate the risk of inadvertent arterial puncture, ultimately enhancing the success rate of axillary venous access. However, to date, no randomized clinical trials have provided comparative data on the safety and efficacy of ultrasound-guided and fluoroscopic AVP during cardiac lead placement.

METHODS

Study design:

The "ZEROFLUOROAXI study: ultrasound guided axillary access vs standard fluoroscopic technique for cardiac lead implantation" is a prospective, randomized, unblinded, single-center trial. The study was registered on ClinicalTrials.gov (NCT05101720). The protocol was approved by the local ethics committee and informed consent was signed by enrolled patients. Our main aim was to demonstrate the efficacy and safety of the ultrasound-guided AVP compared with standard fluoroscopic AVP.

Randomization:

We consecutively enrolled patients undergoing first implantations or upgrades of pacemakers (PM), implantable cardioverter defibrillators (ICD), including cardiac resynchronization therapy devices, at the Electrophysiology Laboratory of the Cardiological Center of the University of Ferrara (Italy) between November 1st, 2021, and December 31st, 2022. Before the index procedure, patients were randomly assigned in a 1:1 ratio to either fluoroscopic-guided axillary vein puncture (AVP) in the standard group or ultrasound-guided AVP in the experimental group. The randomization applied to all planned venous punctures. For instance, in the case of a planned dual chamber pacemaker, two separate venous punctures were required. If a patient was assigned to the ultrasound group, the operator needed to perform both punctures under ultrasound guidance. Randomization was stratified based on the number of planned leads for implantation (one, two, or three leads), and a distinct venous puncture/venous access was utilized for each planned lead. For the purposes of this study, the insertion of leads through a single venous puncture with retained wire or the simultaneous placement of two or more leads within a single vascular access point was not permitted. This strategy amplifies the maneuverability of leads during their deployment within the ventricles or atria and this methodological choice enabled us to optimize the utilization of venous axillary punctures for each

patient. Given the interventional nature of this study, the primary operator had the discretion to switch the approach from one arm to the other in the event of vascular access failure during each venous puncture. Additionally, the operator was permitted to utilize CVC for the second or third lead if it was considered appropriate.

Study population:

Inclusion criteria were: age >18 years, indication for PM or ICD implantation or upgrading according to current European guidelines.

Exclusion criteria were: age <18 years, ongoing pregnancy, inability to express informed consent, implant of a leadless PM or subcutaneous ICD; previous devices undergoing surgery for battery depletion.

Study end points:

The objective of this study was to evaluate the safety and success rate of ultrasound-guided axillary vein puncture (AVP) compared to the standard fluoroscopy-guided AVP approach. The primary endpoint was a composite measure including pneumothorax, hemothorax, clinically significant pocket hematoma (defined as device pocket hematoma leading to prolonged hospitalization (>2 days), surgical reintervention, or interruption of anticoagulant therapy), subcutaneous device pocket and intravascular lead infection, leads dislodgement with or without reintervention, and inadvertent arterial puncture with or without axillary vein compression/narrowing during the index procedure. The assessment of the primary endpoint occurred 30 days after the initial hospitalization. Secondary endpoints included: 1) success rate of the ultrasound approach and the need to switch to the standard radioscopic technique or vice versa; 2) X-ray exposure; 3) time required to obtain venous access; 4) evaluation of individual components comprising the composite primary endpoint.

Implant characteristics and technique:

All PM and ICD implantations were performed according to international recommendations and under appropriate antibiotic prophylaxis [2; 13]. Anticoagulants were interrupted before the implant to minimize bleeding risk if possible and bridge therapy with heparin was completely avoided [14; 15]. At the physician's discretion, a bolus of normal saline solution was administered through a peripheral vascular access in the upper arm on the same side as the pacemaker/ICD implantation before the procedure. This was done to increase intravascular volume in all enrolled patients. In situations where the operator faced challenges in achieving venous access, they had the option to employ a slight head-down tilt to prevent collapse of the axillary vein. Four expert electrophysiologists were involved in the study (MB, MM, CB and FV) trained in both the techniques and with more than four years of experience in CIED implantations in high volume electrophysiology laboratories. After the randomization, the first operator freely decided whether to perform axillary vein puncture before or after skin incision. Conscious sedation was obtained with intravenous opioids and midazolam. Each lead was inserted in a single dedicated vascular access. A distinct venous puncture/venous access was utilized for each planned lead. CVC was possible only as a second vascular access or as a bail out strategy in single chamber devices. Subclavian vein puncture was allowed only as a bail out strategy. The operator was allowed to switch between arms if he experienced difficulties at any time. After venous puncture, CIED implantation procedure was standardly performed, according to European guidelines, in both groups [2]. Active or passive fixation leads were chosen as operator preference. The device was implanted in a subcutaneous or intramuscular pocket.

Fluoroscopy-guided axillary vein puncture:

The skin in the clavicular region was cleaned with chlorhexidine topical solution. After the pocket incision was made medially to the deltoid-pectoral groove an 18 G needle was inserted inside the

incision or before the incision at operator preference. *The needle, affixed to a syringe, was carefully advanced under anterior-posterior fluoroscopic view guidance (0°) while being gently aspirated. This process involved relying solely on the bony landmarks of the outer border of the first rib, maintaining an angle of 30° to 60° from the clavicle. In the anterior-posterior view (0°), the needle was carefully advanced toward "zone 2" on the outer border of the first rib, as previously described. [16] (see Figure 1). Following this initial step, a caudal fluoroscopic view of 35° to 45° was utilized at the operator's discretion to adjust the needle angle, either increasing or decreasing it. This ensured an accurate angle to reach the outer border of the first rib while avoiding interference with the anterior lung contour.* The operator was also allowed to use a guidewire from the cephalic vein as a roadmap. A maximum of three attempts were possible and then ipsilateral contrast venography was allowed. Venography was also possible in upgrades to check if there were venous obstructions. After cannulation of the axillary vein, a 0.035-inch J tipped guidewire was inserted using the standard Seldinger technique. The process was repeated if a second or third sheath was needed. During this maneuver, accidental axillary artery puncture was recorded.

