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Management of antithrombotic treatment and bleeding disorders in patients requiring venous access devices: A systematic review and a GAVeCeLT consensus statement

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Abstract

Insertion of venous access devices (VAD) is usually considered a procedure with low risk of bleeding. Nonetheless, insertion of some devices is invasive enough to be associated with bleeding, especially in patients with previous coagulopathy or in treatment with antithrombotic drugs for cardiovascular disease. The current practices of platelet/plasma transfusion in coagulopathic patients and of temporary suspension of the antithrombotic treatment before VAD insertion are based on local policies and are often inadequately supported by evidence, since many of the clinical studies on this topic are not recent and are not of high quality. Furthermore, the protocols of antithrombotic treatment have changed during the last decade, after the introduction of new oral anticoagulant drugs. Though some guidelines address some of these issues in relation with specific procedures (port insertion, etc.), no evidence-based document covering all the aspects of this clinical problem is currently available. Thus, the Italian Group of Venous Access Devices (GAVeCeLT) has decided to develop a consensus on the management of antithrombotic treatment and bleeding disorders in patients requiring VADs. After a systematic review of the available evidence, the panel of the consensus (which included vascular access specialists, surgeons, intensivists, anesthetists, cardiologists, vascular medicine experts, nephrologists, infective disease specialists, and thrombotic disease specialists) has structured the final recommendations as detailed answers to three sets of questions: (1) which is an appropriate classification of VAD-related procedures based on the specific bleeding risk? (2) Which is the appropriate management of the patient with bleeding disorders candidate to VAD insertion/removal? (3) Which is the appropriate management of the patient on antithrombotic treatment candidate to VAD insertion/removal? Only statements reaching a complete agreement were included in the final recommendations, and all recommendations were offered in a clear and synthetic list, so to be easily translated into clinical practice.

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Introduction

Every day vascular access experts perform insertion and/or removal of venous access devices (VADs) in patients with bleeding disorders secondary to many different causes (hepatic or renal diseases, sepsis, hematologic malignancy, inherited coagulation disorders, etc.).

Also, due to the increasing age of the population and the related comorbidities, an increasing number of patients requiring insertion/removal of VADs are on oral anticoagulants, low molecular weight heparin (LMWH), and/or single or dual antiplatelet treatment for cardio-vascular diseases. Many of these patients require peripheral or central VADs for intravenous infusion, hemodynamic monitoring, administration of irritant drugs, antiblastic chemotherapy, parenteral nutrition, or dialysis. As the insertion/removal of VADs may be associated with local bleeding complications, in this high-risk population of patients an appropriate strategy is needed so to ensure the efficacy and the safety of the procedure, adopting different solutions that may include a temporary interruption of the antithrombotic treatment or the choice of a VAD with less bleeding risk.

There are currently few guidelines or evidence-based documents addressing these clinical issues, and recommendations are based on few randomized controlled trials (RCTs) and few retrospective studies of very low quality.

Old guidelines recommended that insertion of a central VAD other than a Peripherally Inserted Central Catheter (PICC)—in a nonemergent situation—should be carried out only if platelet count is $>50 \times 10^9$/L and the international normalized ratio of prothrombin time (PT/INR) is below 1.5.[1]

In the last decade, many novelties have changed the clinical scenery: the diffusion of ultrasound guided venipuncture and the introduction of micro-puncture kits with very small needles (21G) have reduced the risk of bleeding associated with VAD insertion[2,3]; central VADs with low risk of bleeding complications, such as PICCs in veins of the arm or Femorally Inserted Central Catheters (FICCs) in the superficial femoral vein[4] have become more popular; new ultrasound-guided peripheral VADs have been introduced in clinical practice[5]; traditional Vitamin K antagonists (VKAs) have been partially replaced by a new generation of direct oral anticoagulants (DOACs) that are becoming the cornerstone of antithrombotic therapy.[6]

These novelties call for a revision of the current recommendations.

Recent guidelines[7–9] focus on the importance of taking into consideration multiple factors: (a) the bleeding risk related to the antithrombotic therapy or to the bleeding disorder of the patient; (b) the bleeding risk inherent the procedure; (c) the thromboembolic risk due to the temporary interruption of the antithrombotic treatment. While the thromboembolic risk is somehow well defined, there is not a uniform definition of the procedural bleeding risk.[3,7,10–14] Also, few documents have tried to define the different procedural bleeding risk associated with the different peripheral and central VADs used in clinical practice.

