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Pocket related complications following cardiac electronic device implantation in patients receiving anticoagulation and/or dual antiplatelet therapy: prospective evaluation of different preventive strategies

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Abstract

Purpose We sought to assess the safety and effectiveness of three different devices: (1) vacuum drainage system, (2) hemostatic gelatin sponge (Stypro®), and (3) compression device (Premofix®) compared to standard of care (control) in patients undergoing cardiac implantable electronic device (CIED) implantation receiving anticoagulation and/or dual antiplatelet therapy (DAPT).

Methods We enrolled all consecutive patients admitted for first permanent CIED implantation receiving anticoagulation and/or DAPT into a prospective registry. The primary endpoint (1°EP) was a composite of hematoma grade > 1 and pocket infection.

Results We included 406 patients (median age 73 years, 71% male) of whom 103 (25%) received a vacuum drainage system, 99 (24%) received Stypro®, 103 (25%) received Premofix®, and 101 (25%) were in the control group. One hundred eighty patients (44%) were treated with anticoagulation (median INR 2.0), 176 (43%) received DAPT, and 50 (12%) both. The occurrence of the 1°EP was reduced by Stypro® (hazard ratio (HR) 0.38 (95% confidence interval (CI) 0.16–0.94) and Premofix® (HR: 0.37 (95% CI 0.15–0.90)) compared to controls ($p < 0.05$ for both). The incidence of hematoma grade 2 or 3 was exclusively lowered by Premofix® compared to control (6% versus 15%; $p < 0.05$) and was not affected by the type of CIED, INR (≥ 2.5 versus < 2.5), body mass index (≥ 30 versus < 30), or CIED implantation under anticoagulation plus DAPT. The vacuum drainage system did not affect the 1°EP or the incidence of hematoma.

Conclusions In patients receiving anticoagulation and/or DAPT undergoing CIED implantation, the use of Premofix® and Stypro® significantly lowered the 1°EP occurrence compared to control. Premofix® additionally lowered the frequency of pocket hematomas >grade 1.

Keywords Pocket hematoma · CIED · Premofix · Stypro · Vacuum drainage · Anticoagulation

1 Introduction

More than 3 million cardiac pacing systems and 200,000 implantable cardioverter defibrillators (ICD) are implanted yearly worldwide [1], of these 70,000 are implanted in Germany [2]. Considering this number of cardiac implantable electronic devices (CIED) implantations, any strategy leading to a reduction in complication rates will significantly improve patient's health and reduce medical cost. Even in populations under oral anticoagulation (OAC) undergoing CIED implantation without heparin-bridging strategy (the latter decreases the incidence of clinically significant pocket hematomas by 80% [3]), pocket hematoma is still a frequent complication. It accounts for up to 25% of early re-operations [4, 5], and pocket-related complications (e.g., increased risk of pocket infections following pocket hematoma [6]) prolong the hospital stay by an average of 3.1 days, and additionally increase the procedure cost up to $6995 [7].

Several devices (vacuum drainage [8, 9], hemostatic sponges [10, 11], or liquid hemostats [12]) have been used to lower the incidence of hemorrhage and fluid retention at

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the surgical site. However, systematic analyses of the efficacy and safety of these hemostatic devices with relevant numbers of patients with a high risk of bleeding complications are not available.

Our investigation was prospectively conducted to evaluate the safety and efficacy associated with the use of three different hemostatic devices following CIED implantation as to compare to standard of care in patients receiving anticoagulation and/or dual antiplatelet therapy (DAPT).

2 Methods

We designed this study as a prospective registry of patients receiving anticoagulation and/or DAPT admitted for first permanent CIED implantation (pacemaker (PM), ICD, cardiac resynchronization therapy (CRT), and cardiac contractility modulation (CCM)) at our institution. In order to establish the optimal prevention of pocket hematoma formation in such patients, we collected the data of all consecutive patients under treatment with anticoagulation and/or DAPT from June 2015 until May 2017. During the first 6 months (June until November 2015), all patients received the standard of care. During December 2015 until May 2016, all patients received a vacuum drainage system (Dahlhausen & Co., Cologne, Germany). From June 2016 until November 2016, all patients received a hemostatic sponge (Stypro® hemostat, Curasan AG, Kleinostheim, Germany) and during the period from December 2016 until May 2017 the patients received the Premofix® PM/ICD compression device (Andanza, Meinhard, Germany) in addition to the standard of care. There was no "blanking period" between the different strategies because of the low number of operators and the single center design of the study. The study was not funded by the manufacturers of the devices. The study protocol was approved by the institutional review board.