Ultrasound-guided axillary vein puncture:

The skin in the clavicular region was cleaned with chlorhexidine topical solution. We utilized a linear ultrasound probe (Philips L12-3 broadband linear array transducer, operating at a frequency range of 12 - 3 MHz; Philips Healthcare, USA) equipped with a sterile drape, alongside an 18 G needle affixed to a syringe. The ultrasound examinations were conducted using a Philips CX50 portable ultrasound machine (Philips Healthcare, USA). The puncture was performed inside the skin incision or directly on the skin before the incision and medially to it at operator discretion but always before creation of the subcutaneous pocket to avoid air under the skin for better visualization of the axillary vein. Diameter, depth and collapses during inspiration of the axillary vein were recorded. The ultrasound probe was aligned perpendicular and parallel to the axillary vein to locate the artery and to visualize

the pleura (figure 2). The vein was differentiated from the artery by compression. Right handed operators used the vascular probe with the left hand and the needle with the right hand. When the ultrasound probe was parallel to the vein, the needle was inserted directly below the probe. Indentation of the needle tip confirmed its location. After that, a longitudinal image of the axillary vein was obtained to visualize the needle. The needle attached to a syringe was advanced aspirating gently until compression of the vein was obtained. When the needle was over the vein and tenting was visible gentle rotations were done to easily conquer the vein. After cannulation of the axillary vein, a 0.035-inch J tipped guidewire was inserted using the standard Seldinger technique. The process was repeated if a second or third sheath was needed. During this maneuver, accidental axillary artery puncture was recorded.

Follow up:

At 24 hours from the index procedure a CIED electronic interrogation was performed. A chest X ray was also done to assess possible complications related to CIED implantation. Sutures were removed after 14 days. Device electronic interrogation was repeated after 30 days. Death and death cause were also recorded.

Sample size calculation and statistical analysis:

In order to obtain statistical power ≥80% (alpha 5%) we planned to enroll 260 patients. Continuous variables were expressed as mean ± standard deviation when normally distributed, as estimated by Shapiro-Wilk test, or as median and interquartile range if non-normally distributed. Categorical variables were expressed as counts and percentages. Continuous variables were compared using the Student t test or the Mann-Whitney U test and categorical variables using the chi-squared test. An intention to treat analysis was planned. Per protocol and as treated analyses were also performed. In the per protocol analysis only patients who received their assigned randomized treatment were

included in the final analysis. In the as treated analysis patients were evaluated according to the intervention group taking into account the crossover between arms. The sample size was calculated considering that for the primary outcome, we expected a 15% occurrence in the standard treatment arm. The effect size estimated for a clinically meaningful difference was a 10% absolute risk reduction in the occurrence of the primary outcome. The number of patients to enroll was calculated with alpha = 0.05, beta = 0.2, and a ratio of 1:1 for the standard to experimental arm. This calculation considered a two-sided test of proportion and a critical Z value for the given α and β parameters. Each baseline and procedural variable of interest, including crossover between study arms, was tested for association with the primary outcome by logistic regression. Only variables which exhibited a statistically significant association were employed to build a full multivariable model verifying collinearity assumption. Backward elimination was carried out to obtain the minimal model. The same approach was adopted to test association between baseline and procedural variables with inadvertent arterial puncture. P-values <0.05 were considered statistically significant. Statistical analysis was performed using STATA 17 (StataCorp, College Station, Texas, USA) and R version 4.2.2 (R Core Team, 2022) by MM.

RESULTS

Study Population and Implantation

From November 1st, 2021 to December 31st, 2022, 283 patients referring for PM/ICD implantation/upgrading were screened for eligibility. Nine patients were not enrolled due to inability to express informed consent or refused to participate. Four patients were implanted with leadless pacemakers and so excluded. We enrolled and randomized 270 consecutive patients (standard group, n 134 and experimental group, n 136). At one month of follow-up fifteen patients died (7 vs 8; p=1) and one patient was lost at follow-up in the experimental group. The baseline characteristics are shown in table 1. All the continuous variables were not normally distributed. The median age was 80 years old in the experimental group and 81 years old in the standard group (p=0.75). Patients were mostly males in both groups (62% vs 56%; p=0.33). There was a high prevalence of hypertension (81% vs 87%; p=0.25), and up to one third of the patients had dyslipidemia, diabetes mellitus, heart failure, and coronary artery disease. The median BMI was 27 [23 - 29], with no significant difference observed between the groups (27 vs 26.5; p=0.78). More than 80% of patients in both groups were taking single antiplatelets drug and up to one third was taking anticoagulant drugs for atrial fibrillation/venous trombo-embolism. We placed 357 leads in pacemakers and 48 in ICDs. 295 leads were inserted via axillary vein access and 110 via cephalic vein access. We placed 247 active fixation pacing leads (69%) in PMs and 38 (79%) in ICDs. There were no notable differences between the groups for both PMs (138 (77%) vs. 144 (81%); p=0.31) and ICDs (19 (76%) vs. 20 (86%); p=0.34). In twelve patients, 7 in experimental group and 5 in standard group, the physician could not get axillary vein and cephalic access was the only vascular access used and were excluded from the per protocol analysis (Figure 3). The subclavian vein was never used as vascular access. Patients were implanted mostly with single and dual chamber pacemakers (87% vs 88%; p=1), while slightly more than 10% in both groups were ICDs (13% vs 12%; p=0.85). Use of CVC as second or third vascular access was slightly higher in the standard group without reaching statistical significance (29% vs

24%; p=0.33). Total median procedural duration time and total time to achieve all vascular accesses did not differ between groups (68 vs 64 min, p =0.24; 86 vs 142 sec, p=0.12). A total of 87 patients (32%) experienced crossover between the two study arms. The crossover among the two study arms happened mainly during the first venous puncture and did not differ between the two study groups (28% vs 36%; p=0.19). Main reasons for change from experimental group to standard group were difficult visualization of the AV, AV depth > 5 cm from the skin and complete collapse of the AV due to poor volemic status. On the other hand, main reasons to shift from fluoroscopy guided AVP to ultrasound were unfavorable angle between the clavicle and the first rib with a vertical takeoff of the clavicle and failure in progression of the guidewire due to venous valves near the crossing angle between the first rib and the clavicle. Venous vasospasm was not one of the main reasons to change approach. Peripheral venography was performed in less than a third of the patients in the standard group. In the ultrasound group we had a good visualization of the AV in 80% of the patients and we also found a good visualization of the CV in 27%. In the ultrasound group the mean depth from the skin of the AV was 3.5 ± 1 cm. Within the ultrasound group, we performed the puncture within the skin incision for 118 patients, and for 18 patients, we opted to puncture the skin directly. The crossover ratio (45 patients (38%) vs. 4 (22%); p = 0.19) and the rate of success on the first attempt (76 (64%) vs. 15 (83%); p = 0.11) showed no significant differences between individuals who underwent the puncture within the skin incision and those who were punctured directly on the skin. Median number of attempts to obtain venous access did not differ for first, second and third access. Patients in the ultrasound group who underwent two axillary venous punctures showed no difference in the median time (90 seconds [32 - 269] vs 40 seconds [13 - 141]; p=0.36) and median number of attempts (4 [1 - 3] attempts vs 3 [1 - 2]; p=0.14) to get the venous access between the first and second venous punctures.