In absence of strong evidence from the literature, Gruppo Accessi Venosi Centrali a Lungo Termine (GAVeCeLT)—the Italian multidisciplinary group for venous access devices—developed a consensus document on this clinical topic, aiming to propose general recommendations for the management of the patients with coagulation disorders or antithrombotic therapy who may require insertion/removal of different types of VADs.

Methods

Most guidelines and recommendations on the management of patients with bleeding disorders or on antithrombotic therapy undergoing venous catheter insertion are based on studies with poor quality evidence, since very few RCTs are available in this area. Current clinical practice and hospital protocols may be highly variable among different clinicians and are mostly based on expert's opinion.

Considering the impact of this issue on the daily clinical practice and the scarcity of strong evidence from high quality studies, a consensus was considered the most appropriate tool for providing recommendations in this area.

The consensus was developed by GAVeCeLT, the Italian Group for Venous Access Devices, and coordinated by two members of GAVeCeLT (MGA and MP). A panel of experts was identified, consisting of surgeons, intensivists, anesthetists, cardiologists, vascular medicine experts, nephrologists, infective disease specialists, and thrombotic disease specialists. Panelists were selected for their expertise in venous access devices, and/or in coagulation disorders, and/or as authors of relevant papers in this field. The consensus was not sponsored directly or indirectly by any commercial company, but exclusively supported by GAVeCeLT. It was conducted in three stages, with web-based meetings.

Before the formulation of the statements, a literature search was performed on PubMed, Ovid and Elsevier, and Cochrane Library for published randomized and observational studies in English from January 2000 to September 2021. Keywords as "venous catheter," "long term vascular

device," "totally implanted vascular device," "tunneled catheter," "dialysis catheter," "port," "long-term oral anticoagulant," "chronic oral anticoagulant," "antiplatelet drugs," "periprocedural anticoagulant," "perioperative anticoagulant," "unfractionated heparin," "venous complications," "hematoma" were used. References of articles and previous meta-analysis were also reviewed, to confirm that no studies were missed. Studies both in adults and in pediatric patients were included.

The consensus process was carried out according to the RAND/University of California at Los Angeles (UCLA) Appropriateness Methodology as a three-stage consensus process.[15] The method is a modification of the Delphi method, a structured process for collecting and condensing knowledge from a group of experts through a series of questionnaires. A first draft of the paper was developed by the two coordinators of the panel; this document included all the available evidence from the literature and a first preliminary draft of recommendations. During a first web-based meeting, the whole panel discussed the preliminary draft and agreed to structure the recommendations into three sets of questions:

(1) Which is an appropriate classification of VAD-related procedures based on the specific bleeding risk?
(2) Which is the appropriate management of the patient with bleeding disorders candidate to VAD insertion/removal?
(3) Which is the appropriate management of the patient on antithrombotic treatment candidate to VAD insertion/removal?

A questionnaire—including three sets of recommendations—was developed and forwarded to the panelists via email. Each panelist was asked to state his/her agreement level to each statement (disagree, uncertain, agree) and to comment on controversial issues. Based on the answers of the panel, a second questionnaire was customized and presented to the panel for final approval. After a second web-based meeting, the final statements were defined. Only statements reaching a complete agreement were included in these recommendations. After the meeting, the recommendations and a summary of the consensus were circulated to the whole panel for review and final approval.

Results

(Q1) Which is an appropriate classification of VAD-related procedures based on the specific bleeding risk?

Multiple factors contribute to the bleeding risk of a procedure, such as the presence of patient-related bleeding diathesis and the invasiveness of the procedure itself. The risk of bleeding after peripheral or central venous cannulation is related to multiple different factors dependent on the procedure, the patient, and the clinician performing the maneuver. The clinician's expertise, the number of repeated attempts, the occurrence of accidental arterial puncture, the size of the vein and its location, the patient's compliance, the type of device, the adoption of ultrasound guidance, etc., can all affect the bleeding risk.

