Management of antithrombotic therapy in patients undergoing electrophysiological device surgery

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The aim of this review is to formulate practical recommendations for the management of antithrombotic therapy in patients undergoing cardiac implantable electronic device (CIED) surgery by providing indications for a systematic approach to the problem integrating general technical considerations with patient-specific elements based on a careful evaluation of the balance between haemorrhagic and thromboembolic risk. Hundreds of thousands of patients undergo implantation or replacement of CIEDs annually in Europe, and up to 50% of these subjects receive antiplatelet agents or oral anticoagulants. The rate of CIED-related complications, mainly infective, has also significantly increased so that transvenous lead extraction procedures are, consequently, often required. Cardiac implantable electronic device surgery is peculiar and portends specific intrinsic risks of developing potentially fatal haemorrhagic complications; on the other hand, the periprocedural suspension of antithrombotic therapy in patients with high thromboembolic risk cardiac conditions may have catastrophic consequences. Accordingly, the management of the candidate to CIED surgery receiving concomitant antithrombotic therapy is a topic of great clinical relevance yet controversial and only partially, if at all, adequately addressed in evidence-based current guidelines. In spite of the fact that in many procedures it seems reasonably safe to proceed with aspirin only or without interruption of anticoagulants, restricting to selected cases the use of bridging therapy with parenteral heparins, there are lots of variables that may make the therapeutic choices challenging. The decision-making process applied in this document relies on the development of a stratification of the procedural haemorrhagic risk and of the risk deriving from the suspension of antiplatelet or anticoagulant therapy combined to generate different clinical scenarios with specific indications for optimal management of periprocedural antithrombotic therapy.

Keywords

Antiplatelet therapy • Anticoagulation • Implantable cardioverter defibrillator • Haemorrhage • Pacemaker
Coronary stent • Bleeding

Introduction

Over the last 60 years, we have witnessed a constant and exciting technological evolution and an exponential growth in the number of implantations of cardiac implantable electronic devices (CIEDs).1 Initially limited to few clinical indications, CIEDs are currently available for treatment of various cardiac rhythm disorders and prevention and treatment of numerous heart diseases.1 A 2009 worldwide survey covering 80% of the overall procedures performed on a global scale reported 1 002 664 pacemaker (PM) and 328 027 implantable cardioverter-defibrillator (ICD) implantations, while PM and ICD replacements accounted for 264 824 and 222 407 procedures, respectively.2 Representative real-life data of the population in Europe indicate an overall number of 471 284 PM implantations and 74 151 ICD implantations in 2009.3 The increase in implantations and replacements has resulted in an increase in the rate of complications, mainly of infective nature, related to CIEDs and, as a consequence, in the number of transvenous lead extractions, a gold standard in the treatment of infective complications and often required in the management of malfunctions.4

The complexity of patients candidate to CIED implantation has shown a parallel increase, both in terms of cardiac and non-cardiac comorbidities, and of concomitant therapy.5–7 In particular, the number of patients receiving antithrombotic therapy has significantly increased. The greater use of oral anticoagulant therapy (OAT), or single and dual antiplatelet therapy (DAPT), is attributable to the

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Aging of the population, which is also partly accountable for the higher incidence of atrial fibrillation (AF),\textsuperscript{8} and the growing number of patients with heart and endovascular prostheses secondary to the great diffusion of coronary and peripheral interventions.\textsuperscript{9,10} Data on contemporary populations from clinical studies or surveys indicate a rate of use of anticoagulant therapy ranging from 15% in patients with PMs\textsuperscript{5} to 35% in patients with ICDs,\textsuperscript{6} reaching almost 50% in patients with cardiac resynchronization therapies (CRTs).\textsuperscript{7} Approximately 50% of these patients make use of single or DAPT.\textsuperscript{5–7}

The implantation procedure is the first, crucial step for therapeutic success in patients requiring a CIED. The primary objective of the procedure is patient safety, ideally devoid of complications. The secondary objective is the quality of the therapy through the achievement of long-term reliability and efficiency of the CIED, depending on optimal management of diverse factors, such as venous access, position, and electronic parameters of the leads. A haemorrhagic complication could compromise each step of this delicate process, with clinically significant consequences for the patients. The management of patients candidate to CIED implantation or replacement receiving concomitant antithrombotic therapy is thus a current clinical topic, potentially involving hundreds of thousands of patients each year, yet it remains a controversial issue, and only marginally the object of evidence-based recommendations in current guidelines.\textsuperscript{11,12} Recent data on European clinical practice indeed portray a continent, which is almost equally divided between operators who perform the procedures without interruption of OAT and those who discontinue administration of the drug, switching to parenteral heparins adopting approaches that vary even within the same center.\textsuperscript{13} Given the scanty availability of data, management of antithrombotic therapy in case of transvenous lead removal appears to be even more controversial. Starting from these assumptions, this review was inspired by the need to provide guidance for a systematic approach to the problem, integrating general technical considerations and patient-specific elements based on a careful haemorrhagic/thromboembolic risk assessment. The authors of this consensus document therefore intend to formulate practical recommendations for the management of antithrombotic therapy in candidates to CIED surgery, derived from an extensive analysis of the data available in the literature. The results of such analysis were used to create an algorithm/treatment regimen ensuing from continuous consultations between clinical and interventional cardiologists representing the Associazione Nazionale Medici Cardiologi Ospedalieri and Associazione Italiana Aritmologia e Cardiostimolazione of the Tuscany Region. The aspects pertaining to periprocedural antithrombotic management in patients candidate to transvenous lead removal are analysed separately.

### Haemorrhagic risk associated with device implantation

#### General considerations and definition of haemorrhagic risk

The implantation of PMs or ICDs is generally considered a minor surgical procedure not associated with an increased inherent risk of bleeding. Conversely, such risk is acknowledged in case of periprocedural administration of antithrombotic agents.\textsuperscript{14} Actually, CIED implantation presents some technical peculiarities that may predispose to the development of specific haemorrhagic complications ranging from mild to potentially life-threatening. Dissection and separation of infraclavicular fascial planes and lack of repair of the solution of continuity created to house the device may favour the occurrence of pocket haematoma.\textsuperscript{15} Moreover, the main characteristic of PM or ICD implantations is the need to obtain venous vascular access for the introduction, handling, and placement of leads inside the right cardiac chambers and the coronary venous system when CRT-P/CRT-D are being implanted. These procedures involve a higher exposure to the risk of traumaism to vascular structures,\textsuperscript{7,16} and potentially of cardiac perforation causing hemopericardium and eventually cardiac tamponade.\textsuperscript{17}