Primary endpoints

The primary endpoint was a composite of pneumothorax, hemothorax, inadvertent arterial puncture, pocket hematoma, pocket infection, lead dislodgement and death. The primary endpoint was assessed at 30 days from the index hospitalization. In the intention to treat analysis the incidence of the primary endpoint at 30 days after the index procedure was significantly lower in the experimental group (standard group 32% vs experimental group 21%; p=0.041) (Figure 4), on the contrary no differences were present at the per protocol analysis (standard group 33% vs experimental group 23% ; p=0.052) and as treated analysis (standard group 25% vs experimental group 28%; p=0.68). The incidence of acute serious procedural complications did not differ and were shown in table 3. There were no differences in pneumothorax, hemothorax, pocket hematoma, pocket infection, lead dislodgement and death after 30 day. Incidence of pocket hematoma did not differ between standard and experimental groups (standard group 10% vs experimental group 6%; p=0.28). The main difference was in the lower incidence of inadvertent axillary arterial puncture in the experimental group (standard group 17% vs experimental group 6%; p=0.004). In the intention-to-treat analysis, all inadvertent arterial punctures were documented prior to the occurrence of crossover. The per-protocol analysis revealed an unchanged incidence of inadvertent arterial punctures. As for the as-treated analysis, we recorded 19 inadvertent arterial punctures in the fluoroscopic approach and 12 in the ultrasound-guided approach, showing no statistical significance (p = 0.445). However, we have to mention that in this analysis, inadvertent arterial punctures were recorded both before and after the crossover event. The detailed results for both the as-treated and per-protocol analyses can be found in the supplement. We performed uni- and multivariable analyses to identify factors associated with the primary endpoint. At the multivariable analysis, the experimental group had a protective effect on the acute composite endpoint (OR 0.57; 95% CI 0.33 - 0,99) as shown in the forest plot (figure 5). Because of this finding we also assessed factors associated with inadvertent axillary arterial puncture. At the univariate analysis experimental group (OR 0.31, 95% CI 0.13 – 0.7), single chamber pacemaker (OR 0.28, 95% CI 0.11 – 0.7), implantation of single lead (OR 0.29, 95% CI 0.12 – 0.67)

and anticoagulant therapy (OR - 0.32, 95% CI 0.12 – 0.86) appeared as protective factors while dual chamber pacemaker (OR 3.52, 95% CI 1.55 – 7.96), implantation of two leads (OR 3.01, 95% CI 1.36 – 6.94), hemoglobin values (OR 1.29, 95% CI 1.06 - 1.57), crossover between the study arms (OR 2.52, 95% CI 1.18 - 5.38) and use of cephalic vein as second or third venous access (OR 2.63, 95% CI 1.22 - 5.66) increase the risk of inadvertent axillary arterial puncture. The multivariable analysis showed that only the ultrasound guided approach has a protective role in preventing inadvertent axillary arterial puncture in our study population (OR 0.28, 95% CI 0.12 – 0.67) while higher number of implanted leads (OR 2.48, 95% CI 1.05 – 5.88) and the necessity of crossovers between study arms (OR 2.56, 95% CI 1.15 – 5.72) increase the risk of inadvertent arterial puncture (figure 6).

Secondary endpoints

The success rate of the ultrasound approach was similar to the success rate at the first attempt of AVP with fluoroscopy (standard group 61% vs experimental group 67%; p=0.37). Need to switch from ultrasound to fluoroscopy and vice versa was not different between two study groups (standard group 28% vs experimental group 36%; p=0.19). While total procedural duration time (standard group 68 vs experimental group 64 min, p=0.24 and total time to achieve all vascular accesses (standard group 86 vs experimental group 142 sec; p=0.12) did not differ between groups, total fluoroscopy time (standard group 257 vs experimental group 202 sec; p=0.002), vascular access fluoroscopy time (standard group 45 vs experimental group 0 sec; $p < 0.001$) were significantly lower in the experimental group. Despite up to one third of the patients experienced crossover between the study groups both total procedural (standard group 10344 µGy x cm2 vs experimental group 7119 µGy x cm2; p=0.002) and vascular access X ray exposure (standard group 1097 µGy x cm2 vs experimental group 0 µGy x cm2; $p < 0.001$) were also significantly lower in the ultrasound guided group.

Body mass index subgroup analysis

We conducted a subgroup analysis that included patients with BMI < 30 and those with BMI ≥ 30. In both patient categories, we observed no significant differences in the crossover ratio (standard group 36% vs. experimental group 31%; p = 0.46) and the first-attempt success rate (standard group 54% vs. experimental group 67%; p = 0.065) between the standard group and the experimental group. Even within the ultrasound group, the presence of BMI ≥ 30 did not have a significant impact on the crossover ratio (standard group 39% vs. experimental group 35%; p = 0.64) and the first-attempt success rate (standard group 64% vs. experimental group 68%; p = 0.65)

DISCUSSION

The key finding of the present study is that ultrasound-guided axillary vein puncture (AVP) significantly reduced the occurrence of primary composite endpoints, including pneumothorax, hemothorax, inadvertent arterial puncture, pocket hematoma, pocket infection, lead dislodgement, and death within 30 days. This outcome was primarily attributed to a significant reduction in inadvertent arterial puncture incidents. Historically, CVC and AVP have been proven to be superior and to subclavian access in terms of procedural safety with lower serious complications and better long-term lead outcomes [6; 7; 17]. Despite these data, SVP is still frequently used and AVP is largely underperformed and when performed it is done mainly under fluoroscopic guidance. AVP has a slightly lower bleeding risk than CVC with the same safety profile [6] and with the same rate of acute success of SVP [3]. The main problem with AVP under fluoroscopic guidance is the risk of inadvertent arterial puncture with subsequent muscle hematoma / venous spasm causing troubleshooting venous access. Furthermore, the use of ionizing radiations may be an issue, to which both patients and operators are exposed. Despite great interest in ultrasonography guidance for AVP this approach till today was not standardized, and its benefits were not validated by randomized clinical trials. The main finding of the present study is that ultrasound-guided AVP is safer than fluoroscopic AVP for CIED implantation. In particular, ultrasound approach results in a 43% reduction in the odds of the primary outcome compared to fluoroscopic approach (OR 0.57; 95% CI 0.33 - 0,99). Of note the difference is mainly driven by reduction of inadvertent arterial puncture during the implant procedure underlying once again that ultrasound optimizes the benefits of AVP. However, at the as-treated analysis (standard group 25% vs experimental group 28%; p=0.68) and at the per protocol analysis (standard group 33% vs experimental group 23%; p=0.052) the primary endpoint did not differ between groups. This result suggests that in cases where the ultrasound visualization of the axillary vein is not optimal, the fluoroscopic approach may still be necessary. Ideally, a proficient implanter should be proficient in both methods for axillary vein puncture. There are several mechanisms through which the ultrasound-guided approach provides advantages: 1.

