

ORIGINAL ARTICLE

Predictors of pocket hematoma after cardiac implantable electronic device surgery: A nationwide cohort study

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Abstract

Purpose: Clinically significant pocket hematoma (CSH) is a common complication to cardiac implantable electronic device (CIED) surgery. We aimed to evaluate predictors of CSH after CIED surgery.

Methods: We performed a nationwide population-based prospective cohort study with systematic patient chart review of all Danish patients undergoing CIED surgery during a 12-month period. Multiple logistic regression analysis was used to estimate adjusted odds ratios (aOR) with 95% confidence intervals for association between predictors and CSH.

Results: We included 5918 consecutive patients, 63% males, mean age 72.6 years. A total of 148 (2.5%) patients experienced CSH, including 10 patients (0.2%) requiring re-operation with hematoma evacuation. The risk of CSH was significantly increased in patients treated with aspirin (aOR 1.8; 1.2–2.7), aspirin and clopidogrel (aOR 3.9; 2.3–6.5), or heparin (aOR 2.1; 1.1–4.1), and in patients with INR \geq 2.0 (aOR 2.0; 1.2–3.2). Patients operated by low-volume operators (aOR 2.7; 1.6–4.6) or undergoing more complex CIED surgery such as cardiac resynchronization therapy (aOR 2.0; 1.1–3.5) or dual-chamber defibrillator (aOR 2.1; 1.2–3.8) also had significantly increased CSH risk.

Conclusion: In a large nationwide cohort of consecutive patients undergoing CIED surgery, the risk of CSH was 2.5%, with 0.2% necessitating evacuation. CSH risk was increased both in patients receiving aspirin, dual antiplatelet therapy or continued vitamin K-antagonist therapy. Dual antiplatelet therapy had the highest risk (aOR) of CSH. Both low operator volume and more complex CIED surgery were independently associated with higher CSH risk. These data should be considered when planning CIED surgery.

KEYWORDS

artificial cardiac pacemaker, cardiac implantable electronic device, pocket hematoma, predictors, risk factors

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1 | INTRODUCTION

Clinically significant pocket hematoma (CSH) occurs in 1.2%–7.3% of patients after cardiac implantable electronic device (CIED) surgery.^{1–7} CSH causes discomfort, poor wound healing, prolonged hospital stay or readmission, prolonged interruption of anticoagulation therapy,⁸ a possible need for re-intervention,⁹ and an increased risk of infections.^{2,10,11} All of which makes identification of predictors of CSH imperative.

For patients treated with vitamin K-antagonists (VKA), guidelines during CIED surgery changed from heparin bridging¹² to continued VKA therapy.^{13,14} The BRUISE CONTROL study¹ showed that continued VKA therapy is associated with an 80% risk reduction of postoperative bleeding compared with heparin bridging without affecting the risk of thromboembolic complications, and these results are supported by other studies.^{2,4,15–19}

Continued VKA therapy has been the preferred strategy in Danish CIED centers for the past 10–15 years, and heparin has been used only in carefully selected patients. Therefore, our study population is well suited to examine CSH risk with continued VKA strategy. We aimed to provide complete and valid data on risk of CSH after CIED surgery and to identify independent predictors of CSH in a real-life setting.

2 | METHODS

2.1 | Study design and study population

A nationwide, population-based, prospective cohort study was performed including all Danish patients who underwent transvenous CIED surgery during a 12-month period from May 2010 to April 2011. No exclusion criteria were applied. We reported early complication rates from this cohort in a previous publication.²⁰

2.2 | Data sources

The national clinical database, Danish Pacemaker and ICD register (DPIR) was used to identify eligible patients and their baseline characteristics for this study. Implanting physicians at all Danish centers enter clinical and technical details of every CIED surgery into DPIR. Data on CSH were recorded from a systematic manual review of all patient charts. One investigator conducted these reviews. Data on stroke within 30 days of CIED surgery was obtained from The Danish National Patient Register (DNPR), a register that holds nationwide data on all hospital admissions, including information on diagnoses and treatment dates.²¹ Linking data from DPIR, patient charts and DNPR is possible using The Danish Civil Registration System, where every Danish resident has a unique personal identification number.²²

The Danish Data Protection Board, the DPIR Steering Committee, and all CIED centers approved the study.