2.1 Perioperative management and follow-up

In patients on treatment with intravenous unfractionated heparin (UFH) was discontinued 4 h before CIED implantation and re-instituted 4 h after the implantation procedure without giving a bolus at the previous infusion rate to maintain the partial thromboplastin time (PTT) between 1.5 and 2.5 times the control value. The PTT was measured 6 h after the initiation of heparin therapy and after dosage adjustments, which were made according to a standardized nomogram used at our institution. In patients receiving weight adjusted low molecular weight heparin (LMWH), this medication was terminated 12 h before the operation and restarted 12 h after surgery. Only less than 1% of the patients in our study received either LMWH or UFH and was the result of a preoperative temporary pacemaker via the femoral route for complete atrio-ventricular block in all cases.

All patients receiving oral anticoagulation treatment or dual antiplatelet therapy continued their medication. For patients receiving oral anticoagulation, an international normalized ratio (INR) of > 1.7 was required to qualify for the registry [13]. Patients on medication with direct thrombin inhibitors or direct factor Xa inhibitors were excluded from this registry. Patients were examined daily until hospital discharge by the same physicians (JCG and MAO) and 3 months post-implantation in the outpatient clinic. At 3 months follow-up, the physician responsible for device interrogation and pocket assessment was not aware of the initial treatment. Patients were instructed to contact the CIED clinic of the hospital if a hematoma or if a skin erosion or clinical signs of pocket infection (inflammatory skin changes including pain, swelling, or redness) developed after hospital discharge. The grading of hematomas and definition of pocket infections used in our study is shown in Table 1.

2.2 Operative technique and standard of care

2.2.1 Operative technique

All procedures were performed by experienced cardiologists. Approximately 700 CIEDs are implanted each year at our clinic. Each of the implanting physicians had an experience of at least 200 implantation procedures. After administration of prophylactic antibiotics (Cefazolin—a first-generation cephalosporin [16]) and local anesthesia, a pectoral incision was made. Venous access was achieved through puncture of the subclavian vein (one puncture per lead), and the leads were implanted under fluoroscopic guidance in the Cath lab. All atrial leads had active fixation; most ventricular leads had also active fixation especially in cases of severe tricuspid regurgitation, pulmonary hypertension, or implantation of an ICD. In patients treated with cardiac resynchronization, all left ventricular leads were inserted through the coronary sinus. CIEDs were placed in a sub-fascial pocket localized in the pre-pectoral region. Patients with submuscular placement of the CIED were not included into the registry.

2.2.2 Local standard of care

Intraoperative hemostasis was meticulously secured by use of electrocautery, non-treated cotton pledgets, and after the procedure, a small sandbag on the pocket was applied for 24 h in combination with bed rest (Fig. 1a).

Table 1 Grading of pocket hematomas and definition of pocket infections [2, 14, 15]

Grading of pocket hematoma (as proposed in 12)		Definition of pocket infection (adapted from 13)	
Grade 1	Ecchymosis or mild effusion, no swelling or pain to CIED pocket	Definitive pocket infection	Purulent discharge at the pocket site, either spontaneous or expressed upon palpation of the site, regardless of whether an organism is cultured from the site, or Erythema, tenderness, and induration (any two of the three) at the pocket site with serous or serosanguinous discharge, either spontaneous or expressed upon palpation, in the presence of a positive pocket site culture
Grade 2	Larger effusion in the pocket leading to swelling and causing functional impairment or pain to CIED pocket		
Grade 3	Any pocket hematoma requiring: re-operation and/or resulting in prolongation of hospitalization (defined as extended hospitalization or re-hospitalization for > 24 h, post-index surgery, primarily due to hematoma) and/or requiring interruption of anticoagulation (defined as reversal or intentional withholding, in response to pocket hematoma, resulting in sub-therapeutic anticoagulation for > 24 h)	Probable pocket infection	Erythema, tenderness, induration (any two of the three) at the pocket site with serous or serosanguinous discharge, either spontaneous or expressed upon palpation, in the absence of an exit site culture, or in the presence of a pocket site culture revealing no growth or one not considered positive, as described above, or Erythema, tenderness, and induration (any two of the three) at the pocket site without any discharge (even with expression) where alternative causes can be ruled out
Grade > 1	Includes definition of grade 2 + 3		

2.3 Vacuum drainage system

The closed vacuum drainage system used in our registry is a sterile single use active high-negative-pressure drain (0.9 bar) (Dahlhausen & Co., Cologne, Germany). The outer diameter of the drainage is 10 Fr (3.3 mm) and the end intended to be in the wound is equipped with several lateral holes to facilitate fluid removal. The reservoir holds a maximum of 400 cc of fluid (Fig. 1 Panel B). The drainage system was left in place for at least 24 h in combination with bed rest for 24 h. However, it was removed after a maximum of 48 h to avoid an increased risk of ascending bacterial infections associated with longer periods [17].