In most guidelines, insertion of peripheral VADs is not considered associated to any bleeding risk. On the other hand, the insertion of central VADs (including tunneled VADs and totally implanted VADs) is usually classified as a procedure with low bleeding risk.[8]

There are few reports in literature, and mostly retrospective, regarding the different bleeding risk of central venous catheters, tunneled dialysis catheters or totally implanted venous access devices (TIVADs). On the contrary, there are many studies addressing the bleeding risk associated with placement of cardiac implantable electronic devices (CIEDs), a procedure somehow similar to TIVADs implantation. In these procedures, the most common hemorrhagic complication is the formation of a pocket hematoma. The hematoma is considered clinically significant when associated with intense local pain, patient discomfort, prolonged hospitalization time, need of repeated follow-up visits, need of surgical revision and/or blood transfusions. The timing of hematoma formation can vary, although most studies report its occurrence during the first week post-procedure.[16–18] Each hematoma almost doubles the risk of infection, particularly if surgical drainage is required (up to 15-fold). Hematoma and bleeding complications increase the cost of implantation by almost $7000 (expressed in 2006 USD) and add an average of 3 days to the hospitalization. In case of infected hematoma, mortality is increased by 4.4–7.7-fold with an incremental cost per admission of $14,360–16,498.[19] One of the difficulties in the interpretation of these studies is the variability of the definition of hematoma. A hematoma can be defined by its diameter, by its elevation above the surrounding skin, or whether it requires reintervention and/or anticoagulation cessation and/or blood transfusion. In a retrospective study on 200 patients undergoing CIED implantation, the hematoma was defined as a blood accumulation requiring surgical evacuation, extended hospital stay or transfusion.[20]

There is limited data about bleeding during/after insertion of peripheral VADs (short cannulas, long peripheral catheters, and midline catheters); the clinical impact of such complication is minimal, the formation of hematoma unlikely and the phenomenon can be successfully prevented by local application of cyanoacrylate glue.[5,21]

Bleeding risk associated with Central Inserted Central Catheter (CICC) insertion has a reported incidence of 0.5%–1.6% in adult patients.[22,23] In children, early formation of hematoma occurs in less than 2% after CICC

insertion.[24] As for TIVADs, minor hematomas of the chest wall in the pocket of the reservoir have been reported in up to 8% of patients.[25] In tunneled dialysis catheters, the bleeding risk may range from 0.095%[26] to 1.36%[27] or even to 5.6%.[28] Most studies reporting experiences with insertion of PICCs[29–31] and FICCs[4] do not report the occurrence of hematoma, though sometimes accidental arterial puncture is mentioned. Though evidence is still scarce, it seems likely that ultrasound-guided puncture of the common femoral vein at the groin may have more risk of bleeding than ultrasound-guided puncture of the superficial femoral vein at mid-thigh. It is commonly accepted that placement of a tunneled catheter—especially a long-term dialysis catheter—or the placement of a totally implanted venous access device (port) may somehow be associated with increased risk of local bleeding and formation of hematoma. The tunneling procedure is certainly less invasive for PICCs than for CICCs or FICCs, and the risk of hematoma is negligible. For dialysis catheters, a specific risk factor for bleeding is the underlying chronic renal disease; such catheters are also characterized by large caliber (10–15 Fr), so that the procedure may be regarded as relatively more invasive.

Due to the scarcity of data, a classification of VADs in terms of the invasiveness of the maneuver for their insertion is inevitably based on experts' consensus and not on hard evidence from the literature.

Grading the invasiveness of the procedures of VAD insertion, the panel has considered a variety of factors: the size and location of the vein; the diameter of the catheter; the need for additional invasive maneuvers such the creation of a tunnel or a pocket; the predicted difficulty of the venipuncture; the type of potential bleeding complication (oozing from the exit site, or local ecchymosis or hematoma or hemothorax); the feasibility of compressing maneuvers for reducing the bleeding (high after a venipuncture at the upper or lower limb, low after a venipuncture in the supra/infraclavicular area); and so on.

Q1 – Panel recommendations

(1) While all venous access procedures are currently considered by most guidelines as low bleeding risk, the panel proposes to further classify such maneuvers based on the invasiveness:

   a. Minimally invasive venous access procedures—insertion or removal of the following VADs: short peripheral cannulas; long peripheral catheters (mini-midline); midline catheters; nontunneled PICCs; non-tunneled FICCs at mid-thigh (access to the superficial femoral vein)
   b. Moderately invasive venous access procedures—insertion or removal of the following VADs: non-tunneled CICCs; non-tunneled FICCs at the groin (access to the common femoral vein); tunneled PICCs; nontunneled dialysis catheters
   c. Highly invasive venous access procedures—insertion or removal of the following VADs: tunneled CICCs; tunneled FICCs; tunneled-cuffed dialysis catheters; ports (including PICC-ports, chest-ports, and femoral ports)

(2) For all maneuvers, from minimal to high invasiveness, the panel strongly recommends a proper and specific training of the operator performing the procedure and the adoption of ultrasound for the insertion of all central VADs and for peripheral VADs to be inserted in deep veins of the arm. Also, whenever available, the use of micro-introducer kits with small gauge needles (21G) and floppy straight tip 0.018″ guidewires for the insertion of central VADs may be useful in order to reduce the trauma to the vein, particularly in case of high risk of bleeding and vascular abnormalities.