2.3 | Study outcomes

CSH was defined as hematoma requiring re-intervention, prolonged hospitalization, hospital re-admission, or additional out-patient visits. Hematomas with no treatment consequences were not included. Sensi et al.²³ have introduced a 3-level grading system of hematomas, with our definition of CSH corresponding to hematoma grade 3.

The study examines stroke as secondary outcome. We defined stroke as ischaemic or hemorrhagic stroke within the first 30 days after CIED surgery.

2.4 | Predictors of CSH

We included the following baseline parameters as possible predictors for CSH: gender, age, antiplatelet (AP) therapy, VKA therapy, international normalized ratio (INR), CIED type, surgery type, and operator volume. Patients were considered to receive AP therapy when treated with aspirin within 10 days before surgery or when treated with clopidogrel within the last 5 days. AP therapy was divided into four groups: no AP therapy, aspirin, clopidogrel, and combined aspirin and clopidogrel (DAPT). A heparin group was formed by patients that within the last 24 h before surgery received unfractionated heparin, low molecular weight heparin, or fondaparinux. INR was used to categorize warfarin treatment in three groups: INR ≤ 1.2 (no warfarin), 1.3–1.9, or ≥ 2.0 . Data on direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) was not included, since our data derives from the time before common usage of these medications.

CIED types were categorized as single- and dual-chamber pacemakers, cardiac resynchronization therapy device with (CRT-D) or without defibrillator (CRT-P), single-chamber implantable cardioverter defibrillator (ICD), and dual-chamber ICD. Surgery type consisted of three groups: first implant, generator replacement, and surgical change of pacing mode (system upgrade) or lead revision. Operator volume was defined as average annual surgery number of each operator for the period ranging from one year prior to start of study period to end of study and was divided into two groups: low operator (0–49 surgeries/year) and high operator (≥ 50 surgeries/year). Categorization of all potential predictors was pre-specified.

2.5 | CIED surgery and follow up

CIED surgery and follow-up of CIED patients are performed in 14 centers in Denmark. The Danish population includes 5.6 million people. Electrophysiologists or cardiologists perform all transvenous CIED surgery. Generators are routinely placed subcutaneously, with only few placed submuscular. Leads are implanted through either cephalic vein cut-down or subclavian vein puncture. Prophylactic antibiotic treatment is used for all patients. AP and VKA treatment follow this protocol: No heparin therapy from the day before surgery until 2 days after surgery. VKA therapy is discontinued from

0–3 days prior to the CIED surgery (defined as continued VKA therapy). AP therapy is continued. To secure hemostasis during surgery, most centers use bipolar electrocautery and a pressuring dressing afterwards, but the choice is at the operator's discretion. Routinely, no local antibiotics were used in any center.

2.6 | Statistical analysis

Absolute risk of CSH was reported according to baseline characteristics. Odds ratios (OR) with 95% confidence intervals were generated to describe the association between selected covariates and CSH. Multiple logistic regression analysis was used to adjust for a priori selected confounders (gender, age, AP therapy, heparin, INR, CIED type, surgery type, and operator volume). A p -value $< .05$ was considered statistically significant. Statistical analysis was performed using STATA IC for Windows, version 11.2 (StataCorp).

3 | RESULTS

3.1 | Study cohort and baseline characteristics

A total of 5942 patients underwent CIED surgery during the study period. We excluded 24 patients receiving epicardial systems, leaving a final study population of 5918 patients. Baseline clinical and demographic characteristics of the population are shown in Table 1. Mean age at implantation was 72.6 years. Few patients received heparin prior to surgery. Table 2 shows AP and VKA therapy according to device type.

3.2 | Risk of CSH

A total of 345 patients (5.8%) developed a pocket hematoma. For 197 (3.3%) patients this was without treatment consequences, while 148 (2.5%) patients had CSH. Figure 1 shows treatment consequences for patients with CSH. The most common consequence of CSH was prolonged hospitalization ($n = 78$, 1.3%), typically 1–2 days. Ten patients (0.2%) required re-operation with hematoma evacuation because of severe pain or leakage from the wound. Of the 10 patients in this group, two received no VKA or AP therapy, four received aspirin, three received DAPT therapy and one received VKA therapy ($\text{INR} \geq 2$). No patient needed blood transfusion.