Direct visualization of the venous and arterial circulation, along with their anatomical relationship; 2. Assessment of the patient's volume status; 3. Visualization of the needle's advancement through the tissue and its interaction with the vein; 4. Identification of the pleura during the procedure. Furthermore, as we expected, the success rate between fluoroscopy and ultrasound guidance did not differ with up to 60% in both groups of venous access obtained at first attempt and with the same ratio of crossover between groups. Also, the time to obtain vascular access did not differ between the two study groups. These findings demonstrate that ultrasound-guided axillary vein puncture does not require more time compared to the standard fluoroscopy approach, while achieving an equivalent success rate. Additionally, ultrasound significantly reduces both fluoroscopy time and X-ray exposure during vascular access and the entire implant procedure. This finding is particularly significant considering recent evidence indicating that interventional cardiologists are exposed to up to three times more radiation per year compared to radiologist physicians [18]. Furthermore, this approach aligns with the ALARA (as low as reasonably achievable) principles, as outlined in a consensus document by the American College of Cardiology in 1998 aiming to minimize risks [19].

Limitations

This is a single center study. Patients enrolled were mainly acute patients with the need of a PM as demonstrated by the relatively low prevalence of ICDs and biventricular devices. The crossover ratio was up to 30% in both groups because the operators were free to change between arms at any moment of the implantation due to the interventional nature of the study. Crossovers tend to be related to patient characteristics and operator choice and their impact on the results is difficult to know. The short follow-up period was chosen due to the safety outcomes related to acute implant complication, but it is known that AVP with CVC have a high lead safety profile at follow-up.

CONCLUSIONS

In conclusion, axillary vein puncture under ultrasound guidance offers a safer approach with regards to acute complications, specifically by avoiding inadvertent axillary arterial puncture, while maintaining a comparable success rate to fluoroscopy-guided puncture. Furthermore, it minimizes X-ray exposure for both operators and patients, and is not more time consuming.

REFERENCES

1. *Raatikainen MJP, Arnar DO, Merkely B, Nielsen JC, Hindricks G, Heidbuchel H et al. 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;19:ii1–90*
2. *Burri H, Starck C, Auricchio A, Biffi M, Burri M, D'Avila A, Deharo JC, Glikson M, Israel C, Lau CP, Leclercq C, Love CJ, Nielsen JC, Vernooy K; Reviewers:, Dagres N, Boveda S, Butter C, Marijon E, Braunschweig F, Mairesse GH, Gleva M, Defaye P, Zanon F, Lopez-Cabanillas N, Guerra JM, Vassilikos VP, Martins Oliveira M. EHRA expert consensus statement and practical guide on optimal implantation technique for conventional pacemakers and implantable cardioverter-defibrillators: endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin-American Heart Rhythm Society (LAHRS). Europace. 2021 Jul 18;23(7):983-1008.*
3. *Chan NY, Kwong NP, Cheong AP. Venous access and long-term pacemaker lead failure: comparing contrast-guided axillary vein puncture with subclavian puncture and cephalic cutdown. Europace 2017;19:1193–7*
4. *Parsonnet V, Roelke M. The cephalic vein cutdown versus subclavian puncture for pacemaker/ICD lead implantation. Pacing Clin Electrophysiol. 1999 May;22(5):695-7.*
5. *Migliore F, Siciliano M, De Lazzari M, Ferretto S, Valle CD, Zorzi A, Corrado D, Iliceto S, Bertaglia E. Axillary vein puncture using fluoroscopic landmarks: a safe and effective approach for implantable cardioverter defibrillator leads. J Interv Card Electrophysiol. 2015 Sep;43(3):263-7*
6. *Atti V, Turagam MK, Garg J, Koerber S, Angirekula A, Gopinathannair R, Natale A, Lakkireddy D. Subclavian and Axillary Vein Access Versus Cephalic Vein Cutdown for*

Cardiac Implantable Electronic Device Implantation: A Meta-Analysis. JACC Clin Electrophysiol. 2020 Jun;6(6):661-671

7. *Benz AP, Vamos M, Erath JW, Hohnloser SH. Cephalic vs. subclavian lead implantation in cardiac implantable electronic devices: a systematic review and meta-analysis. Europace 2019;21:121–9*
8. *Jimenez-Diaz J, Higuera-Sobrino F, Piqueras-Flores J, Perez-Diaz P, Gonzalez- Marin MA. Fluoroscopy-guided axillary vein access vs cephalic vein access in pacemaker and defibrillator implantation: randomized clinical trial of efficacy and safety. J Cardiovasc Electrophysiol 2019;30:1588–93*
9. *Burri H, Sunthorn H, Dorsaz PA, Shah D. Prospective study of axillary vein puncture with or without contrast venography for pacemaker and defibrillator lead implantation. Pacing Clin Electrophysiol 2005;28:S280–3*
10. *Balla C, Brieda A, Righetto A, Vitali F, Malagù M, Cultrera R, Bertini M. Predictors of infection after "de novo" cardiac electronic device implantation. Eur J Intern Med. 2020 Jul;77:73-78*
11. *Esmaiel A, Hassan J, Blenkhorn F, Mardidyan V. The use of ultrasound to improve axillary vein access and minimize complications during pacemaker implantation. Pacing Clin Electrophysiol. 2016;39:478-482.*
12. *Migliore F, Fais L, Vio R, De Lazzari M, Zorzi A, Bertaglia E, Iliceto S. Axillary vein access for permanent pacemaker and implantable cardioverter defibrillator implantation: Fluoroscopy compared to ultrasound. Pacing Clin Electrophysiol. 2020*
13. *Malagù M, Vitali F, Brieda A, Cimaglia P, De Raffele M, Tazzari E, Musolino C, Balla C, Serenelli M, Cultrera R, Rapezzi C, Bertini M. Antibiotic prophylaxis based on individual infective risk stratification in cardiac implantable electronic device: the PRACTICE study. Europace. 2022 Mar 2;24(3):413-420.*