The most common haemorrhagic complication is the formation of pocket haematoma. Albeit differently described in the literature, a haematoma should be considered severeclinically significant when associated with intense local pain and patient discomfort, prolonged hospitalization, need of repeated follow-up visits, surgical revision of the implant with evacuation of the blood, or need of transfusions.\textsuperscript{15,18,19} Historically, the incidence of pocket haematoma reported in the literature was up to 5% of procedures, with higher rates in case of ICD implantation.\textsuperscript{15} More recent case studies report pocket haematomas in \textasciitilde2.5% of ICD implantations,\textsuperscript{16} >3% in case of CRT-P/CRT-D implantation, and up to 4.2% in case of upgrading of a previous implant to CRT-P/ CRT-D.\textsuperscript{7} In case of surgical revision of the implant with repositioning due to dislocation or placement of a new lead, the risk of pocket haematoma is reported to be 4.3%.\textsuperscript{20} The formation of pocket haematoma is likely to have serious consequences for the patient, including a paradoxical increased risk of thromboembolism due to prolonged suspension of antithrombotic therapy. This haemorrhagic complication has been associated with a potential increase in the risk of CIED infection,\textsuperscript{21} the need of repeat surgery in up to 44% of cases,\textsuperscript{15} and finally, hospitalization prolonged by 3.1 days with an incremental cost of $6995, as calculated in a North American case study.\textsuperscript{16} The timing of haematoma formation can be insidious, although most, virtually all, studies report it to occur during the first week post-procedure\textsuperscript{15} with mean times between 3.5 and 5.1 days post-implantation.\textsuperscript{22,23} This time frame should be considered especially for high haemorrhagic risk patients for whom earlier follow-up should be warranted instead of the conventional 4–6 weeks after discharge for the first check-up, rather than a prolonged period of observation during hospitalization.

A certain amount of risk of developing pocket haematomas is also described in cases of generator replacements. Data obtained from the REPLACE registry account for an overall risk of 3.5% on a population of 1750 patients, and a 0.7% risk of severe haematoma.\textsuperscript{20} Also in this case, haematoma formation predisposes to a higher risk of CIED infection (22.7 vs. 0.98%, \(P = 0.002\)).\textsuperscript{24}

Diffuse intraprocedural haemorrhage from muscular, fascial, or vascular structures, reported in 0.5–1.0% of interventions, is another complication that may prolong surgical times, and thus be associated with a higher risk of infection.\textsuperscript{7,15} The occurrence of hemothorax due to subclavian vein or artery injury\textsuperscript{25} or due to simultaneous pericardial and pleural perforation is anecdotal,\textsuperscript{26} albeit very rare, this is a major and potentially life-threatening complication.
Fortunately, cardiac perforation is not a common complication in PM and ICD implantation procedures and seems to occur more frequently with defibrillation leads.27 Despite the incidence reported for clinically manifest perforations ranges from 0.1 to 0.8% with PMs and ICDs, prevalently due to atrial leads, with no difference in the electronic parameters of the leads.28 Although the consequences or the timing of such asymptomatic perforations are not known, percutaneous drainage by pericardiocentesis was reported as necessary in 70% of cases (1618) in the event of acute perforation. In case of placement of left-ventricular pacing leads via the coronary venous system, cardiac tamponade rates of 0.3–0.5% were reported, with coronary sinus dissection between 1.0 and 1.7%,7 the latter complication generally not being associated with untoward clinical consequences, except for the potential need to postpone the procedure, but potentially important and risky in case of ongoing anticoagulant therapy.11 Implantable cardioverter-defibrillator or CRT-D implantation procedures complicated by hemopericardium/tamponade resulted in hospitalization prolonged by 1.9 days, with an incremental cost of $8249, mainly deriving from the high cost of the interventions performed due to the occurrence of the complication.16 In the context of implantation activity, the only procedure virtually devoid of risks is the implantation of subcutaneous devices, namely implantable loop recorders (ILRs), for which no haemorrhagic complications of any nature have been reported.29 Conversely, transvenous lead extraction can be considered as the procedure potentially portending the highest risks, including haemorrhagic (hemopericardium and tamponade from perforation, hemotorax from subclavian vein laceration, pocket haematoma), even though the reported rate of complications is fortunately rather low.30 Given the technical peculiarities of the extraction procedure and its performance limited to highly specialized centres, management of antithrombotic therapy in this scenario is discussed in a dedicated section of this paper (Periprocedural management of antithrombotic therapy in patients undergoing transvenous lead extraction).

The severity of haemorrhagic complications (i.e. minor bleeding vs. major bleeding) is not uniformly defined in the different intervention- al and surgical specialties, nor is univocal the grading of the intrinsic procedural risk, the procedures being categorized as low or high risk depending on the frequency of the occurrence of bleeding (enhanced risk of bleeding with an incidence >1.5% independently of the type of complication and extent—quantity and quality—of the bleeding event)31,32 and the possible onset of bleeding which is either uncontrollable or occurring in anatomically critical sites (e.g. intracranial or pericardial)13 in patients on antithrombotic therapy. If these criteria are rigorously/strictly applied to CIED surgery, virtually all procedures, except generator replacements and ILR implantations, should be considered high risk given the pocket haematoma formation rate and the potential risk of cardiac perforation and pericardial effusion. Although of pivotal interest when dealing with the periprocedural antithrombotic therapy management, the classification of the haemorrhagic risk of CIED surgery as reported in the literature is controversial. In the 2012 guidelines of the American College of Chest Physician (ACCP) on the perioperative management of antithrombotic therapy, similar to bowel polipectomy PM insertion is regarded as a minor bleeding risk procedure, in isolation, yet the perioperative antithrombotic drug administration confers the procedure itself an increased bleeding risk.14 Conversely, in a more recent European Heart Rhythm Association document, PM or ICD implantation is classified as an intervention with low bleeding risk.34 In the opinion of the authors, a correct stratification of procedural haemorrhagic risk should be based on the development of an assessment parameter combining incidence and clinical significance of the bleeding, thus avoiding an overestimation of the risk for events that are frequent but without any clinical-prognostic implications, and for potentially fatal but rare events. Based on this principle, the definition of procedural haemorrhagic risk used in this review is reported in Table 1. The recommendations in the document are of a general nature, provided that a high haemorrhagic risk can be attributed in a case-specific manner based on the clinical judgment of the operator and on concomitant conditions.

A detailed analysis of factors associated with enhanced risk of haemorrhagic complications as well as of technical measures for reducing the risk of developing haemorrhagic complications is provided in two sections of the Supplementary material online, Data.

### Risk associated with discontinuation of antiplatelet therapy

The risk associated with discontinuation of antiplatelet therapy in patients with ischaemic heart disease (IHD) is influenced by numerous factors, namely:

- acute or stable IHD;
- time from the index event [acute coronary syndrome (ACS) and/or stenting];
- previous stent (type, number, and implantation technique);
- reason for discontinuation (planned or induced by adverse events);
- discontinuation of one or both antiplatelet drugs;
- duration of discontinuation of antiplatelet therapy;
- prothrombotic potential of the surgical procedure.

| Table 1 Periprocedural bleeding risk stratification |
|----------------|----------------|
| Risk           | Procedure                  |
| Low            | ILR implantation            |
|                | Device replacement           |
| Intermediate   | Lead/implantation revisions |
|                | Upgrading procedures         |
|                | PM, ICD or CRT implantation |
| High           | Transvenous lead extraction |
|                | Selected intermediate risk cases deemed at increased risk due to concomitant conditions (i.e. emergency/ urgency, transvenous temporary pacing, re-implantation following extraction/removal, complex anatomies including congenital cardiopathies) |

CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; ILR, implantable loop recorder; PM, pacemaker.
The quantification of the risk associated with discontinuation of antiplatelet therapy in individual patients is therefore a very complex prognostic issue due to the numerous and reciprocal interactions of the factors involved and the paucity of randomized controlled trials (RCTs) on the topic, the evidence available being almost exclusively based on observational studies, registries, or post-hoc analyses of RCTs performed for other purposes.