3.3 | Predictors of CSH

We identified several independent predictors of CSH, Figure 2. Patients on AP therapy with aspirin (aOR 1.8; 1.2–2.7) or DAPT therapy (aOR 3.9; 2.3–6.5) had significantly higher risk of CSH than patients with no AP therapy. Heparin also increased CSH risk (aOR 2.1; 1.1–4.1). Furthermore, patients with $\text{INR} \geq 2.0$ had a higher risk

of CSH (aOR 2.0; 1.2–3.2). A total of 51 patients had $\text{INR} > 3.0$ with one patient experiencing CSH, which needed additional out-patient visits. INR between 1.3 and 1.9 was not significantly associated with CSH compared with $\text{INR} \leq 1.2$.

Supplemental analysis showed that triple therapy with anticoagulants, aspirin, and clopidogrel ($n = 56$), carried a significantly increased risk of CSH (aOR 3.7; 1.5–8.9).

Patients operated by low-volume operators (aOR 2.7; 1.6–4.6) and patients with more complex CIEDs (CRT-D and dual-chamber ICD) were significantly more likely to develop CSH. We found no association between gender, age, or surgery type and CSH.

3.4 | Stroke

Within 30 days after implantation, a total of 24 patients (0.4%) were hospitalized with stroke, classified as ischaemic stroke ($n = 14$; 0.24%), intracerebral hemorrhagic stroke ($n = 4$; 0.07%), or stroke of unspecified origin ($n = 6$; 0.10%). Three of these 24 patients previously had stroke. One patient had CSH needing prolonged hospitalization.

Among the 24 stroke patients, six were on VKA therapy; they all had INR 1.3–1.9, and three were on additional aspirin. No stroke patients had $\text{INR} > 2$ at the time of CIED surgery. Nine stroke patients were on aspirin and four were treated with DAPT therapy. One patient was treated with heparin, while four patients had no VKA or AP treatment.

4 | DISCUSSION

The present study provides detailed and validated data on risk and predictors of CSH after CIED surgery in a large nationwide, real-life cohort of consecutive CIED patients. Risk of CSH was 2.5%, yet rarely needing evacuation. CSH risk was increased both in patients receiving aspirin, DAPT therapy or continued VKA therapy. DAPT therapy had the highest risk (aOR) of CSH. Both low operator volume and more complex CIED surgery were independently associated with higher CSH risk.

4.1 | Risk of CSH

The incidence of CSH was 2.5%. This is consistent with recent studies reporting an incidence ranging from 1.2%–7.3%.^{1–7} Importantly, different definitions of CSH among older studies make comparisons difficult. The risk of re-operation due to CSH was very low (0.2%), likely a result of strict conservative treatment strategy whenever possible.

4.2 | Predictors of CSH

Our study shows that single AP therapy with aspirin carries a two-fold increased risk of CSH. Conflicting data on this matter has been

TABLE 1 Baseline clinical and demographic characteristics.

	Total		No CSH		CSH	
	(n = 5918)		(n = 5770)		(n = 148)	
	n	%	n	%	n	%
Gender						
Male	3707	63	3611	63	96	65
Female	2211	37	2159	37	52	35
Age, mean (SD)	72.62	13.7	72.6	13.7	73.66	11.4
Antiplatelet therapy						
No therapy	2726	46	2684	47	42	28
Aspirin	2590	44	2517	44	73	49
Clopidogrel	110	2	108	2	2	1
Aspirin and clopidogrel	492	8	461	8	31	21
Heparin						
No	5739	97	5601	97	138	93
Yes	179	3	169	3	10	7
INR						
≤1.2	4545	77	4443	77	102	69
1.3–1.9	786	13	763	13	23	16
≥2	587	10	564	10	23	16
CIED type						
PM (single- and dual chamber)	4189	71	4101	71	88	59
CRT-P	209	4	205	4	4	3
CRT-D	445	8	424	7	21	14
Single-chamber ICD	684	12	668	12	16	11
Dual-chamber ICD	391	7	372	6	19	13
Surgery type						
New implant	4355	74	4242	74	113	76
Generator replacement	1136	19	1115	19	21	14
System upgrade or lead revision	427	7	413	7	14	9
Operator volume						
Low (0–49/year)	349	6	332	6	17	11
High (≥50/year)	5569	94	5438	94	131	89

Note: Categorical variables are reported as absolute frequencies and percentages. Abbreviations: CIED, cardiac implantable electronic device; CRT-D, cardiac resynchronization therapy devices with defibrillator; CRT-P, cardiac resynchronization therapy devices without defibrillator; CSH, Clinically significant pocket hematoma; ICD, implantable cardioverter defibrillator; INR, international normalized ratio; PM, pacemaker.