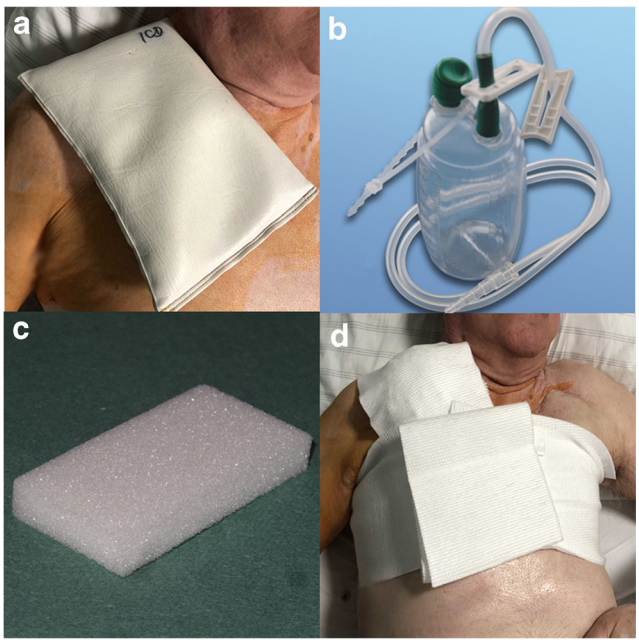

Fig. 1 (**a**) Standard of care. (**b**) Vacuum drainage. (**c**) Hemostatic sponge. (**d**) Premofix compression device

2.4 Stypro® hemostatic sponge

Stypro® hemostatic sponge (Curasan AG, Kleinostheim, Germany) is a sterile resorbable denatured bovine gelatin sponge. It is commercially available and indicated for use in the local management and control of bleeding. The biomaterial consists of more than 80% proteins and has a neutral pH. A microporous and inter-connective structure of the sponge activates the coagulation cascade, although the main mode of action is a tamponade effect. It offers a high absorption capacity (up to 50 times of the own weight), is biocompatible, and its full resorption is completed *in vivo* after 2–3 weeks when applied within the tissue, but much faster (in 2–3 days) when used to cover or seal wounds (Fig. 1c). Patients receiving the Stypro® hemostatic sponge were advised to keep bed rest for 24 h. As previous studies report on different immunogenetic potential of various collagen implants, demonstrating increased antibody titers against collagen *in vivo* in some of them [12], C-reactive protein and Immunoglobulin E were determined in all patients 24 h after the implantation procedure.

2.5 Premofix® PM/ICD compression device

The Premofix® PM/ICD (Andanza, Meinhard, Germany) is a single-use bandaging system intended for ICD/pacemaker implantation aftercare. This bandaging system is produced with a five-layer elastic material. A special semipermeable internal layer of the bandage is designed to protect the operation site against bacterial infection. Included into the commercially available set is a pressure disc to increase the local pressure on the CIED pocket (Fig. 1d). The device was applied for 24 h in combination with bed rest.

2.6 Endpoints

The primary endpoint was a combination of hematoma grade 2 or 3, and pocket infection. The secondary endpoint was the occurrence of hematoma grade 3 (any pocket hematoma requiring: re-operation and/or resulting in prolongation of hospitalization (defined as extended hospitalization or re-hospitalization for > 24 h, post index surgery, primarily due to hematoma) and/or requiring interruption of anticoagulation (defined as reversal or intentional withholding, in response to pocket hematoma, resulting in sub-therapeutic anticoagulation for > 24 h)).

2.7 Statistical analysis

Continuous variables are reported as mean value ± standard deviation or median or interquartile ranges (25th–75th percentiles) as appropriate. Categorical variables are presented as absolute (n) and relative (%) frequencies. Normal distribution of variables was assessed using the D'Agostino-Pearson omnibus normality test. The Mann–Whitney-test and Fisher's exact test were used, as appropriate. Relative risks for developing an endpoint and the corresponding 95% confidence intervals were calculated. All tests were two-tailed and a probability value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the GraphPad Prism version 6.02 for windows (GraphPad Software, La Jolla, CA, USA).

3 Results

During the study period, a total of 1.456 patients received a CIED (PM, CRT-P, ICD, CRT-D, and CCM). Among them, 406 patients (27.9%) received the first permanent CIED and were on anticoagulation and/or DAPT and were included in this registry (Fig. 2).

The number of patients receiving Stypro®, vacuum drainage system, Premofix®, or standard of care was 99 (24.4%), 103 (25.4%), 103 (25.4%), and 101 (24.9%), respectively.