Risk associated with discontinuation of antiplatelet therapy in patients with ischaemic heart disease without previous stent

In a meta-analysis conducted on more than 50,000 patients with IHD enrolled in six clinical studies, Biondi-Zoccai et al. have shown that the risk of major adverse cardiac events increases three-fold with discontinuation of aspirin. Such effect was more evident in patients who had previously received a drug-eluting stent (DES) [relative risk (RR) = 89.78, P < 0.0001] but remained significant also in patients diagnosed with IHD independent of the presence of a stent (RR = 1.82, P < 0.0001) and in candidates to coronary artery bypass grafting (CABG) (RR = 2.4, P < 0.002). The risk specifically associated with discontinuation of aspirin in patients candidate to elective surgery was assessed in a RCT. The study, markedly underpowered with respect to the clinical endpoint (220 patients), has nevertheless shown a significantly higher incidence of major cardiac events [myocardial infarction (MI), severe arrhythmias, cardiac arrest, and cardiovascular death] in the first 30 days following surgery in the placebo group compared with the group treated with aspirin (9.0 vs. 1.8%, P = 0.02). Discontinuation of aspirin treatment in the secondary prevention of vascular disease has also been associated with an increased risk of ischaemic stroke in the first four weeks following discontinuation. The increased risk of adverse events observed after discontinuation of aspirin is possibly, and at least partly, attributable to a rebound effect of discontinuing the therapy (increase in thromboxane A2 activity, inhibition of fibrinolytic systems).

The risk associated with discontinuation of clopidogrel in patients with ACS treated conservatively was assessed in a retrospective study on 1568 patients enrolled in the ‘Department of Veterans Affairs Veterans Health Administration Cardiac Care Follow-up Clinical Study’. The authors observed an increased risk of death and adverse event was of only 10 days, with 30% of events within the first 90 days after discontinuation (60.8, 21.3, and 9.7% of events in the 0–90, 91–180, and 181–270 days intervals from discontinuation, respectively). Such increased risk was also present in patients discontinuing clopidogrel more than 9 months after hospitalization for ACS.

Risk associated with discontinuation of antiplatelet therapy in patients with stents

In patients with stents, discontinuation of antiplatelet therapy involves an additional risk compared to the situation previously described, namely stent thrombosis. This aspect has gained particular significance in recent years with the introduction and subsequent increasingly widespread use of DES. The initial studies on predictors of DES thrombosis indeed showed a close association between DAPT discontinuation and stent thrombosis at one year or longer following implantation. However, most data on the prognostic impact of DAPT discontinuation on stent thrombosis are derived from observational or retrospective studies, in which the large majority of discontinuations was not planned and caused, in more than 70% of cases, by bleeding events or the need to perform surgery, often for neoplasia. In these cases, it is difficult to distinguish between a genuine cause–effect relationship and a simple statistical association in which discontinuation of DAPT is only an epiphenomenon associated with a number of prothrombotic factors (haemorrhage, transfusions, surgery, and tumours), which are the real cause of stent thrombosis. In contrast, in studies where DAPT discontinuation was planned per protocol 3 to 6 months after implantation of sirolimus- or paclitaxel-eluting stent instead of being triggered by a spontaneous event, the incidence of late stent thrombosis was 0.3–0.4%/year, i.e. about ten-fold lower than the observational studies that assessed the impact of unplanned discontinuation.

Moreover, these observational studies indicate that the risk of thrombosis is higher when antiplatelet treatment is discontinued in the first 30 days after stenting (either with BMS or DES), with a prevalence reaching as high as 10% of cases in some series, and with an increased relative risk more than four-fold higher than non-discontinuation [hazard ratio (HR) = 4.5, confidence interval (CI) = 2.0–10.4, P < 0.001]. In the case of first-generation (sirolimus- or paclitaxel-eluting) DES, the risk of stent thrombosis associated with discontinuation of DAPT still increases significantly between 30 and 180 days, but discontinuation of clopidogrel alone appears to be associated with stent thrombosis only in some studies (HR 2.4, CI: 1.2–4.9, P = 0.01), whereas in others the risk appears to be limited to cases where both antiplatelet agents are discontinued. In the series reviewed by Eisenberg et al., the median time interval between discontinuation of clopidogrel alone and thrombotic event exceeded 90 days: a time interval of little interest in the case of temporary discontinuation of clopidogrel for PM implantation. Conversely, in the case of simultaneous discontinuation of both antiplatelet agents, the median interval between discontinuation and adverse event was of only 10 days, with 30% of events within 5 days. Discontinuation of clopidogrel alone did not appear to significantly increase the risk of adverse events more than 180 days after DES implantation (HR 1.7, CI 0.9–3.1, P = NS), with the exception perhaps of the paclitaxel-eluting stent.

The relevance of antiplatelet therapy discontinuation after the first 30 days following stenting is perhaps further reduced with the use of new generation everolimus- or zotarolimus-eluting stents, which show a lower tendency to late thrombosis. In a recent observational study on 1622 patients who had received a second-generation DES in 55% of cases, discontinuation of DAPT after the first 30 days following implantation, especially if limited to clopidogrel alone, did not significantly increase the risk of adverse events (HR 1.29, CI 0.31–5.34, P = 0.725). The retrospective review of the main XIENCE trials, including over 13,000 patients, did not show a significant increase in thrombotic risk in patients who discontinued DAPT after the first 3 months following implantation of an everolimus-eluting stent [Stone GW, Rutledge DR, Sudhir K, et al. Stent thrombosis and dual antiplatelet interruption. Insights from the XIENCE V everolimus-eluting coronary stent system trials (abstract). Abstract Presented at Transcatheter Therapeutics, San Francisco,
Evidence for antiplatelet therapy management

Antiplatelet therapy is a well-known risk factor for developing a pocket haematoma, which can cause serious consequences for patients as described in the section dedicated to haemorrhagic risk. While the simple systematic discontinuation of antiplatelet therapy may expose patients to thrombotic events, continuing the routine administration of antiplatelet drugs may expose patients to unnecessary haemorrhagic risk. In the context of an inevitable evaluation between the thrombotic risks of the underlying heart disease and the haemorrhagic risks associated with CIED implantation, it seems intuitively appropriate to accurately assess the actual indication for DAPT at the time of planning the implantation procedure. Considering that, with the exception of intracranial neurosurgery and transurethral prostatectomy, in which fatal bleeding is reportedly associated with the use of aspirin, low doses of aspirin during any type of surgery appear to increase bleeding only quantitatively, and not always significantly, without changing the type of bleeding, and, therefore, without making it higher risk, they can absolutely be tolerated in the case of CIED implantation. Instead, performing the implantation procedure with a second antiplatelet agent in combination with aspirin should be the object of more careful consideration. In the PRODIGY study, 2013 patients receiving BMS or DES, in 74% of cases suffering from ACS, were randomized to receive clopidogrel therapy for 6 or 24 months in combination with aspirin. The study results showed that a general prolongation of DAPT beyond 6 months is not associated with a reduction in death, MI, intra-stent thrombosis, and stroke, but is accompanied by excessive bleeding. The authors of this document agree that unobjectionable indications for DAPT that do not allow its discontinuation, because the thrombotic risk of the underlying disease justifies the increased haemorrhagic risk associated with implantation when DAPT is in place, include the following clinical conditions:

1. Within 6 months of an ACS, regardless of the treatment given;
2. Within 6 months of coronary implantation of DES, including biodegradable stents;
3. Within 1 month of coronary implantation of a BMS or angioplasty with balloon only, including drug-eluting balloons;
4. Within 1 month of carotid, renal, peripheral stenting, or transcatheter aortic valve implantation, percutaneous closure of the left atrial appendage, closure of patent foramen ovale, or other defect of the interatrial septum, aortic endoprostheses implantation or similar percutaneous interventions with endovascular implantation of metal devices.