(Q2) Which is the appropriate management of the patient with bleeding disorders candidate to VAD insertion/removal?

Invasive procedures are frequently performed in patients with bleeding disorders. Congenital bleeding diathesis, sepsis, renal, or liver dysfunction may increase the patient bleeding risk.

Whether to correct the coagulopathy or transfuse platelets in case of thrombocytopenia is still a matter of debate, and it is a clinical decision mostly based on very old clinical observations. In a recent analysis of the literature that included one randomized controlled trial and 21 observational studies, for a total of 13,256 inserted catheters (4213 of them being in patients with severe coagulopathy), the severity of coagulopathy did not predict the risk of bleeding.[32] No study demonstrated a beneficial effect from the prophylactic administration of platelets or fresh-frozen plasma (FFP) to prevent bleeding complications. Retrospective studies suggest that correction of the pre-procedural coagulopathy is not needed if PT/INR is below 3.0 and platelet count is higher than 20×10^9/L. Also, transfusion of platelets or may be harmful, due to the possibility of adverse effects (acute lung injury, cardiac overload, blood-related infections, allergic reactions).

In a recent RCT, 81 patients with PT/INR ranging between 1.5 and 3.0 were randomly assigned to receive FFP 12 mL/kg or nothing before different procedures including central VAD insertion, thoracentesis, percutaneous tracheostomy, drainage of abscess: no difference in bleeding complications was found between the two groups.[33] Though, a common flaw of most studies on surgery or bedside procedures in patients with coagulation disorders and/or thrombocytopenia is the lack of standardized definition/assessment of the bleeding complication.[34] Zeidler and coworkers demonstrated that there is no

association between platelet count ($>20 \times 10^9$/L) and bleeding risk when ultrasound guided venipuncture is adopted, and the operator is properly trained.[35] The association between bleeding risk and prolonged activated partial thromboplastin time (aPTT) (45 s or more) has been investigated only in few studies.[32]

Two Cochrane systematic reviews[36,37] could not provide recommendations about FFP transfusion in coagulopathic patients undergoing central VAD insertion, due to the very low quality of evidence of the studies. From an analysis of the recent literature, no evidence was found to determine whether platelet transfusion may be required prior to central VAD insertion in patients with thrombocytopenia or which may be the appropriate threshold for platelet transfusion.[38,39] Furthermore, due to the low quality of the studies, no evidence was found to determine whether platelet transfusion affected the risk of death, of minor or major bleeding or of other severe side effects.[39] In a retrospective study on tunneled-cuffed dialysis catheters, no difference was found in terms of bleeding comparing patients on oral antithrombotic medications (warfarin, clopidogrel or acetylsalicylic acid) vs. patients treated intravenously with unfractionated heparin (UFH) vs. patients who were not receiving any antithrombotic treatment.[40] In a small population of patients on clopidogrel treatment, insertion of tunneled-cuffed dialysis catheters was not associated with any hemorrhagic complication.[41]

In a retrospective analysis of ultrasound guided radiological implantation of 1200 TIVADs in patients with thrombocytopenia, the threshold of platelet transfusion was $<50 \times 10^9$/L; the success of insertion was 100% in all patients, and there was no difference in terms of complications between patients with normal platelet count versus patients with platelet $<50 \times 10^9$/L but treated with pre-insertion platelet transfusion.[42] In patients with chronic liver disease undergoing invasive procedures, the threshold to correct PT/INR should probably be higher than in general population in order to minimize unnecessary transfusions.

Although conclusive evidence is still lacking, current guidelines recommend platelet count of $>50 \times 10^9$/L and PT/INR < 1.5 before insertion of central VADs.[1,2] Correction of coagulopathy with fresh frozen plasma (FFP) or platelet transfusion prior to central VAD insertion is a clinical practice not universally adopted.