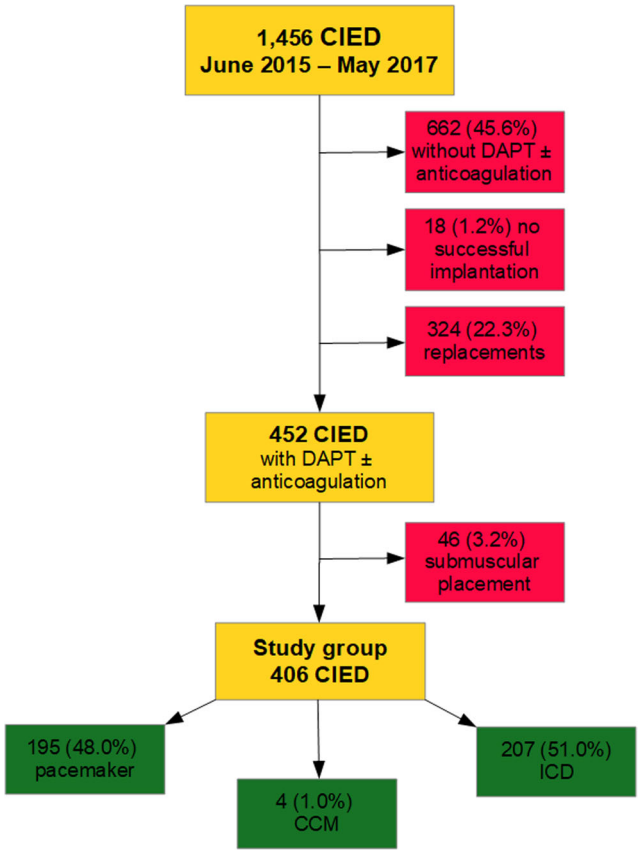

Fig. 2 Flow chart of the devices. *CCM* cardiac contractility modulation, *CIED* cardiac implantable electronic device, *DAPT* dual antiplatelet therapy, *ICD* implantable cardioverter defibrillator

Baseline characteristics were equally distributed among the groups, except prevalence of coronary artery disease ($p < 0.01$) and implantation of a coronary stent ($p < 0.05$) which was significantly lower in the Premofix® group. Median INR at the time of implantation was 2.0 (IQR 1.9–2.25) ranging from 1.74 to 3.1, and without significant differences among the groups. Less than 1% of the patients in our study received either LMWH or UFH and was the result of a preoperative temporary pacemaker via the femoral route for complete atrio-ventricular block in all cases; details are shown in Table 2.

There was no statistically significant difference in the number of leads implanted in each group. Most of the CIEDs implanted were ICDs (207/406 (51%)), and the majority of CIED types were dual chamber pacemakers (32%) and CRT-ICDs (24%). One vacuum drainage was artificially removed during transfer from the operating table to the patient's bed and this patient was excluded from the analysis.

The median duration of the procedure was 70 (interquartile range (IQR) 58–95) min for CRT CIEDs, 40 (IQR 30–65) min for two-lead CIEDs, and 35 (IQR 25–50) min for one-lead CIEDs and did not differ among the groups. For details, refer to Table 3.

Table 2 Baseline characteristics, indications for anticoagulation and/or DAPT, medication, and laboratory parameters