Except for such conditions, DAPT may be discontinued with an acceptable risk of recurrence of ischaemic events in order to reduce bleeding complications associated with implantation. In these cases, clopidogrel should be discontinued 5 days before the implantation procedure, while aspirin should be continued indefinitely. The use of platelet function tests may be considered in order to reduce implantation waiting times. Dual antiplatelet therapy may be resumed 48 h after implantation, checking for haemostasis and provided that no complications occur. When implanting a CIED in the course of DAPT, particular attention should be paid to haemostasis to prevent pocket haematoma. The recommendations for management of antiplatelet therapy in patients candidate to CIED implantation or replacement are summarized in Table 2.

Bridging therapy with intravenous antiplatelet drugs

The bridging therapy protocol with intravenous short half-lived inhibitors of platelet receptors GPIIb/IIa is reserved for patients at high risk of stent thrombosis, for whom the operator requires discontinuation of the DAPT due to an unacceptable risk of bleeding. Savonitto et al. conducted a prospective feasibility study on 60 patients with DES, considered at high risk of stent thrombosis undergoing major or ophthalmic surgery. Bridging therapy with tirofiban withdrawn 4 h prior to and resumed 2 h after the procedure was not associated with any adverse event, defined as death, MI, stent thrombosis, and repeated surgery due to bleeding. Major bleeding, according to the TIMI classification, occurred in two patients, while three were presented with a minor bleeding. Given this limited evidence, bridging therapy with tirofiban should not be considered in patients undergoing CIEDs implantation, with rare exceptions.
Another scenario could perhaps be possible when a new and potent intravenous antiplatelet drug will become available, capable of competitively inhibiting platelet receptor P2Y_{12}: cangrelor. This drug is administered parenterally, has a half-life of 5–9 min, and allows complete recovery of platelet function ~1 h after discontinuation of the infusion. The BRIDGE study assessed intravenous administration of cangrelor, as bridging therapy, in patients undergoing CABG surgery. The primary efficacy endpoint of the study was represented by platelet reactivity assessed by VerifyNow assay. The safety endpoint was major bleeding associated with the cardiac intervention. The study, conducted on 210 patients treated with thienopyridine, showed that patients treated with cangrelor had significantly lower platelet reactivity values compared with patients treated with placebo [P2Y_{12} reaction units (PRU) < 240: 98.8 vs. 19.0%, OR 353, 95% CI 45.6–2728, P < 0.001]. No increase in major bleeding was observed in patients treated with cangrelor compared with placebo, while there was an increase in minor bleeding in the cangrelor group. Based on these data, albeit derived from a small study with surrogate endpoint and limited to patients undergoing CABG, we could hypothesize the use of cangrelor as bridging therapy in other contexts, such as patients with an indication for DAPT candidate to CIEDs surgery and at non-negligible risk of haemorrhage. Ad hoc clinical studies will be needed to support this hypothesis.

**New oral antiplatelet drugs**

In recent years, two new oral antiplatelet agents have been introduced for clinical treatment of patients with ACS: prasugrel and ticagrelor. Prasugrel is a new thienopyridine that determines a faster and more intense platelet inhibition than clopidogrel by irreversibly binding the usual platelet receptor P2Y_{12} via an active metabolite similar to clopidogrel’s but more favourably bioavailable. The TRITON-TIMI 38 study has shown that administration of prasugrel in moderate–high-risk patients with ACS and candidate to percutaneous coronary intervention (PCI) is associated with a significant reduction in the primary endpoint of cardiovascular death, non-fatal MI, or stroke compared with clopidogrel therapy (9.8 vs. 11.7%, HR 0.84; 95% CI 0.77–0.92, P < 0.001). In the subgroup of patients who underwent surgical revascularization within 7 days of discontinuation of thienopyridine, the incidence of major bleeding associated with CABG surgery was found to be four-fold higher in patients treated with prasugrel. Nonetheless, these patients had a lower overall mortality (3.7 vs. 9.0%).

Ticagrelor belongs to a new class of antiplatelet drugs, which inhibits platelet receptor P2Y_{12} through irreversible binding and has a plasma half-life of ~6–8 h. Like prasugrel, it has a higher antiplatelet activity and more rapid onset of response compared with clopidogrel. In the PLATO trial, which included patients with ACS regardless of the interventional strategy, therapy with ticagrelor resulted in a significant reduction in the combined endpoint of death, non-fatal MI, or stroke compared with clopidogrel therapy (9.8 vs. 11.7%, HR 0.84; 95% CI 0.77–0.92, P < 0.001). A significant reduction (from 5.1% to 4.0%, P = 0.001) in cardiovascular mortality was also observed in patients undergoing ticagrelor treatment, the methods of which are currently being studied, but may, at least in part, also depend on the
pleiotropic effects of the drug. Treatment with ticagrelor, as expected from the use of a more potent antiplatelet drug than clopidogrel, was associated with a significant increase in bleeding not related with CABG surgery. Similar to the TRITON-TIMI 38 study, in the PLATO study also patients undergoing CABG within 7 days of discontinuation of antiplatelet therapy showed a significant reduction in total mortality (from 9.7 to 4.7%, HR 0.49, P < 0.01) and cardiovascular death (from 7.9 to 4.1%, HR 0.52 P < 0.01) in the group treated with ticagrelor compared with the group treated with clopidogrel. This protective effect was not associated with a different incidence of bleeding, which was similar in the two groups, whereas pulmonary sepsis was reduced in patients treated with ticagrelor.66

Overall, the data obtained from the two studies indicate that an effective antiplatelet action in the perioperative period of coronary surgery could be associated with a protective effect in terms of mortality, regardless of the haemorrhagic risk. However, at present the tendency is to discontinue these drugs mainly considering the haemorrhagic risk and neglecting the potential benefits that an effective antiplatelet therapy can provide in preventing ischaemic events. Hence, in regard to discontinuation of such drugs be required before a surgical procedure with non-low risk of bleeding, the current guidelines of the European Society of Cardiology recommend to discontinue ticagrelor at least 5 days before surgery (like clopidogrel), whereas a discontinuation of at least 7 days is recommended in the case of treatment with prasugrel.67 With respect to CIED implantation that can be considered as a surgical procedure at lower risk of bleeding than CABG, a DAPT continuation strategy would appear to have a rationale, although it has never been tested in clinical studies, especially with prasugrel and ticagrelor. In particular, during the TRITON-TIMI 38 study, only 40 patients underwent implantation of a PM and 28 of an ICD. The study protocol recommended for discontinuation of the drug 5 days before any type of elective surgery without making distinctions in terms of the haemorrhagic risk caused by the procedure. Of the 68 patients undergoing CIED implantation, only one patient experienced minor bleeding and belonged to the clopidogrel arm. No major bleeding or clinically relevant ischaemic events occurred in these patients.63