14. *Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Vanassche T, Potpara T, Camm AJ, Heidbüchel H; External reviewers. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021 Oct 9;23(10):1612-1676.*
15. *Malagù M, Trevisan F, Scalone A, Marcantoni L, Sammarco G, Bertini M. Frequency of "Pocket" Hematoma in Patients Receiving Vitamin K Antagonist and Antiplatelet Therapy at the Time of Pacemaker or Cardioverter Defibrillator Implantation (from the POCKET Study). Am J Cardiol. 2017 Apr 1;119(7):1036-1040*
16. *Vurgun VK, Candemir B, Gerede DM, Goksuluk H, Altin AT, Akyurek O, Erol C. Extrathoracic subclavian-axillary vein location and morphological features over the first rib for pacemaker and defibrillator lead implantation. Pacing Clin Electrophysiol. 2018 May 23*
17. *Anagnostopoulos I, Kossyvakis C, Kousta M, Verikokkou C, Lakka E, Karakanas A, Deftereos G, Spanou P, Giotaki S, Vrachatis D, Avramidis D, Deftereos S, Giannopoulos G. Different venous approaches for implantation of cardiac electronic devices. A network meta-analysis. Pacing Clin Electrophysiol. 2022 Jun;45(6):717-725*
18. *Gaita F, Guerra PG, Battaglia A, Anselmino M. The dream of near-zero X-rays ablation comes true. Eur Heart J. 2016 Sep 21;37(36):2749-2755. doi: 10.1093/eurheartj/ehw223. Epub 2016 Jun 26.*
19. *Limacher, M.C.; Douglas, P.S.; Germano, G.; Laskey,W.K.; Lindsay, B.D.; McKetty, M.H.; Moore, M.E.; Park, J.K.; Prigent, F.M.;Walsh, M.N. ACC Expert Consensus Document. Radiation Safety in the Practice of Cardiology. American College of Cardiology.J. Am. Coll. Cardiol. 1998, 31, 892–913*

FIGURE TITLES AND LEGENDS

Figure 1. Fluoroscopy-guided axillary vein puncture. Green dashed line: first rib; Orange dashed line: second rib. Red hatched area: target area on the first rib. Zone 1, 2 and 3 are the same as described by Vurgun VK et al [16]

Figure 2. Ultrasound-guided axillary vein puncture. The first line of images shows long-axis views of the axillary vein and artery laterally, along with a shot-axis view in the center. The second line displays short and long-axis views highlighting all relevant anatomical structures. In the third line, the central image demonstrates the needle advancement with tenting observed on the axillary vein, while the right image depicts the presence of a guidewire within the vein. Purple dashed line: axillary vein; Red dashed line: axillary artery; Green dashed line: muscular fascia; Orange dashed line: second rib; Light blue dashed line: pleura.

Figure 3. Diagram illustrating the study flow with three planned analyses. The intention-to-treat analysis is represented by the green line, the per-protocol analysis by the orange line, and the as-treated analysis by the light blue line.

Figure 4 (central image) The upper segment of the figure illustrates the intention-to-treat analysis through the crossover ratio for both groups: fluorguided AVP (depicted in orange) and ultrasound-guided AVP (depicted in blue). In the lower section, the reduction of the primary composite endpoint (intention-to-treat analysis) is displayed for both groups, with the inadvertent arterial puncture highlighted in red as the main contributing factor leading to this outcome

Figure 5. Forest plot of the multivariable analyses for the primary endpoint (intention-to-treat analysis). Left side of the reference line shows better results for the experimental arm.

Figure 6. Forest plot of the multivariable analyses for inadvertent arterial puncture (intention-to-treat analysis). Left side of the reference line shows better results for the experimental arm.

Table 1. Demographics and baseline clinical parameters (intention to treat analysis).

	Total (N = 270)	**Standard Group (N = 134)**	**Experimental Group (N = 136)**	**p**
Age, years, (IQR)	81 [73 - 85]	81 [73 - 85]	80 [74 - 85]	0.747
Male, n (%)	159 (59)	83 (62)	76 (56)	0.325
Body Mass Index, kg/m2, (IQR)	27 (23 - 29)	27 (24 - 29)	26.5 (23 - 29)	0.781
Hypertension, n (%)	227 (84)	109 (81)	118 (87)	0.247
Diabetes, n (%)	82 (30)	37 (28)	45 (33)	0.356
Heart failure, n (%)	88 (33)	44 (33)	44 (32)	1.000
LV Ejection Fraction, (IQR)	56 [50 - 60]	59 [50 - 60]	55 [49 - 60]	0.256
Ischemic Heart Disease, n (%)	80 (30)	39 (29)	41 (30)	0.894
Estimated Glomerular Filtration Rate, ml/min, (IQR)	51.5 [36 - 70]	55 [42 - 73]	48 [33 - 67]	**0.043**
Dialysis, n (%)	6 (2.2)	2 (1.5)	4 (2.9)	0.684
Antiplatelet use, n (%)	229 (85)	113 (84)	116 (85)	0.866
Anticoagulant use, n (%)	95 (35)	41 (31)	54 (40)	0.128
Diuretic use, n (%)	128 (47)	63 (47)	65 (48)	0.904

LV: left ventricle

Table 2. Procedural data (intention to treat analysis).

	Total (N = 270)	**Standard Group (N = 134)**	**Experimental Group (N = 136)**	**p**
Pacemaker, n (%) • Single chamber, n (%) • Dual chamber, n (%) • Biventricular device, n (%)	237 (87) 117 (43) 120 (44) 0 (0)	117 (87) 55 (41) 62 (46) 0 (0)	120 (88) 62 (46) 58 (43) 0 (0)	1 0.464 0.624 //
ICD, n (%) • Single chamber, n (%) • Dual chamber, n (%) • Biventricular device, n (%)	33 (12) 23 (8.5) 5 (1.9) 5 (1.9)	17 (13) 12 (9) 2 (1.5) 3 (2.2)	16 (12) 11 (8.1) 3 (2.2) 2 (1.5)	0.854 0.831 1.00 0.683
Upgrade, n (%)	9 (3.3)	5 (3.7)	4 (2.9)	0.748
Active fixation leads • PM • ICD	247/357 38/48	138/179 19/25	144/178 20/23	0.313 0.345
Procedure duration (min), (IQR)	65 [50 - 86]	68 [54 - 90]	64 [49 - 83]	0.242
Time to vascular access (sec), (IQR)	99 [33- 399]	86 [28 - 364]	142 [40 - 413]	0.117
Total procedure fluoroscopy time (sec), (IQR)	231 [147 - 355]	257 [180 - 402]	202 [122 - 332]	**0.002**
Vascular access fluoroscopy time (sec), (IQR)	26 [0 - 121]	45 [5.5 - 149]	0 [0 - 74]	**<0.001**
Total procedure dose area product (µGy x cm2)	8853 [4716 - 15381]	10345 [6374 - 16800]	7119 [3931 - 13578]	**0.002**
Vascular access dose area product (µGy x cm2)	556 [0 - 3270]	1098 [191 - 4178]	0 [0 - 1532]	**<0.001**
Use of Cephalic as second or third access, n (%)	71 (26.3)	39 (29.1)	32 (23.5)	0.334
Good visualization of AV with ultrasound, n (%)	//	//	106 (80)	//
Good visualization of CV with ultrasound, n (%)	//	//	32 (27)	//
AV depth form the skin (cm), ± SD	//	//	3,5 ± 1	//