Variable	Total $n = 406$	Standard of care $n = 101$	Vacuum drainage $n = 103$	Stypro® hemostatic sponge $n = 99$	Premofix® compression device $n = 103$
Characteristic					
Age (years)					
Median (IQR)	73 (66–79)	72 (67–78)	71 (65–80)	72 (66–79)	75 (67–79)
Range	40–96	45–96	40–90	42–90	47–90
Sex (male)—no. (%)	287 (70.7%)	74 (73.3%)	72 (69.9%)	67 (67.7%)	74 (71.8%)
Body mass index (kg/m^2)					
Median (IQR)	28 (25–31)	27 (25–30)	27 (25–30)	28 (26–31)	29 (25–32)
Range	15–47	18–39	15–47	18–41.5	18–46
Coronary artery disease—no. (%)	300 (73.9%)	80 (79.2%)	77 (74.8%)	79 (79.8%)	**64 (62.1%)§**
Diabetes—no. (%)	156 (38.4%)	42 (41.6%)	37 (35.9%)	32 (32.3%)	45 (43.7%)
Hypertension—no. (%)	368 (90.6%)	92 (91.1%)	95 (92.2%)	87 (87.9%)	94 (91.3%)
LVEF (%)					
Median (IQR)	40 (30–55)	35 (25–55)	35 (30–50)	40 (30–55)	45 (30–55)
Range	10–75	10–75	15–68	15–65	10–70
Indications for anticoagulation—no. (%)					
Atrial fibrillation or atrial flutter	244 (60.1%)	61 (60.4%)	57 (55.3%)	65 (65.7%)	61 (60.4%)
Mechanical aortic/mitral valve replacement	49 (12.1%)	13 (12.9%)	10 (9.7%)	10 (10.1%)	16 (15.5%)
Other	4 (1.0%)	0 (0.0%)	2 (1.9%)	0 (0.0%)	2 (2.0%)
Indications for DAPT—no. (%)					
Recent coronary stent	196 (48.3%)	52 (51.5%)	54 (52.4%)	56 (56.6%)	**34 (33.0%)***
Recent percutaneous valve	26 (6.4%)	4 (4.0%)	8 (7.8%)	6 (6.1%)	8 (7.8%)
Medications—no. (%)					
Oral anticoagulation	179 (44.3%)	40 (39.6%)	48 (46.6%)	38 (38.4%)	51 (49.5%)
LMWH or UFH	3 (0.7%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)
Dual antiplatelet therapy	176 (43.4%)	48 (47.5%)	47 (45.6%)	45 (45.5%)	36 (35.3%)
Anticoagulation + dual antiplatelet therapy	50 (12.3%)	12 (11.9%)	8 (7.8%)	15 (15.2%)	15 (14.6%)
Laboratory parameters					
Creatinine (mg/dl), median (IQR)	103 (80–132)	106 (86–133)	97 (84–127)	97 (76–121)	108 (83–136)
Platelets (10^3/μl), median (IQR)	199 (161–251)	197 (159–239)	207 (167–259)	190 (168–250)	199 (157–248)
Preoperative INR, median (IQR)	2.0 (1.9–2.25)	2.1 (2.0–2.2)	2.0 (1.9–2.3)	2.15 (1.96–2.26)	2.02 (1.91–2.28)
Range	1.74–3.1	1.8–2.8	1.74–2.6	1.8–3.1	1.79–2.8
C-reactive protein (mg/l)					
Pre-implantation, median (IQR)	4.8 (1.9–16)	5.0 (2.1–13)	4.6 (2.2–19)	3.4 (1.6–13)	5.7 (2.0–16)
Postimplantation, median (IQR)	25 (12–48)	16 (11–39)	16 (7.0–52)	**32 (17–57)***	24 (12–42)
Delta, median (IQR)	15 (4.0–30)	11 (6.0–19)	11 (2.1–21)	**28 (13–45)¶**	13 (3.0–20)
Immunoglobulin E; postimplantation (IU/ml)					
Median (IQR)	45 (15–131)	46 (17–111)	**22 (6.1–137)***	56 (18–204)	42 (9–117)

Bold values denote significant values compared to standard of care

DAPT dual antiplatelet therapy, *INR* international normalized ratio, *IQR* interquartile range, *LMWH* low molecular weight heparin, *LVEF* char ventricular ejection fraction, *UFH* unfractionated heparin

*p value < 0.05 compared to control; §p value < 0.01 compared to control; ¶p value < 0.001 compared to control

3.1 Primary endpoint

The median follow-up was 87 (IQR 30–110) days without differences among the groups. Application of Stypro® or use of Premofix® significantly lowered the incidence of the primary endpoint (relative risk 0.38 (95% CI 0.16–0.94) and 0.37 (95% CI 0.15–0.90); $p < 0.05$) compared to standard of care. Use of a vacuum drainage did not lower the incidence of the primary endpoint.

3.2 Effectiveness endpoint

3.2.1 Incidence of hematoma formation after CIED implantation

The application of Premofix® resulted in a significant reduction of the total number of hematomas (relative risk 0.49 (95% CI 0.26–0.93)), the incidence of grade 2 hematomas (relative risk 0.27 (95% CI 0.08–0.95), and also of grade 2 or 3 hematomas (relative risk 0.39 (95% CI 0.16–0.97); $p < 0.05$ for all). However, the use of Premofix® did not affect the incidence of grade 3 hematoma (secondary endpoint): relative risk 0.25 (95% CI) 0.028–2.2). The use of a vacuum drainage or use of Stypro® did not affect the incidence of the total number of hematomas (Fig. 3), although the latter reached borderline significance for hematomas grade 2 or 3 (relative risk 0.41 (95% CI 0.17–1.0); $p = 0.06$).