Although the use of ticagrelor has been associated with the onset of bradyarrhythmias and ventricular pauses, the frequency of PM implantation in the PLATO study was identical in the ticagrelor arm and in the clopidogrel arm (0.9 vs. 0.9%, P = 0.87). Eighty-four out of 9235 patients enrolled in the ticagrelor arm were implanted with a CIED compared with 79 out of 9186 patients enrolled in the clopidogrel arm. According to the protocol, the drug under study was discontinued and we are not aware of events subsequent to this therapeutic procedure.66

Prasugrel and ticagrelor antiplatelet drugs are currently recommended in combination with aspirin in the majority of patients with ACS, and such therapy should be continued for 12 months. At the moment, no data are available on PM implantation in patients treated with the new antiplatelet drugs. Given that CIED implantation is far from a remote possibility in the first 12 months after an ACS, additional data are required to proceed with management recommendations for patients treated with prasugrel and ticagrelor who must undergo CIED implantation. In the meantime, we will have to scrupulously follow the indications on the fact sheets that indicate, where possible, to discontinue the drugs before implantation (5 days before for ticagrelor and 7 days before for prasugrel). The authors of this study do not consider a bridging therapy with tirofiban or cangrelor to be justifiable in all patients with recent ACS and treated with prasugrel or ticagrelor who need to be implanted with a PM or ICD. Conversely, bridging therapy with heparin (s.c. or i.v.) does not fully meet the needs of high-risk patients with an indication for antiplatelet treatment. In addition, heparin stimulates platelet activity, hence it is not a suitable alternative to antiplatelet therapy. Therefore, the authors consider the widespread tendency to replace antiplatelet therapy with low molecular weight heparin (LMWH) as inappropriate and incorrect. Patients and referring physicians should first inform implant operators of all therapies in place in order to best plan the procedure.

Risk associated with discontinuation of oral anticoagulant therapy

Periprocedural management of patients undergoing OAT is based on:

(1) THROMBOEMBOLIC risk assessment;
(2) Periprocedural BLEEDING risk assessment.

The answer to these questions allows one to decide whether the therapy can be discontinued in the periprocedural period and whether or not an alternative bridging therapy is indicated. Currently, there are no patterns of risk stratification, validated by ad hoc studies, to categorize patients treated with vitamin-K antagonists (VKAs) in levels of risk for thromboembolism and bleeding. As a result, many indications are based on indirect evidence and indications of consensus among experts.

(1) THROMBOEMBOLIC risk

The three main clinical indications for use of VKAs are: (a) prosthetic heart valves; (b) AF; and (c) venous thromboembolism (VTE). The risk of thromboembolic complications associated with discontinuation of therapy is very different in patients with mechanical mitral valve prosthesis (with possible AF complications) compared to patients who suffered venous thrombosis more than 6 months earlier. Again different is the risk of AF patients with a high CHADS2 score (e.g., because of diabetes and history of previous stroke) compared to patients with a CHADS2 score of 1–2 (without a history of previous stroke). A proposal for a classification based on risk—derived from the 2012 ACCP guidelines on antithrombotic therapy—defines three classes of risk: High (annual risk of thromboembolic event > 10%); Moderate (5–10% annual risk of thromboembolism); and Low (annual risk of thromboembolic event < 5%) (Table 3). A limitation of this scheme—as with all attempts at simplification—is that some elements peculiar to individual patients are not included and can lead the clinician to perceive a different thrombotic risk from this scheme, e.g., a CHADS2 score associated with a history of previous stroke or of a non-recent but serious VTE (such as massive pulmonary embolism).

(2) BLEEDING risk

For details on the assessment of haemorrhagic risk, refer to the section (Haemorrhagic risk from implantation) in this article.
Evidence for management of oral anticoagulant therapy

A key point in the management of these patients is that an integrated management has to be planned between patient, a clinician experienced in the management of antithrombotic therapies, and the operator who performs the procedure. The patient should be informed about and share the choice, and receive a detailed plan on how to discontinue therapy, and (if applicable) on how to replace it with other therapies.68,69

In general, the main issue concerns the decision, in a patient on OAT, on whether or not to adopt the so-called bridging strategy, to minimize thromboembolic risk in high-risk patients, and haemorrhagic risk after procedures at high risk of bleeding. The first point to remember is that, despite the use of anticoagulant substitution therapy in high-risk procedures is considered a standard treatment, it is a procedure assessed only in two RCTs and therefore remains a matter of controversy.19,70–73 It is based on discontinuation of VKA and its substitution with LMWH, discontinued before the procedure (12–24 h) and reintroduced later (24–48 h).

Discontinuation of vitamin-K antagonists

Discontinuation of VKAs to achieve normal or near-normal haemostasis at the time of the procedure is based on the pharmacodynamic effects of the drug and the associated time required for the regeneration of vitamin K-dependent coagulation factors. This time can be estimated based on the half-life of VKAs,74–77 8–11 h for acenocoumarol and 36–42 h for warfarin.

Based on these data, the oral anticoagulant should be discontinued 5 (if the patient is taking warfarin) or 3 (if the patient is taking acenocoumarol) days before the procedure: in almost all the studies available, however, all VKAs were discontinued 5 days before (although most data refer to warfarin, and only a minority to acenocoumarol). No RCT has directly compared the effects on bleeding of early discontinuation of oral anticoagulants (5–6 days) compared with a more delayed discontinuation (<5 days). The only data available were generated in a small retrospective study on 21 patients78 who discontinued warfarin 36 h before a polypectomy and had a mean international normalized ratio (INR) of 2.3 at the time of the procedure: none of them developed major bleeding complications, but all the procedure was performed using endoscopic clips to reduce the risk of bleeding. In a prospective study on 224 patients in whom warfarin was discontinued 5 days before surgery, only 15% of patients had an INR > 1.5 at the time of the procedure.79 Another retrospective study involving delayed discontinuation (2–3 days) of warfarin assessed that this was not sufficient to achieve an INR < 1.5 (the mean INR at the time of surgery was 1.8).80 Finally, a RCT compared a discontinuation strategy of 5 days prior to surgery vs. 1 day prior, with concomitant administration of vitamin K: the mean INR at the time of surgery was 1.24 in the first group and 1.61 in the second.81

Resumption of therapy with vitamin-K antagonists

For most procedures—and thus also following CIED implantation—the resumption of VKAs is possible in the evening of the following day. A prospective study on 650 patients showed that the mean time to regain an INR within range after resumption of warfarin is 5.1 ± 1.1 days.69 One study assessed the strategy for reintroduction of warfarin at a doubled dose in the first two days of therapy resumption, with a mean time to regain an INR > 2.0 of 4.6 days.69,79

Bridging therapy

In addition to the decision as to whether or not to apply the bridging therapy, a significant issue is to determine the ‘type’ of bridging therapy. Indeed, three different regimens were studied: (i) HIGH-dose bridging therapy (equivalent to the dose used in VTE treatment): use of LMWH at anticoagulant dose, e.g. enoxaparin 1 mg/kg twice a day; dalteparin 100 IU/kg twice a day; (ii) LOW-dose bridging therapy (equivalent to the dose used in VTE prophylaxis), e.g. enoxaparin 40 mg daily; dalteparin 5000 IU daily; (iii) INTERMEDIATE-dose bridging therapy (equivalent to 70 anti-FXa units/kg twice a day).
The latter—i.e., INTERMEDIATE-dose bridging therapy—was validated in an Italian study on 1262 patients,82 demonstrating its feasibility, safety, and efficacy: the data, however, are not conclusive for patients at high thromboembolic risk with mechanical prosthetic valves, poorly represented in the study (15%).