Contrast venography, n (%)	//	29 (22)	//	//
Success rate at first attempt, n (%)	173 (64)	82 (61)	91 (70)	0.375
Crossover, n (%)	87 (32)	38 (28)	49 (36)	0.194
Crossover, n (%) - First access - Second access - Third access	87 (32) 24 (8.9) 0	38 (28) 10 (7.5) 0	49 (36) 14 (10) 0	0.194 0.522 //
Attempts to vascular access, (IQR) - First access - Second access - Third access	2 [1 - 3] 1 [1 - 2] 1 [1 - 1,5]	2 [1 - 4] 1.5 [1 - 3] 1 [1 - 1,5]	2 [1 - 3] 1 [1 - 2] 1 [1 - 1,5]	0.632 **0.036** 0.731

AV: axillary vein; CV cephalic vein.

Table 3: Endpoints (intention to treat analysis).

	Total (N = 270)	**Standard Group (N = 134)**	**Experimental Group (N = 136)**	**p**
Composite Endpoint (acute), n (%)	72 (26.7)	43 (32.1)	29 (21.3)	**0.041**
● **Pneumothorax, n (%)**	5 (1.9)	3 (2.2)	2 (1.5)	0.683
● **Hemothorax, n (%)**	0 (0.0)	0 (0.0)	0 (0.0)	//
● **Pocket hematoma, n (%)**	23 (8.5)	14 (10.4)	9 (6.6)	0.283
● **Pocket infection, n (%)**	4 (1.5)	3 (2.2)	1 (0.7)	0.369
● **Inadvertent arterial puncture , n (%)**	31 (11.5)	23 (17.2)	8 (5.9)	**0.004**
● **Lead dislodgement , n (%)**	5 (1.9)	2 (1.5)	3 (2.2)	1.000
● **Death, n (%)**	15 (5.6)	7 (5.2)	8 (5.9)	1.000
Lost at follow-up (30 days), n (%)	1 (0.4)	0 (0.0)	1 (0.7)	1.000