The 2007 guidelines of the British Committee for Standards in Hematology (BCSH)[1] recommend a platelet count $>50 \times 10^9$/L and PT/INR < 1.5 prior to insertion of a central VADs other than a PICC, without further distinction between nontunneled, tunneled, and totally implanted VADs.

The British and Irish Society of Anesthesiology (BISA)[2] recommends that in case of coagulopathy and/or thrombocytopenia central VADs should be inserted by well-trained operators, possibly choosing an insertion site that allows easy compression of vessels, such as the femoral site. Correction of coagulopathy is not recommended by BISA when platelet count is $<50 \times 10^9$/L, and/or aPTT > 1.3 times normal and/or PT/INR > 1.8. These guidelines do not give further indications about the quantity and type of transfusion.

The guidelines from the America Association of Blood Banks[43] recommend prophylactic platelet transfusion for patients requiring elective central VAD placement if platelet count is $<20 \times 10^9$/L, with a grade of weak recommendation and low quality of evidence.

The Consensus document of the Society of Interventional Radiology (SIR)[8] recommends that PT/INR should be <2.0; platelet transfusion is recommended if platelet count is $<20 \times 10^9$/L for all procedures of insertion and removal of central VADs (nontunneled central VADs, including tunneled catheters, and ports), including PICC insertion.

Isolated prolonged aPTT is not a contraindication if due to the presence of Lupus Anticoagulant (LAC) syndrome and if no active bleeding is evident. In case of prolonged isolated aPTT, consultation with an expert in hemostasis and thrombosis is recommended.

As no evidence is specifically available in pediatric patients, the panel's recommendations are to be extended also to neonates and children with bleeding disorders.

The benefits of both real time ultrasound guidance and adequate training of the operator have been discussed in a few studies.[44–46] Some of these studies[3,4,46] have also recommended the use of micro-puncture kits (21G needles and 0.018″ nitinol guidewires) with the purpose of reducing puncture-related trauma to the tissues. Though this strategy may not be available in every hospital and/or in every Country, the panel suggested to consider this option in most cases, and especially in patients with increased risk of bleeding.

Q2—Panel recommendations

Considering patients with disease-related bleeding disorders (i.e., not pharmacologically induced for therapeutic reasons), the panel proposes the following recommendations:

(1) Venous access procedures should be postponed and scheduled electively, whenever possible, if an improvement of coagulation parameters or platelet count is expected. If an emergency venous access is required, it should be carried out regardless of the bleeding risk, but preferably choosing the least invasive device and least invasive technique.
(2) Both elective and emergency procedures should be performed by well-trained operators, choosing the safest puncture site (i.e., the best compressible site, such as the upper limb or groin or thigh). The use of ultrasound guidance is mandatory. The adoption of micro-puncture kits (i.e. 21 G echogenic needle,

atraumatic 0.018″ nitinol guidewire and microintroducer) may be advisable, so to minimize the risks associated with repeated punctures or accidental arterial puncture.

(3) For patients with disease-induced coagulopathy, with PT/INR > 1.5 and/or aPTT ratio > 1.3:

   a. No contraindication to minimally invasive procedures
   b. Relative contraindication to moderately invasive procedures
   c. Absolute contraindication to highly invasive procedures. Previous normalization of PT/INR value <1.5 is recommended to safely perform such procedures

(4) For patients with platelet count $<50 \times 10^9$/L:

   a. No contraindication to minimally invasive procedures
   b. Relative contraindication to moderately invasive procedures
   c. Absolute contraindication to highly invasive procedures. Platelet transfusion is mandatory to safely perform such procedures, if the procedure cannot be postponed. A choice of a less invasive device may be indicated in case of low platelet count.

(Q3) Which is the appropriate management of the patient on antithrombotic treatment, candidate to VAD insertion/removal?

Periprocedural management of patients on antithrombotic drugs involves a multidisciplinary team and often varies between institutions. Knowledge of the bleeding risk of the procedure, of the thrombotic risk of the patient and pre-existing comorbidities (e.g., renal dysfunction) and of the pharmacologic characteristics of the drugs are of paramount importance before taking any decision about interrupting/modifying the antithrombotic treatment.