How should these indications be applied in patients who need to undergo CIED implantation? A 2012 meta-analysis83 compared for the first time the data in the literature on the safety and efficacy of a treatment based on continuation of OAT or application of a bridging therapy. Six trials were included,84–89 which compared a strategy based on bridging therapy with the continuation of OAT in patients at high thromboembolic risk candidate to CIED implantation procedures. Taken together, the studies enrolled 629 patients in the OAT continuation arm, compared to 403 patients in the bridging therapy arm. Four studies used warfarin,85,87,88 two used acenocoumarol.84,86 Two studies adopted bridging therapy with LMWH,85,89 while four used unfractionated heparin with the aim of reaching an aPTT between 55 and 90 s.86–88 The risk of pocket haematoma was significantly reduced in the OAT continuation arm compared with bridging therapy (OR 0.29, 95% CI 0.17–0.49); the result was similar when considering pocket haematoma that required revision/drainage (OR 0.15, 95% CI 0.04–0.54). No difference in the incidence of thromboembolic events, which was low overall (three patients with thromboembolic event, with no difference between the two groups; OR 0.48, 95% CI 0.07–3.54, P = 0.48) was observed. The limits of the results of this meta-analysis are related to the fact that 5 out of 6 of the included trials are not randomized; the number of patients included in each study is low, and alone none of the studies reaches definitive results; the bridging therapy arm includes ‘different’ uses of ‘different’ types of heparin. This data is noteworthy: the study by Marquie,90 in 2006, indeed showed that administration of heparin post-implantation—in patients with prosthetic valves and AF—was associated with an almost 14-fold increase in the risk of bleeding complications. This study, however, used unfractionated heparin i.v., introduced on average 3 h after the procedure. We cannot consider all types of bridging therapy as being equal: obviously, commencing heparin so early and the use of heparin i.v. to achieve an aPTT of 60 s cannot be considered equal to the use of LMWH, commenced 24 h after implantation and at intermediate dose. This reasoning is useful for evaluating the results of a meta-analysis by Feng et al., in which the six trials included adopted different types of heparins, commenced at different times and at different doses.83 Moreover, the type of implanted cardiac device is different in the six studies, and this may result in a bias for the different haemorrhagic risk associated with each device. Finally, a crucial point is the consideration on the type of patients enrolled: the mean INR of the patients at the time of the procedure was between 2.0 and 2.5. The analysis of the populations in the different studies shows how in all of them—with the exception of the study by Tolosana et al.86 (in which the percentage of patients with mechanical prosthetic valves was 39%, with 20 patients)—the percentage of patients with mechanical mitral valve prosthesis (for whom maintenance of a therapeutic INR range between 2.5 and 3.5 is indicated) is about 20% (four studies with percentage ≤ 10%). This data is important because it suggests caution in extrapolating the results to this category of patients.

In 2012, Ghanbari et al.87 published the results of a new meta-analysis that included eight studies (5 cohort studies85,87–89 and 3 RCTs84,86,92) comparing the OAT continuation strategy with bridging therapy in the course of CIED implantation on a total of 2321 patients. Continuation of OAT was confirmed to be associated with a significantly lower risk of bleeding (OR 0.30, 95% CI 0.18–0.50), with no difference in the risk of thromboembolic events (OR 0.65, CI 0.14–3.0). Only the two meta-analyses presented—putting together the results of the different small-size studies having different designs—were able to achieve this result. Individually, no RCT was adequately sized to give meaningful answers, until the design and implementation of the BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial), the results of which were published in May 2013.17 The trial enrolled 668 patients at intermediate–high risk of thromboembolism (risk of events > 5% per year). In the OAT continuation arm, the goal was to have an INR ≤ 3.0, with the exception of patients with one or more mechanical valves for whom an INR of 3.5 was accepted. In the bridging therapy arm, HIGH-dose LMWH or unfractionated heparin was administered (full-dose anticoagulant) after 5 days of discontinuation of the oral anticoagulant, with discontinuation 24 h before the procedure (4 h in the case of unfractionated heparin i.v.) and resumption 24 h later. The mean INR at the time of the procedure in the OAT continuation arm was 2.3. About 16% of the enrolled patients had mechanical mitral valves. In case of concomitant use of aspirin, this was continued; in case of concomitant use of clopidogrel, this was discontinued 5 days before with the exception of patients stented since < 1 year. The primary endpoint—pocket haematoma requiring revision, prolongation of hospitalization, or discontinuation of anticoagulant therapy—occurred in 3.5% of patients in the OAT continuation group, and in 16% of patients in the heparin arm. Three risk factors were independently associated with the formation of pocket haematoma: continuation of OAT and diabetes associated with a significantly lower risk (RR 0.16, 95% CI 0.08–0.32, P < 0.001 and RR 0.48, 95% CI 0.26–0.86, P = 0.01), and use of aspirin associated with an increased risk (RR 2.04, 95% CI 1.19–3.48, P = 0.01).19

Based on the current outlook, the possible explanation for this result is that, if the patient undergoes the procedure in the course of OAT, any excessive bleeding is visible and treatable during surgery.19,83–89 Conversely, in the other case, the bleeding may become apparent only when full-dose anticoagulant therapy is resumed and the wound is already closed. The results of this trial demonstrated the greater safety of an OAT continuation strategy (mean INR of 2.3 at the time of the procedure) compared with the bridging therapy in high–intermediate risk patients undergoing CIED implantation procedures. A logical consequence of these results is to assume that OAT discontinuation could be applied in patients at low thromboembolic risk (< 5%) without any bridging therapy: however, we need RCTs purposely designed to answer this query (Table 4) before considering this indication as evidence-based.

It is the opinion of the authors that the data regarding the category of patients at very high thromboembolic risk, i.e., mitral valve prostheses with AF and/or previous stroke and multiple prosthetic valves with AF and/or previous stroke, are not yet conclusive. These categories for which the therapeutic INR range is between 2.5 and 3.5 (and between 3.0 and 4.0 for the ‘old’ caged ball or single tilting disc valve prostheses) were underrepresented in all studies; therefore, caution should be taken in applying these
results. The authors propose to carefully assess the benefit/risk profile of these patients and, after assessment and sharing all information with the patient, decide whether to apply an INTERMEDIATE-dose bridging therapy to be re-commenced 24–48 h after the procedure (Table 4).