Pocket hematoma occurred in 81/406 (20.0%) patients and developed in all patients before hospital discharge (median 2 days post-implantation); in seven patients (8.6%), operative evacuation was required with no need for blood transfusion. The mode of anticoagulation in hematomas needing redo-surgery was coumadin therapy in four (57.1%), heparin in two cases (28.6%), and triple therapy in one (14.3%). The incidence of grade 2 or 3 hematomas was the lowest in the DAPT group (one hematoma among 180 patients = 0.6%), and 4/109 (3.4%) for coumadin therapy. The incidence of hematomas grade 2 or 3 (overall 9.4%) was affected by the type of pulse generator. Implantation of (smaller) pacemaker device was associated with lower and implantation of an ICD was associated with higher incidence of pocket hematoma. CIED implantations while the INR was ≥2.5 or if patients were under triple therapy almost doubled the incidence, whereas hematomas grade 2 or 3 were less likely in obese (BMI ≥ 30) patients (Table 4).

3.3 Safety endpoints

3.3.1 Incidence of infection after CIED implantation

Pocket infection developed in 3/406 (0.7%) patients (two in the vacuum drainage group and one in the standard of care group). Two pocket infections occurred in < 4 weeks after CIED implantation and one patient experienced a pocket erosion after 9 weeks which was classified as infection—. All patients underwent operative removal of the CIED and the leads with re-implantation after successful antibiotic therapy.

3.3.2 Other complications

One patient in the Premofix® group developed a tension bulla, which resolved under conservative therapy. One death was procedure associated (pericardial tamponade during CRT-D implantation); the remaining three deaths were not related to CIED implantation. The overall number of complications (all cause death, lead displacement, pneumo−/hemothorax, and pericardial effusion) was not different among the groups – Table 4.

Table 3 Device type and operative details

Variable	Total $n = 406$	Standard of care $n = 101$	Vacuum drainage $n = 103$	Stypro® hemostatic sponge $n = 99$	Premofix® compression device $n = 103$
Device type					
Pacemaker implant—no. (%)	195 (48.0%)	43 (42.6%)	48 (46.6%)	52 (52.5%)	52 (50.5%)
Single chamber	28 (6.9%)	8 (7.9%)	6 (5.8%)	10 (10.1%)	4 (3.9%)
Dual chamber	130 (32.0%)	29 (28.7%)	35 (34.0%)	31 (31.3%)	35 (34.3%)
Cardiac resynchronization therapy	37 (9.1%)	6 (5.9%)	7 (6.8%)	11 (11.1%)	13 (12.7%)
ICD implant—no. (%)	207 (51.0%)	56 (55.4%)	55 (53.4%)	47 (47.5%)	49 (48.0%)
Single chamber	72 (17.7%)	18 (17.8%)	20 (19.4%)	24 (24.2%)	10 (9.8%)
Dual chamber	37 (9.1%)	9 (8.9%)	14 (13.6%)	5 (5.1%)	9 (8.8%)
Cardiac resynchronization therapy	98 (24.1%)	29 (28.7%)	21 (20.4%)	18 (18.2%)	30 (29.4%)
Cardiac contractility modulation	4 (1.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	2 (2.0%)
Total number of implanted leads	822	213	180	193	236
Duration of device implantation; (min). Median (IQR)	45 (30–65)	50 (30–63)	45 (34–65)	40 (30–65)	45 (30–65)
Single chamber devices	35 (25–50)	33 (25–40)	35 (25–49)	40 (30–65)	35 (25–45)
Dual chamber devices	40 (30–65)	45 (30–65)	40 (35–55)	45 (30–64)	40 (30–53)
Cardiac resynchronization therapy devices	70 (58–95)	60 (55–71)	75 (64–98)	65 (60–106)	70 (55–100)

CRT cardiac resynchronization therapy, *DDD* dual chamber, *ICD* implantable cardioverter defibrillator, *IQR* interquartile range, *PM* pacemaker, *VVI* ventricular single chamber

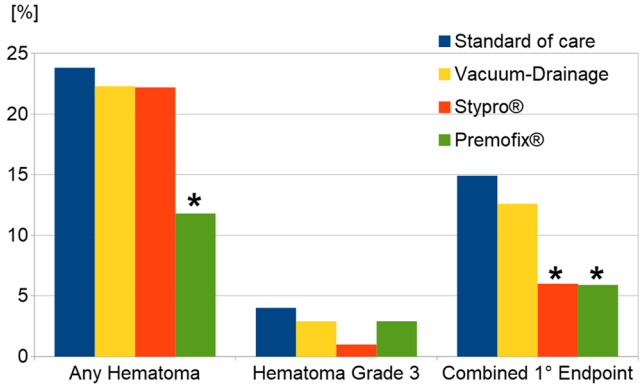

Fig. 3 Incidence of the primary (1°) endpoint and incidence of post-operative hematoma in patients under anticoagulants and/or DAPT undergoing CIED implantation. Asterisk denotes significant values

3.3.3 Antigenicity, immunogenicity, and inflammation

Post-operative Immunoglobulin E (IgE) levels were comparable among patients receiving Stypro®, Premofix®, and standard of care. The group of patients receiving a vacuum drainage had significantly lower levels of IgE 24 h postimplantation, whereas post-operative mean IgE level was the highest in the hemostatic sponge group. The post-operative increase of C-reactive protein (CRP) was significantly higher in the Stypro® Group. The increase of post-operative CRP levels in patients receiving vacuum drainage or Premofix® were not different compared to those in the standard of care group—Table 2.