Definition of thromboembolic risk

The specific risk of thromboembolic events (TE) for each patient on chronic anticoagulant therapy needs to be considered. Populations at high risk of TE include patients with nonvalvular atrial fibrillation (NVAF) and associated cardiovascular risk factors (congestive heart failure, hypertension, advanced age, diabetes, stroke/transient ischemic attack, peripheral arterial disease, previous myocardial infarction, and aortic atheroma). Patients with a history of previous venous thromboembolic event or with underlying malignancy or with a significant cardiovascular disease are also considered at high risk. Each thrombotic event is associated with high mortality.[10,47] The history of previous TE and the time of occurrence are especially important, because the recurrence of TE is more frequent within 30 days since the previous event and decreases after 3 months from the initial event. Venous thrombosis carries a higher risk of complications if occurring in deep and proximal veins than in superficial and distal veins.[8,10,47]

The thrombotic risk of patients with artificial cardiac valves depends on valve location—the mitral location being at a higher risk. Mechanical valves are also associated with a higher risk. If patients with mechanical valves have concomitant atrial fibrillation (AF), the thromboembolic risk is especially high. Patients with coronary artery disease and cardiac stents are considered at high risk if there is history of recent (<3 months) implanted stents or of acute coronary syndrome in the last 12 months.[8,48] When the latest acute event (acute coronary syndrome and/or stent implantation) has occurred more than 1 year before, patients are generally considered at low thrombotic risk. Bifurcation lesions, thrombus-containing lesions, long lesions, extensive coronary artery diseases, incomplete revascularization are considered at high risk.[48–50] The risk of stent-related thrombotic complications is greatest in the first month after percutaneous coronary intervention (PCI). Patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, ST-elevation myocardial infarction) are usually considered at high risk and thus treated with dual antiplatelet therapy (DAPT) for 12 months.[50,51] Recent guidelines on CIED implantation classify the thrombotic risk after PCI as intermediate/low (>month after PCI or >6 months after ACS and PCI) or high (<1 month after PCI or < 6 months after ACS and PCI).[52]

Vitamin K antagonists (VKA)

VKAs (such as warfarin) are the most important prescribed oral anticoagulant in patients with mechanical cardiac valves and are still prescribed in patients with AF. Warfarin inhibits a vitamin K-dependent enzyme, preventing the production of the active forms of factors II, VII, IX, and X. It has a half-life of 36–42 h. Given its indirect mechanism of action, once started the warfarin therapy, the onset of effect is expected in 2–3 days. An interruption for 4–5 days before invasive procedures is traditionally recommended.[10,53] Postoperatively, warfarin is usually resumed within 12–24 h after the procedure, at the same preoperative dose. Even in patients at particularly high risk of thrombosis, interruption, and bridging with UFH or LMWH at therapeutic dose is not recommended anymore. On the contrary, it is recommended to adjust the PT/INR to the lower limits of the therapeutical range.

Direct-Acting Oral Anticoagulants (DOACs)

DOACs include dabigatran, a direct thrombin inhibitor, and direct Xa inhibitors such as rivaroxaban, apixaban, and edoxaban. The DOACs have a rapid onset of action with a

peak at 1–3 h and a half-life of 10–14 h. For this reason, interruption and bridging with UHF or LMWH is not necessary.[6] All the DOACs have some degree of renal clearance. Dabigatran has a prevalent renal elimination (80%), which means that in presence of significant renal dysfunction, a longer pre-procedural interruption is recommended. In patients with creatinine clearance (CrCl) $<$ 49–30 mL/min undergoing low risk bleeding procedure, dabigatran should be interrupted 48 h before the procedure.[9] In case of surgical procedures with intermediate or high bleeding risk, dabigatran should be suspended 96 h before the procedure.[54,55] According to the current recommendations from the American College of Cardiology (ACC) and the European Heart Rhythm Association (EHRA),[6,7,12] DOACs should be withheld for a duration equivalent to 2–3 half-lives (approximately 24–36 h) before procedures with low to moderate bleeding risk and 4–5 half-lives (approximately 48) for high bleeding procedures.