TABLE 2 Antiplatelet and anticoagulant therapy according to device type.

Type of device	INR			Antiplatelet therapy				Heparin	
	n (%)			n (%)				n (%)	
	≤1.2	1.3–1.9	≥2	No	Asprin	Clopidogrel	DAPT	No	Yes
PM	3242 (77.4)	602 (14.4)	345 (8.2)	2170 (51.8)	1749 (41.8)	71 (1.7)	199 (4.8)	4056 (96.8)	133 (3.2)
CRT-P	147 (70.3)	25 (12.0)	37 (17.7)	106 (50.7)	89 (42.6)	2 (1.0)	12 (5.7)	207 (99.0)	2 (1.0)
CRT-D	301 (67.6)	60 (13.5)	84 (18.9)	107 (24.0)	264 (59.3)	7 (1.6)	67 (15.1)	431 (96.9)	14 (3.2)
Single-chamber ICD	559 (81.7)	59 (8.6)	66 (9.7)	217 (31.7)	307 (44.9)	24 (3.5)	136 (19.9)	670 (98.0)	14 (2.1)
Dual-chamber ICD	296 (75.7)	40 (10.2)	55 (14.1)	126 (32.2)	181 (46.3)	6 (1.5)	78 (20.0)	375 (95.9)	16 (4.1)

Abbreviations: AP, antiplatelet; CRT-D, cardiac resynchronization therapy devices with defibrillator; CRT-P, cardiac resynchronization therapy devices without defibrillator; DAPT, dual antiplatelet therapy; ICD, implantable cardioverter defibrillator; INR, international normalized ratio; PM, pacemaker.

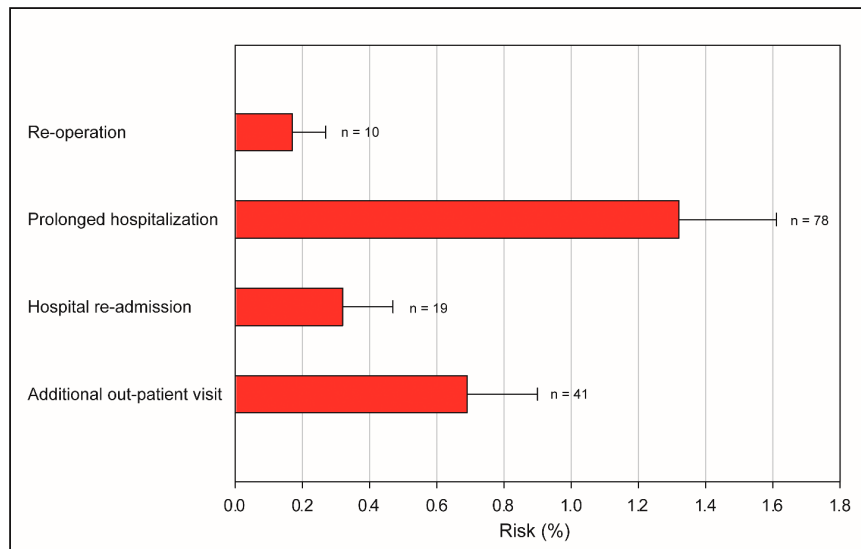


FIGURE 1 Treatment consequences for patients with clinical significant hematoma.