A recent meta-analysis of 17 studies in 10,715 patients, including the BRUISE CONTROL trial, has confirmed the notion that performing device implantation on uninterrupted OAT is associated with lower risk of bleeding compared with heparin bridging, whereas DAPT increases the risk of haemorrhage.93

**Oral anticoagulant therapy associated with antiplatelet therapy**

In the absence of evidence-based data, the authors’ suggestion is to follow the indications given for OAT and antiplatelet therapy separately. We underscore, however, how aspirin has proven to be significantly associated with an increased risk of bleeding in the BRUISE CONTROL.93 Hence, if in the course of OAT, and in the absence of atherothrombotic events in the last 12 months, the opinion of the authors is to discontinue aspirin 5 days before the procedure. No data is available on the scenario of triple therapy in patients needing CIED surgery. Nonetheless, triple therapy with OAT, clopidogrel, and aspirin lead to a significantly higher risk of bleeding as compared to OAT plus clopidogrel alone in a PCI trial,94 and, potentially, warranting caution also should CIED surgery be needed in such patients.

**New oral anticoagulants**

Four new oral anticoagulant agents—dabigatran, rivaroxaban, apixaban, and edoxaban—have proven effective for prevention of thromboembolic events in patients with nonvalvular AF.95–98 These agents have short half-lives, with maximum anticoagulant effects observed immediately after intake (about 4 h) and as quick a reduction of these effects after discontinuation. In the RELY study—which assessed the efficacy and safety of dabigatran 150 mg or 110 mg twice daily compared with standard treatment with VKAs (target INR: 2.0–3.0), 4591 patients [24.7% \( n = 1487 \) of patients assigned to dabigatran 110 mg arm, 25.4% \( n = 1546 \) to dabigatran 150 mg arm, 25.9% \( n = 1558 \) to warfarin arm] discontinued anticoagulant treatment at least once to undergo surgery or invasive procedures.99 The most common procedures (10.3%) included PM or ICD implantation. Data were published relative to 25 patients100 who, in the course of dabigatran intake (23 patients at a dose of 150 mg and 2 at a dose of 75 mg) underwent PM implantation. The last dose of dabigatran was administered 16 ± 15 h before implantation (range: 1–48 h) and the first resumption dose was at 17 ± 16 h after the procedure (range: 2–48 h). In 11 patients dabigatran was continued without missing a dose. The interval between the last dose of dabigatran and the procedure was 26 ± 16 h in patients who had discontinued the therapy and 5 ± 3 h in patients who had not discontinued it. There was no occurrence of thrombotic or haemorrhagic events. One patient, who developed pocket haematoma, was under DAPT with aspirin and clopidogrel, and full-dose dabigatran (150 mg × 2) without discontinuation of the drug, because of a CHADS2 score of 6. Dabigatran has a half-life of 12–14 h in patients with normal renal function. For this reason, its discontinuation is generally recommended 1–3 days before elective surgery and up to 6 days before in patients with renal dysfunction. The results of this study are certainly very preliminary because it was limited to 25 patients, but suggest an increased risk of bleeding in case of concomitant use of other antithrombotic therapies, in addition to the possibility of continuing the therapy without haemorrhagic and/or thrombotic complications. The BRUISE CONTROL 2 trial is currently underway comparing a strategy of continued vs.

### Table 4 Management of oral anticoagulant therapy

<table>
<thead>
<tr>
<th>Bleeding risk</th>
<th>Thromboembolic risk</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Very high</th>
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<td></td>
<td></td>
<td>See Table 3</td>
<td>See Table 3</td>
<td>See Table 3</td>
<td>Mechanical mitral valve prosthesis with AF and/or previous TIA/stroke; multiple mechanical heart valves with AF and/or previous TIA/stroke</td>
</tr>
<tr>
<td>Low</td>
<td>Continue OAT (target INR for procedure ≤ 2.0)</td>
<td>Continue OAT (target INR ≤ 2.0)</td>
<td>Continue OAT (target INR ≤ 2.5)</td>
<td>Continue OAT (target INR ≤ 3.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider OAT discontinuation without bridging therapy</td>
<td>Consider OAT discontinuation without bridging therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Continue OAT (target INR for procedure ≤ 2.0)</td>
<td>Continue OAT (target INR ≤ 2.0)</td>
<td>Continue OAT (target INR ≤ 2.5)</td>
<td>Continue OAT (target INR ≤ 3.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider OAT discontinuation without bridging therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Discontinue OAT without bridging therapy</td>
<td>Discontinue OAT</td>
<td>Discontinue OAT (target INR ≤ 2.5)</td>
<td>Consider bridging therapy at INTERMEDIATE dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider bridging therapy at LOW dose</td>
<td>Consider bridging therapy at LOW dose</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

AT, antithrombin; AF, atrial fibrillation; INR, international normalized ratio; OAT, oral anticoagulant therapy; VTE, venous thromboembolism; TIA, transient ischaemic attack.
interrupted dabigatran at the time of device surgery in patients with moderate to high risk of thromboembolic events (ClinicalTrials.gov identifier NCT01675076). Initial real-world data suggest a low rate of bleeding and thromboembolic complications in patients treated periprocedurally with dabigatran or rivaroxaban.101

Periprocedural management of antithrombotic therapy in patients undergoing transvenous lead extraction

Periprocedural management of antithrombotic therapy in patients candidate to transvenous lead extraction deserves separate discussion. Indeed, lead extraction differs significantly from other CIED procedures. Despite the technological developments of prostheses, the CIED invariably continues to be associated with the development of tenacious chronic intravascular fibrotic adhesions.102,103 Transvenous lead extraction involves the use of multiple materials, techniques, and venous approaches to achieve dissection of adhesions and lead extraction. The invariably traumatic nature of such approaches may, therefore, be associated with major and minor, predominantly haemorrhagic complications, which sometimes include thromboembolic events.104

Despite the high rates of clinical and procedural success (>95%), the analysis of data from registries and RCTs documents a cumulative rate of complications >10%. In particular, albeit rare (2%), major complications (i.e. death, permanent disability, life-threatening event, or requiring surgery) can be fatal in 0.3–0.7% of cases.105–110 They mainly include haemorrhagic events resulting from direct and/or indirect trauma on the vascular and cardiac wall, such as venous laceration, cardiac perforation, tamponade, and hemothorax.106 Conversely, minor complications, 7.2% in our experience, in addition to minor bleeding events such as pocket haematoma, may include low-risk pulmonary thromboembolism (especially in patients with lead endocarditis) and post-extraction deep vein thrombosis (DVT) at the venous entry site.20

The clinical impact of these complications appears to be much more significant when viewed in the light of the overall clinical management of patients undergoing a lead extraction procedure, who often do not require the extraction procedure alone, but rather take part in a therapeutic process that involves re-implantation of a new prosthesis in 2/3 of cases.4,30 Regrettably, to date there are no controlled clinical data on antithrombotic therapy management associated with extraction procedures. However, the potential risk of injury to cardiovascular structures with fatal or disabling complications, and the possible need for emergency percutaneous or surgical procedures, reasonably suggest to consider such procedures as interventions at high haemorrhagic risk104 (Table 1). Stratification of thrombotic/thromboembolic risk is neither less complex nor less peculiar. In addition to traditional clinical predictors (mechanical valve prostheses, AF, DVT), some non-conventional predictors, such as indication (local vs. systemic infection), presence of vegetations (systemic infection with or without endocarditis),112 and the relative size (greater or <2 cm)101 (Table 5) may, indeed, play a non-negligible role, with an additional intrinsic risk of thrombotic/thromboembolic events. These factors can affect not only the procedural, but also the post-procedural emboligenic risk, invariably associated, as in traditional surgery, with the traumatic nature of the procedure, the duration of confinement to bed, and the length of hospitalization. In the face of lacking controlled data,113 it would, therefore, seem most reasonable to include antithrombotic therapy management in a more general context: in this light, the main recommendation is to prevent the most relevant (and potentially disabling/fatal) risk, namely haemorrhage, minimizing ongoing antithrombotic therapy, and taking a series of periprocedural precautionary measures.