Interruption and "bridging"

Data from RCTs in patients on oral anticoagulant therapy (both VKAs and DOACs) undergoing CIED implantation suggest that the incidence of pocket hematoma and major bleeding is quite low (2.1%–3.5% and 0.38%, respectively), even when the treatment is not interrupted.[56–58]

For procedures with low bleeding risk, the incidence of hemorrhage is lower in case of continuation of VKA treatment than when adopting the practice of temporary interruption + bridging with UFH/LMWH. In the BRUISE CONTROL trial (Bridge or Continue Coumadin for Device Surgery Randomized Controlled), carried out in patients undergoing implantation of CIEDs, maintenance of VKA treatment (at INR $<$ 3) was associated with significantly less bleeding than temporary interruption and bridging with UFH/LMWH.[56] In the COMPARE trial (Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation Patients Undergoing Catheter Ablation), carried out in patients undergoing catheter ablation for AF, maintenance of VKA treatment (at INR between 2 and 3) was associated with lower rates of minor bleeding and thromboembolic events than temporary interruption and bridging with LMWH.[58] The BRIDGE trial investigated a total of 1884 patients with AF and concomitant valvular disease, on VKA treatment for 3 months or longer (PT/INR range between 2 and 3), undergoing invasive procedures that would require interruption of VKA; patients were randomly assigned to bridging with dalteparin sodium (100 UI/Kg subcutaneously twice daily) or no bridging at all. There was no difference between the groups in terms of prevention of TE, but the risk of major bleeding was significantly less in the "no bridging" group.[14,59] In a prospective multicenter study on 569 patients receiving chronic antithrombotic therapy and candidate to CIED implantation, interruption of VKA + bridging with UFH/LMWH was associated with a significantly higher incidence of pocket hematoma (12.3%), if compared to uninterrupted DAPT (4%, 2%) or uninterrupted DOACs treatment (2%, 4%) ($p < 0.001$).[60] When interrupting VKA treatment, the risk of hematoma is the same, both bridging with UFH/LMWH or with antiplatelets.[20]

More recently, in the PAUSE study (Perioperative Anticoagulant Use for Surgery Evaluation), a total of 3007 patients on chronic DOACs therapy underwent invasive procedures with only temporary interruption and no "bridging" with UFH/LMWH; the extent of the interruption was decided based on the type of DOAC, on the magnitude of renal dysfunction (evaluated as CrCl), and on the bleeding risk of the procedure.[9,61] Though more than one third of the patients underwent procedures with high bleeding risk, the incidence of clinically relevant bleeding was $<$2% and the incidence of TE $<$ 1%.[62]

As a result of the previous studies, for procedures classified as low/moderate bleeding risk, the latest guidelines recommend the interruption of oral anticoagulants at least 2–3 half-lives of the drug before the procedure (approximately 3 days for VKA and 1 day for DOACs) with resumption of the therapeutic dosage within 1 day after the procedure[7]: bridging with UFH/LMWH is never recommended.

The ACC recommendations

The ACC consensus on periprocedural management of anticoagulation in patients with non-valvular AF[12] recommends:

(1) For patients on VKA: PT/INR level should be measured 5–7 days before the procedure.
   a. Do not interrupt VKA in patients undergoing procedures with minimal or very low bleeding risk, in absence of patient-related factors that may increase the risk of bleeding.
   b. Interrupt VKA in patients undergoing procedures with intermediate or high bleeding risk or in presence of patient-related factors that may increase the risk of bleeding.
   c. In patients with PT/INR 1.5–1.9, VKA should be discontinued 3–4 days prior to the procedure, if a normal PT/INR is desired. The PT/INR should be rechecked within 24 h before the procedure
   d. In patients with PT/INR 2–3, VKA should be discontinued 5 days prior to the procedure. The PT/INR should be rechecked within 24 h before the procedure.
   e. In patients with PT/INR $>$ 3.0, VKA should be discontinued at least 5 days prior to the procedure, INR rechecked, and elective scheduled procedure should be delayed, if possible, until the desired PT/INR is achieved. VKA can be

restarted in the first 24 h after the procedure at the usual dosage.

(2) For patients on DOACs: DOACs should be withheld for a duration equivalent to 2–3 half-lives (approximately 24–36 h) for procedures with low/moderate bleeding risk, and 4–5 half-lives (approximately 48–60 h) before procedures with high bleeding risk. Renal function should be assessed. Following procedures with low/moderate bleeding risk, DOACs should be restarted at full doses on the day following the procedure. In patients without patient-related increased bleeding risk factors and in those undergoing procedures with minimal bleeding risk, DOACs should be held for a single dose, or the procedure should be performed without temporary interruption, but at the nadir of the predicted drug level.
(3) For patients on parenteral heparin: Discontinue unfractionated heparin (UFH) 4–6 h prior to procedure. Discontinue LMWH at least 24 h prior to procedure in patients with normal renal function.