4 Discussion

The results of this prospective registry suggest that the incidence of the primary endpoint (a combination of grade 2 or 3 hematoma or pocket infection) is significantly lower when the Premofix® compression device or a Stypro® is applied in patients at high risk of bleeding due to anticoagulation and/or DAPT undergoing CIED implantation.

4.1 Effectiveness of the investigated devices

The incidence of hematomas in our study is well comparable to data from the literature. The BRUISE control trial [3] reported a 3.5% incidence of "clinically significant pocket-hematoma" which is the same as our secondary endpoint "Grade 3 hematoma" with an incidence of 4% in the control group. The Premofix® compression device was the only tool in our study which significantly lowered the total number of hematomas and also the incidence of hematomas grade 2 or 3. This is mainly attributable to the continuous pressure on the pocket without the risk of dislocation when the patient changes position. Recently, a pilot study of a new compression device from Japan [18] demonstrated a significant drop of the pressure on the pocket in the upright position of the patient with a conventional pressure dressing. In patients with this new device (which is comparable to the device used in our study), the pressure on the pocket was the same in supine and upright position [18]. Another study evaluating a post-surgical vest among 20 patients receiving CIED with uninterrupted warfarin or DAPT treatment [19] demonstrated a significant reduction of moderate or large pocket hematomas. Other (e.g., Kaolin-based) devices are currently under development but have not been tested in patients after CIED surgery [20].

The vacuum drainage system and the Stypro® hemostatic sponge had no significant impact on the incidence of post-operative pocket hematoma. A randomized study including 200 surgical patients demonstrated that insertion of a vacuum drainage system even doubled the incidence of post-operative hematomas [21]. Stypro® controls bleeding mainly by volume expansion and mechanical compression [22]. As the gelatin of this sponge has almost no bio-activity to induce the coagulation cascade, it proved to be inferior to prevent post-operative bleeding after spinal fusion surgery compared to collagen sponges [22]. This might be an explanation for the lack of effect of the Stypro® device in our study, although the reduction of hematomas grade 2 or 3 was borderline significant ($p = 0.06$).

4.2 Safety of the investigated devices

Infections related to CIED implantation have been recognized as a major problem since the early 1970s [23], and pocket infections is the most common type (~90%) [23]. The magnitude of the infection risk for patients undergoing CIED implantations is well studied. In a study using the National Inpatient Sample discharge records (1993–2008), the overall rate of CIED infections was 1.6% per year [24]. The infection burden associated with CIED implantations increased over time, particularly since 2004 (1.5% per year in 2004 to 2.4% per year in 2008) [24]. This was attributed to an increase in patient comorbidities during this time period such as diabetes, renal failure, and heart failure [24]. The infection rate in our cohort is well comparable with these reported infection rates; particularly, there was neither an infectious signal in the drainage nor in the Stypro® group. These two devices can at least theoretically increase the incidence of pocket infection, as ascending bacterial infections can be associated with wound drains [17] and the hemostatic sponge carries, although γ-sterilized, the risk of bacterial contamination [22]. However, a recent multivariate analysis of data from the randomized BRUISE CONTROL INFECTION study demonstrated that the presence of a clinically significant hematoma (which had the same definition as our grade 3 hematoma) was the only variable