Figure 1

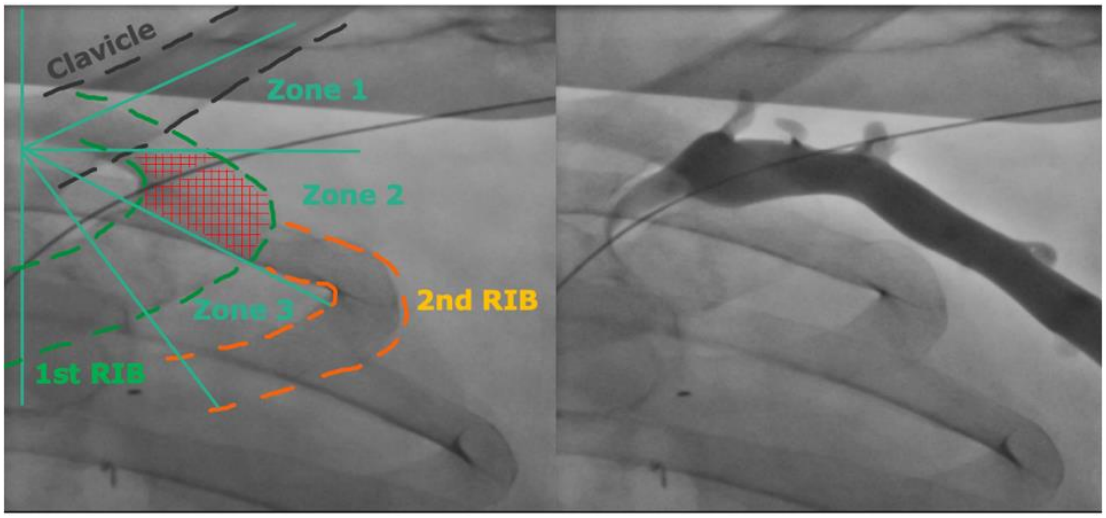


Figure 2

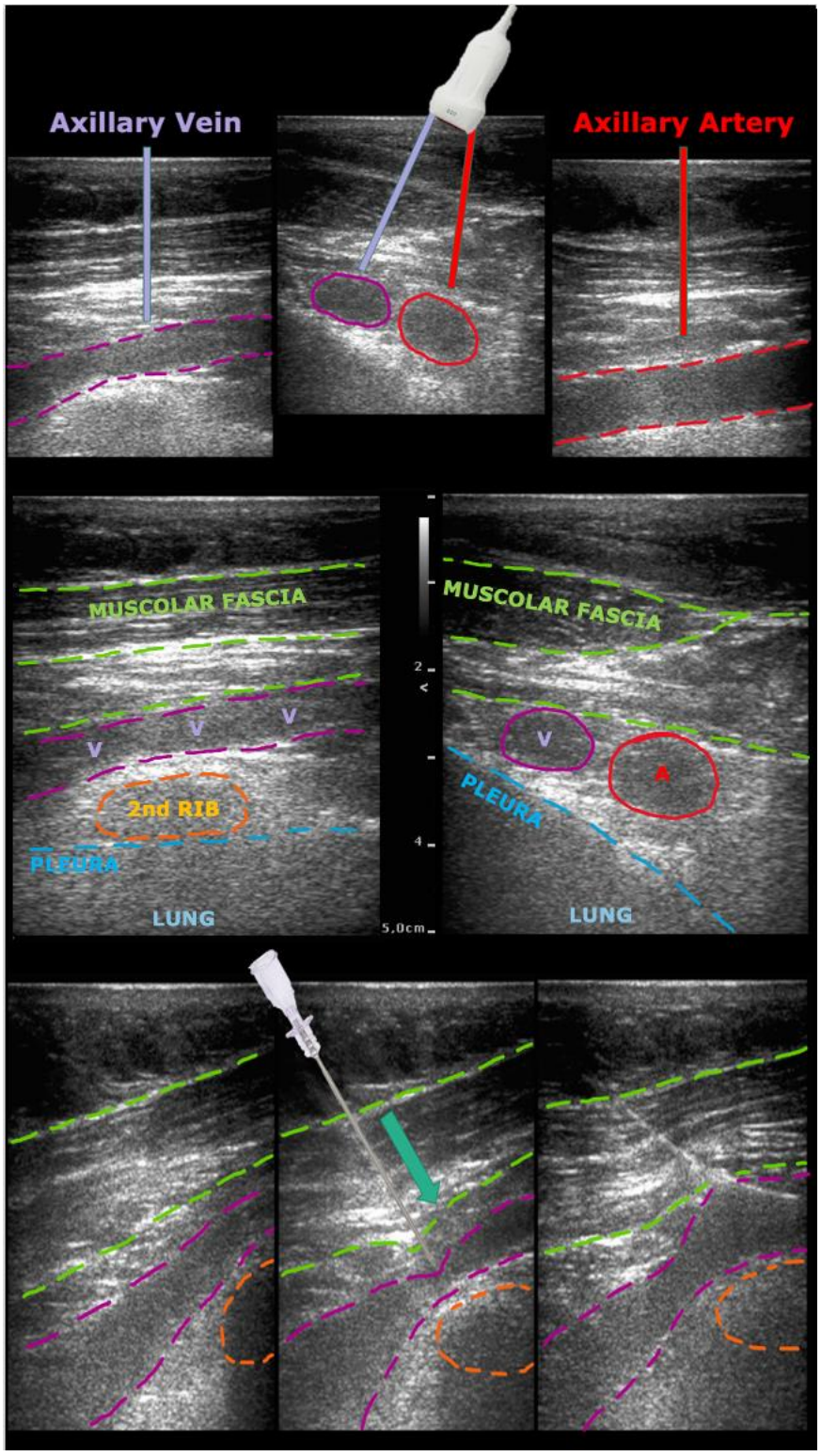

Axillary Vein
Axillary Artery
MUSCOLAR FASCIA
V
V
V
2nd RIB
PLEURA
LUNG
2
4
5,0cm
MUSCOLAR FASCIA
V
A
PLEURA
LUNG