In this respect, we recall that the extraction procedure is elective. Therefore, in the presence of temporary antiplatelet/anticoagulant treatment, the mandatory recommendation is to postpone the procedure so as to allow, wherever possible, the partial or complete discontinuation of antithrombotic treatment. In addition:

(1) To control haemorrhagic risk:

(a) Discontinuation of antiplatelet therapy:
- in toto (low thrombotic risk);
- maintain ASA and discontinue receptor P2Y12 inhibitors (intermediate and high thrombotic risk).

(b) Discontinuation of OAT:
- without LMWH bridging (in low thromboembolic risk patients);
- with LMWH bridging (in medium–high thromboembolic risk patients and high intrinsic risk patients—i.e. vegetations >2 cm) at LOW or INTERMEDIATE dose.

(c) Preprocedural coagulation control (INR < 2)

(d) Availability of concentrated homotype erythrocytes

(e) Placement of postprocedural drain in the pocket.

(2) For prevention of thromboembolic risk:

(a) Placement of temporary PM at the end of the procedure from the ipsilateral subclavian vein (i.e. extraction site) in cases where implantation is not performed at the same time.

(b) Use of active fixation leads in ‘temporary’ mode, to favour early mobilization of patients for whom long confinement to bed and hospitalization times are expected.

(c) Early mobilization (24 h postprocedure).

In conclusion, more than the actual incidence of complications per se, it is the nature of these complications and the management complexity of the procedure that make it difficult to define a safe policy for

<table>
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<th>Table 5</th>
<th>Stratification of intrinsic thrombotic/thromboembolic risk in patients with PM/ICDs undergoing transvenous lead extraction</th>
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<tbody>
<tr>
<td>Risk</td>
<td>Predictors</td>
</tr>
<tr>
<td>Low</td>
<td>Local infection</td>
</tr>
<tr>
<td></td>
<td>Lead malfunction</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Lead endocarditis with vegetations &lt;2 cm</td>
</tr>
<tr>
<td></td>
<td>Systemic infection without vegetations (occult sepsis)</td>
</tr>
<tr>
<td>High</td>
<td>Lead endocarditis with vegetations &gt;2 cm</td>
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</tbody>
</table>
Anticoagulant therapy management in extraction procedures. While waiting more consistent data, the recommendations provided, albeit generated by 20 years of experience in a high-volume national referral center, remain essentially empirical in nature. This aspect, combined with the extreme heterogeneity of the clinical-procedural scenario of patients candidate to extraction, suggests to assess and verify the recommendations each time on a case-by-case basis.

Conclusions

Unlike other surgical procedures, implantation or replacement of CIEDs and transvenous lead extraction are generally elective interventions. This offers the theoretical but often untapped advantage to plan every stage of the procedure, optimizing the management of periprocedural antithrombotic therapy using an approach shared by the various healthcare operators involved in the process, and considered to be the most appropriate for the patient, balancing haemorrhagic and thromboembolic risk. It is important to establish effective communication between electrophysiologist, clinical cardiologist, family physician, and patient that operatively translates into a process characterized by the following stages:

Preprocedural stage: Stratification of thrombembolic risk, stratification of haemorrhagic risk, and planning of antithrombotic therapy (continue, discontinue, potentially optimize the dose or verify the therapeutic effect, bridging), with adequate communication of the timing of any discontinuation (and resumption).

Procedural (intraoperative) stage: Meticulous attention to haemostasis with implementation of technical measures to limit bleeding.

Postprocedural stage: Clear indications (in the case of discontinuation) for antithrombotic therapy resumption methods and timing, and use of non-pharmacological remedies to reduce bleeding.

Supplementary material

Supplementary material is available at Europace online.

Acknowledgements

The manuscript has been adapted with permission from Zacà et al.

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References

Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS
Mauri L, Hsieh WH, Massaro JM, Ho KK, D’Agostino R, Cutlip DE. Stent thrombosis
Bongiorni MG, Soldati E, Zucchelli G, Di Cori A, Segreti L, De Lucia R
Schulz S, Schuster T, Mehilli J, Byrne RA, Ellert J, Massberg S
Kimura T, Morimoto T, Nakagawa Y, Tamura T, Kadota K, Yasumoto H
Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in
Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. On behalf of
Biondi-Zoccai GG, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F
Valgimigli M, Borghesi M, Tebaldi M, Vranckx P, Parrinello G, Ferrari R
Beving H, Zhao C, Albage A, Ivert T. Abnormally high platelet activity after discon-
oral antiplatelet therapy after drug-eluting stent implantation.
Temporal relation between clopidogrel cessation and stent thrombosis after
Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in
oral antiplatelet therapy after drug eluting stent implantation.
Systematic review and meta-analysis on the hazards of discontinuing or not adher-
Beving H, Zhao C, Albage A, Ivert T. Abnormally high platelet activity after discontin-
Biondetti C, Bertagnolli M, Lagiotti M, Agostoni P, Abbate A, Fusaro M, Burzotta F et al. A systematic review and meta-analysis on the hazards of discontinuing or not adher-
Oscarsson A, Gupta A, Fredriksson M, Jarhult J, Nyström M, Pettersson E et al. To con-


the type and/or potency of implanted stent? A pre-specified analysis from the PRONering Dual antiplatelet treatment after Gradening stent-induced Intral hyper-

Antithrombotic therapy in EP device surgery


A case of ridge-related re-entrant atrial tachycardia utilizing the vein of Marshall to span a conduction gap at the mitral isthmus scar

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A 41-year-old man had undergone pulmonary vein isolation and linear ablation at the roof and mitral isthmus (MI) for persistent atrial fibrillation. He subsequently experienced atrial tachycardia (AT). The activation map during the AT revealed macro-re-entrant AT with impulse propagation in a clockwise direction around the mitral annulus and left atrial appendage (LAA), and through the scar tissue bundle at the MI (Figure). We cannulated the vein of Marshall (VOM) using a 2-Fr octapolar electrode catheter. The post-pacing intervals at multiple points along the VOM were equal to the tachycardia cycle length. The fractionated potentials at the left pulmonary vein–LAA (LPV–LAA) ridge expanded to a duration of 110 ms and preceded the electrogram at the main spike of the distal VOM. Accordingly, radiofrequency ablation was applied at the LPV–LAA ridge (Figure), which successfully terminated the AT. Bidirectional block across the MI, distal VOM, and LPV–LAA ridge was confirmed by post-ablation. When a conduction gap is apparent at the MI lesion, as seen in this case, and radiofrequency ablation at the MI does not produce a complete bidirectional block, we suggest applying radiofrequency ablation to the LPV–LAA ridge area.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/a-case-of.pdf.