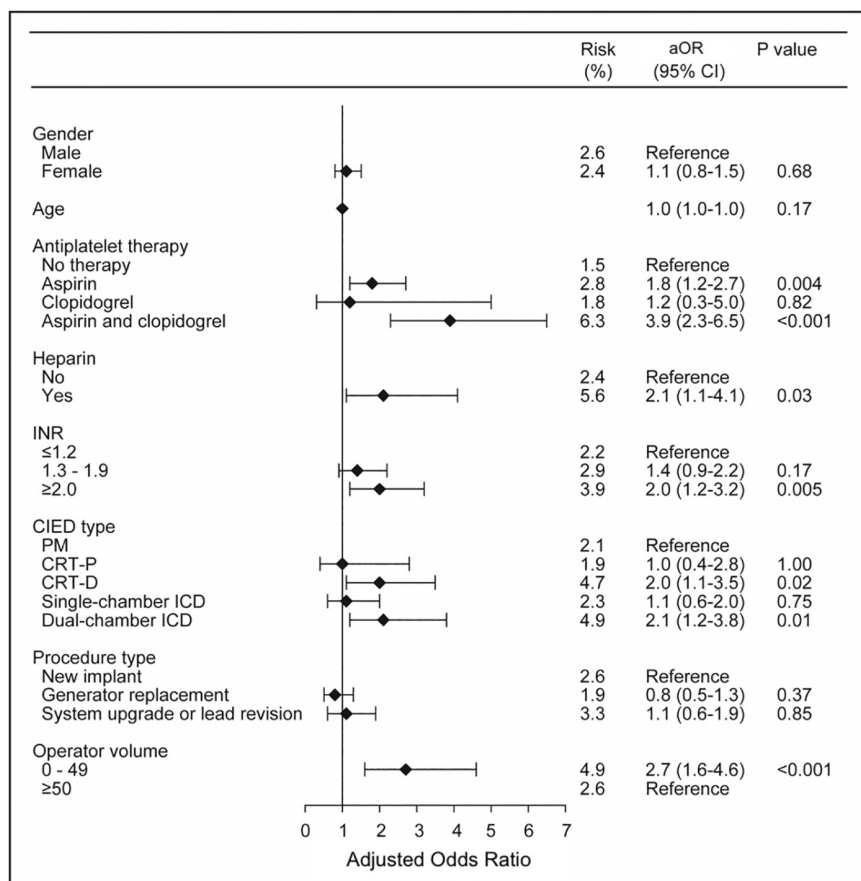


FIGURE 2 Risk and predictors of clinical significant hematomas.

published.^{3,4,6,7,16,19,24-26} However, the BRUISE CONTROL study¹ correspondingly found aspirin to be an independent predictor of CSH (RR 2.04; 1.19-3.48), and a subsequent combined analysis of BRUISE CONTROL 1 and 2 concluded that concomitant antiplatelet therapy doubles the risk of CSH.²⁷ When taking into consideration the widespread use of aspirin, especially among older adults,²⁸ the patient specific benefit/risk of holding aspirin when undergoing elective or semi-urgent CIED surgery, should be carefully considered.

Single AP therapy with clopidogrel was not associated with CSH in the present study, possibly reflecting that this patient group was relatively small in our cohort. Previous data on this matter are limited and inconsistent.^{6,16,19,25,29}

We found a four-fold increased risk of CSH in patients treated with both aspirin and clopidogrel. This is consistent with reports from other studies. A meta-analysis by Bernard et al. reports a five-fold increased risk of bleeding complications (OR 5.0),²⁴ while a

meta-analysis by Yang et al. reports an almost seven-fold increase (OR 6.84).¹⁶ Several other studies support these findings.^{3,4,19,26,29–31} Expert consensus statements suggest short preoperative pausing of clopidogrel while taken the indication for DAPT therapy into consideration.³²

Our results showed no increased risk of CSH in patients with INR 1.3–1.9 compared with patients with INR \leq 1.2. Patients with INR \geq 2 had a two-fold increased risk. These results are similar to findings by Nammas et al.³⁰ Other studies even report that INR values in therapeutic levels have no significant effect on risk of CSH.^{24,31,33,34} When extrapolating our data to current patient groups, understanding the risk of CSH in patients treated with continued VKA versus direct oral anticoagulants is important. The combined analysis of BRUISE CONTROL 1 and 2 recently found no difference in CSH between continued VKA and direct oral anticoagulants.²⁷

Triple therapy with VKA, aspirin, and clopidogrel was associated with a high risk of CSH. Likewise, other studies report a 6–14-fold increased risk.^{6,7} The indication for triple therapy should be carefully evaluated before CIED surgery.

A small number of patients in the present study received heparin. As expected, this group of patients showed an increased risk of developing CSH. However, prior studies have reported the bleeding risk of heparin to be considerably higher (increased 4–8-fold).^{3,4,9,17,18,24,25,31} The lower risk of CSH in this study may be attributed to thorough securing of hemostasis and a strict post-surgery regime with immobilization and pressure dressing. However, based on the size of this group in the present cohort, our estimate of risk may be uncertain, and heparin therapy is still to be considered a relative contraindication for CIED surgery.