Table 4 Complications after CIED implantation

Outcome	Total $n = 406$	Standard of care $n = 101$	Vacuum drainage $n = 103$	Stypro® hemostatic sponge $n = 99$	Premofix® compression device $n = 103$
Primary endpoint—no. (%)					
Hematoma Grade 2 or 3, or pocket infection	41 (10.1%)	16 (15.8%)	13 (12.6%)	**6 (6.0%)***	**6 (5.9%)***
Secondary endpoint—no. (%)					
Grade 3 hematoma	11 (2.7%)	4 (4.0%)	3 (2.9%)	1 (1.0%)	3 (2.9%)
a. Requiring evacuation	7 (1.7%)	4 (4.0%)	2 (1.9%)	0 (0.0%)	1 (1.0%)
b. Prolonging hospitalization	1 (0.2%)	4 (0.0%)	2 (0.0%)	0 (0.0%)	1 (1.0%)
c. Withholding/reversal of OAC	3 (0.7%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)
Other—no. (%)					
Hematoma, any	81 (20.0%)	24 (23.8%)	23 (22.3%)	22 (22.2%)	**12 (11.8%)***
Hematoma, grade 2	27 (6.7%)	11 (10.9%)	8 (7.8%)	5 (5.1%)	**3 (2.9%)***
Hematoma, grade 2 or 3	38 (9.4%)	15 (14.9%)	11 (10.7%)	6 (6.0%)	**6 (5.9%)***
Hematoma, grade 1	43 (10.9%)	9 (8.9%)	12 (11.7%)	16 (16.2%)	6 (5.9%)
Pocket infection	3 (0.7%)	1 (1.0%)	2 (1.9%)	0 (0.0%)	0 (0.0%)
Death from any cause	4 (1.0%)	1 (1.0%)	1 (1.0%)	2 (2.0%)	0 (0.0%)
Pneumothorax	4 (1.0%)	2 (2.0%)	2 (1.9%)	0 (0.0%)	0 (0.0%)
Hemothorax	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pericardial effusion/cardiac tamponade	2 (0.5%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Lead dislodgement	26 (6.4%)	6 (5.9%)	9 (8.7%)	8 (8.1%)	3 (2.9%)
Hematoma grade 2 or 3 related to type of device					
Pacemaker/CRT-P	13/194 (6.7%)	5/43 (11.6%)	5/48 (10.4%)	1/52 (1.9%)	2/51 (3.9%)
Defibrillator/CRT-D	24/207 (11.6%)	9/56 (16.1%)	6/55 (10.9%)	5/47 (10.6%)	4/49 (8.2%)
Hematoma grade 2 or 3 related to INR ≥2.5	7/38 (18.4%)	2/7 (28.6%)	2/5 (40.0%)	0/5 (0.0%)	3/21 (14.3%)
Hematoma grade 2 or 3 related to triple therapy	7/43 (16.3%)	2/12 (16.7%)	2/8 (25.0%)	1/15 (6.7%)	2/8 (25.0%)
Hematoma grade 2 or 3 related to BMI ≥ 30	7/135 (5.2%)	2/32 (6.3%)	3/29 (10.3%)	0/32 (0.0%)	2/42 (4.8%)

Bold values denote significant values compared to standard of care

BMI body mass index, *CRT* cardiac resynchronization therapy, *INR* international normalized ratio, *OAC* oral anticoagulation

*p value < 0.05 compared to control

significantly associated with an increased risk of future development of infection (Hazard ratio 7.7) [6].

4.3 Antigenicity, immunogenicity, and inflammation

After the use of some resorbable hemostats (mainly collagen based), an inflammatory response develops around the hemostat until complete absorption is accomplished [25]. Previous studies discussed on different immunogenetic potential of various gelatin implants, and in general, gelatin is thought to be non-immunogenic because of the absence of aromatic groupings [26, 27]. However, the markers of antigenicity, immunogenicity, and inflammation chosen in our study were either significantly higher (CRP) or showed the highest value of all groups (post-operative Immunoglobulin E) in the Stypro® group.

4.4 Limitations

Several limitations of the study merit further discussion. First, although our registry was designed prospectively, it is subject to limitations inherent in observational studies, and in single-center studies. Secondly, the subjectivity of the assessment of pocket hematoma can lead to difference in interpretation among various observers especially in "visible" devices, and our study included only patients on therapeutic warfarin and not any of the novel anticoagulants (NOACs) and therefore the results might not be applicable to patients on NOACs. Third, given the importance of the use of DAPT and its well-known risk of increasing the incidence of pocket hematomas, the lower prevalence of CAD and consequently DAPT in the Premofix® Group represents another limitation of our study. Finally, we must acknowledge the potential effect of the sequence of interventions. When

hematomas are closely monitored and recorded over time, it is possible that operators modified other aspects of surgical technique or management to improve results over time, independently of the applied device.

5 Conclusion

In patients receiving anticoagulation and/or dual antiplatelet therapy undergoing CIED implantation, the use of Premofix® compression device and Stypro® hemostatic sponge significantly lowered the occurrence of the primary endpoint (a composite of hematoma grade 2 or 3 or pocket infection) compared to standard of care. However, regarding reduction of hematomas who prolong the hospital stay and/or require reoperation (grade 3—secondary endpoint), there was no statistically significant advantage of one of the different preventive strategies. To further reduce the incidence of pocket hematoma following CIED implantation, discontinuation of one antiplatelet agent in patients under "triple therapy" should be considered.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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