Figure 3

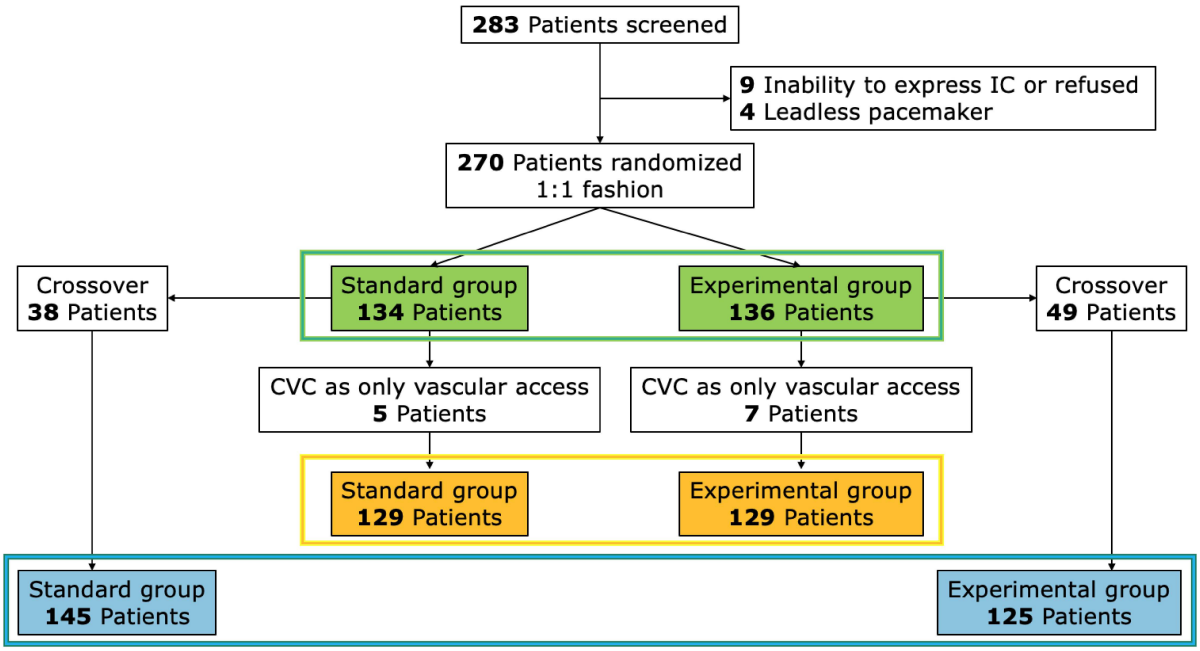


Figure 4

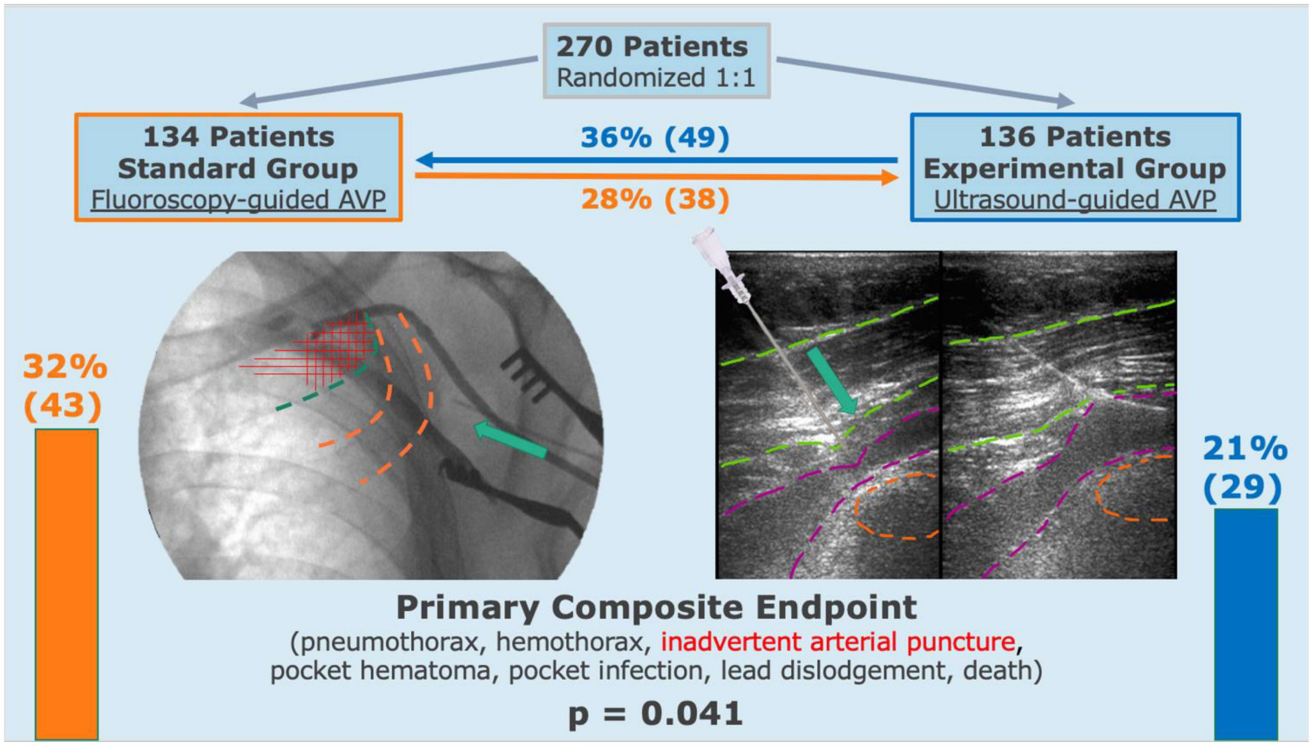


Figure 5

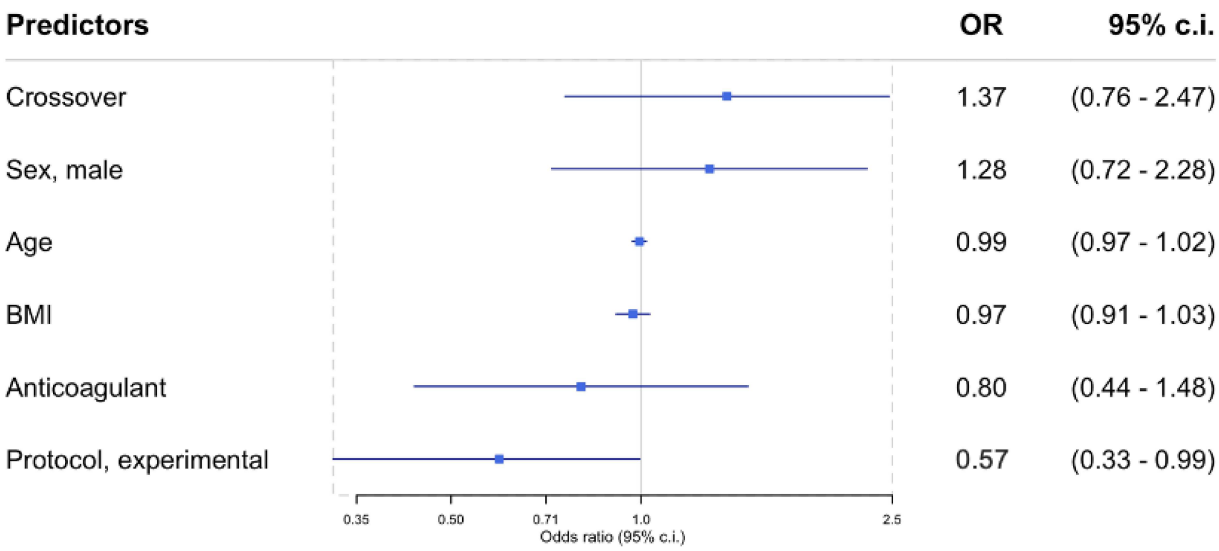
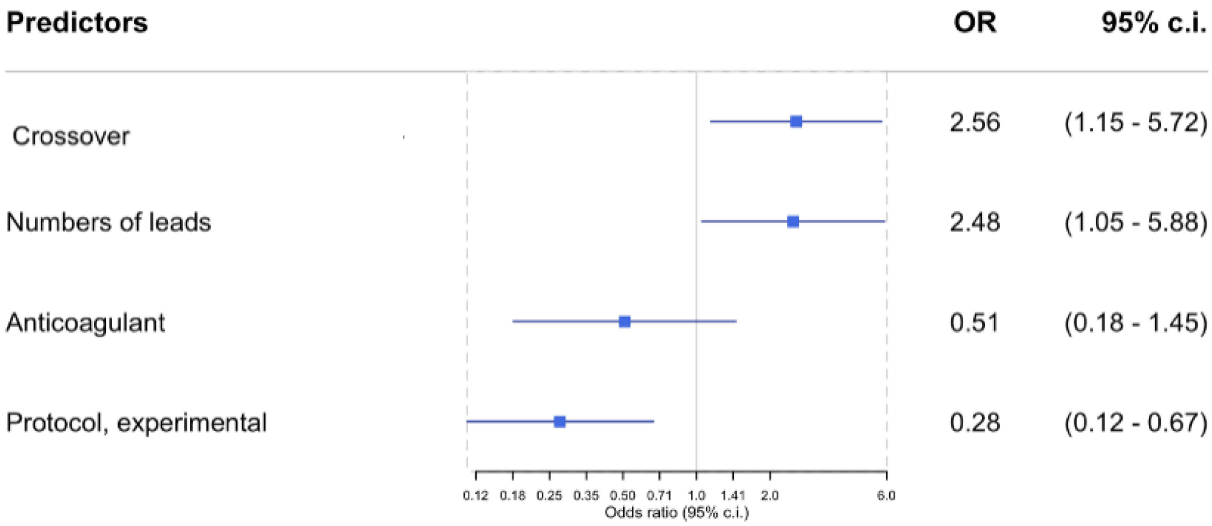

Predictors
OR
95% c.i.
Crossover
1.37
(0.76 - 2.47)
Sex, male
1.28
(0.72 - 2.28)
Age
0.99
(0.97 - 1.02)
BMI
0.97
(0.91 - 1.03)
Anticoagulant
0.80
(0.44 - 1.48)
Protocol, experimental
0.57
(0.33 - 0.99)
0.35
0.50
0.71
1.0
2.5
Odds ratio (95% c.i.)

Figure 6


Predictors
OR
95% c.i.
Crossover
2.56
(1.15 - 5.72)
Numbers of leads
2.48
(1.05 - 5.88)
Anticoagulant
0.51
(0.18 - 1.45)
Protocol, experimental
0.28
(0.12 - 0.67)
0.12
0.18
0.25
0.35
0.50
0.71
1.0
1.41
2.0
6.0
Odds ratio (95% c.i.)