High-complexity CIED surgery such as CRT-D and dual-chamber ICD were associated with significantly higher CSH risk. This is likely explained by multiple leads, higher lead rigidity, larger device volume, and longer procedure time as substantiated by previous studies.^{7,8,16,25,35} However, the indication for a more complex CIED usually is a more complex underlying heart disease and treatment, which places this group of patients at a higher risk of developing CSH. As shown in Table 2, AP and VKA therapy are more frequent with complex CIED types, which likely reflects the more complex underlying disease. To reduce the risk of confounding by indication we adjusted for AP and VKA.

Consistent with other studies, we observed that an annual operator volume $<$ 50 surgeries was associated with increased risk of CSH.⁹ This finding supports that a reasonably high annual operator volume is important for minimizing CIED surgery related complications.

We found no difference in risk of CSH between different surgery types. Few data exist on this topic. However, it is reported that upgrading from pacemaker to ICD is associated with a significant, independent higher risk of CSH.²

Gender and age were found to be of no independent influence on risk of CSH, consistent with the majority of previous studies.^{9,25,26}

4.3 | Stroke

Our results showed a low incidence (0.4%) of any type of stroke within the first 30 days after CIED surgery. Our findings are consistent with stroke risk (0.0%–0.4%) reported in previous studies,^{9,18,24} and further supported by three different meta-analyses on heparin bridging versus continued VKA strategy showing that the risk of thromboembolic events after CIED or other elective surgeries does not differ significantly between the two groups.^{16,24,36} One study even suggests that continued VKA therapy reduces risk of thromboembolic events.¹⁸

Six stroke patients were on VKA therapy, and they all had sub-therapeutic INR levels (INR 1.3–1.9). No patient in therapeutic levels (INR $>$ 2) at the time of surgery suffered from stroke.

These findings support the safety of continued VKA therapy and a target INR in therapeutic level prior to CIED surgery.

4.4 | Study limitations

We cannot rule out influence of confounders not included in the adjusted analysis. Previous studies have found venous access,²⁵ coagulopathy,^{8,31} structural heart disease,^{8,16} and chronic kidney disease^{3,5} to influence the risk of hematoma. Importantly, our analysis included only pre-specified variables, and we included a large, consecutive, nationwide cohort of CIED patients.

Our data derives from the time before common usage of direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) and adequate data on periprocedural management of patients treated with these drugs must be found elsewhere.^{37,38} Also, the present study does not include data on the optimal perioperative management of prasugrel and ticagrelor.

5 | CONCLUSION

In a large nationwide cohort of consecutive patients undergoing CIED surgery, the risk of CSH was 2.5%, yet rarely needing evacuation. CSH risk was increased both in patients receiving aspirin, DAPT therapy or continued VKA therapy. DAPT therapy had the highest risk (aOR) of CSH. Both low operator volume and more complex CIED surgery were independently associated with higher CSH risk. These data should be considered when planning CIED surgery.

AUTHORS' CONTRIBUTIONS

Data collection was preformed by Rikke Esberg Kirkfeldt. Statistical analyses were performed Sie Kronborg Fensman and Rikke Esberg Kirkfeldt. The first draft of the manuscript was written by Sie Kronborg Fensman. All authors critically reviewed the manuscript for intellectual content and approved the final manuscript.

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CONFLICT OF INTEREST

During the conduct of the study, Kirkfeldt RE received grants from Danish Pacemaker and ICD Register, and from Central Denmark Region Research Foundation. Outside the submitted work, Grove EL has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, MSD, MundiPharma, Portola Pharmaceuticals, Lundbeck Pharma and Organon and is an investigator in clinical studies sponsored by AstraZeneca and Bayer and has received unrestricted research grants from Boehringer Ingelheim. Nielsen JC has received grants from Novo Nordisk Foundation (NNF16OC0018658). The remaining authors have nothing to declare.

DATA AVAILABILITY STATEMENT

Available upon reasonable request to the corresponding author.

ETHICS APPROVAL

The Danish Data Protection Board, the DPIR (Danish Pacemaker and ICD register) Steering Committee, and all participating centers approved the study. According to Danish law, ethical committee approval is not required for registry-based studies on anonymized data.

CONSENT TO PARTICIPATE AND FOR PUBLICATION

According to Danish law, individual consent for participation and publication is not required for registry-based studies on anonymized data.

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