The GIFAV recommendations

In 2019, the interdisciplinary French group of vascular access Groupe Interdisciplinaire Francophone Accès Vasculaires (GIFAV) has published recommendations about the implantation of ports in patients on antithrombotic therapy.[63]

- VKA therapy in patients with INR 2–3 and high thrombotic risk: interrupt VKA 5 days before the procedure and start treatment with LMWH at therapeutic dose 3 days before the procedure and until the day before the procedure. Restart VKA the day after the procedure, continuing LMWH until reaching the desired INR.
- VKA therapy in patients with INR 2 and moderate/low thrombotic risk: interrupt VKA 5 days before the procedure, without bridging with LMWH.
- DOACs: interrupt rivaroxaban and apixaban 3 days before procedure and restart the day after; interrupt dabigatran 4– 5 days before the procedure and restart the day after.
- Fondaparinux 2.5 mg: interrupt 24 h before the procedure and restart 16 h later
- Fondaparinux 7.5 mg: interrupt 36 h before procedure and restart 12 h later with a half dose.
- LMWH (100 units/kg/24 h): interrupt 8 h before and restart 12 h later.
- LMWH (150 units/kg/24 h or 100 units/kg/12 h): interrupt 16–20 h before the procedure and restart 12 h later with half dose.
- Clopidogrel, ticlopidine, ticagrelor: withhold 3 days before the procedure and restart the day after.
- Acetyl-salicylic acid 75 mg or 100 mg: withhold 5 days before the procedure and restart the day after
- Prasugrel: withhold 7 days before the procedure and restart the day after.

Q3—Panel recommendations

Based on the most recent studies, and considering that all venous access procedures can be classified at low bleeding risk, albeit with different invasiveness, the panel proposes the following recommendations:

(1) For minimal invasive venous access procedures: do not withhold VKA, DOACs, UFH, LMWH, or antiplatelet drugs
(2) For moderately invasive venous access procedures:

VKA: aim for PT/INR <3 (bridging with LMWH is not recommended). For emergency procedures, in case of PT/INR >4, consider the use of prothrombin factors, fresh frozen plasma, or vit K to counteract the effect of VKA.

DOAC: perform the procedure 12 h after the last dose of DOAC. Restart no less than 6 h after the procedure.

UFH: withhold 4 h before the procedure. Restart 6 h after the procedure.

LMWH: withhold one dose before the procedure. Restart after 12 h after the procedure.

FONDAPARINUX: withhold one dose before the procedure. Restart 12 h after the procedure.

SINGLE ANTIPLATELET THERAPY (SAPT): do not withhold.

DUAL ANTIPLATELET THERAPY (DAPT): in case of emergent procedures, do not withhold. In case of elective procedures, same as high invasive procedure: see below.

(3) For highly invasive venous access procedures:

VKA: in patients with prescribed therapeutic PT/INR range 2–3, do not interrupt VKA and perform the procedure when PT/INR is between 2 and 2.5. If the prescribed therapeutic range is 2.5–3.5 (e.g., in some patients with mechanical prosthetic valve), perform the procedure when PT/INR is between 2.5 and 3.

Perioperative bridging with LMWH/UFH is not recommended.

DABIGATRAN: withhold up to 24–36 h (if CrCl > 50 mL/min) or 48 h (if CrCl < 50 mL/min). Restart 24 h later.

APIXABAN, EDOXABAN, RIVAROXABAN: withhold 24 h (if CrCl > 30 mL/min) or 48 h (if CrCl < 30 mL/min). Restart 24 h later.

UFH: withhold 4–6 h before the procedure. Restart 6–8 h later.

LMWH: perform the procedure 8–12 h after a prophylactic dose, or 24 h after a therapeutic dose. Restart no less than 12 h after the procedure.

FONDAPARINUX 1.5–2.5 (prophylactic dose): withhold 24 h. Restart 12 h later.

FONDAPARINUX 5.0–7.5–10 mg (therapeutic dose): withhold 36 h (if CrCl > 50 ml/min). Restart 12 h after the procedure. In patients with acute or chronic renal failure (CrCl < 50 mL/min) the use of fondaparinux is contraindicated.

SINGLE ANTIPLATELET THERAPY (SAPT): do not withhold

DUAL ANTIPLATELET THERAPY (DAPT): in patients at low/intermediate thrombotic risk, do not withhold acetyl salicylic acid but withhold the other drug (TICAGRELOR: withhold 3 days, CLOPIDROGREL, DIPYRIDAMOLE: withhold 5 days, PRASUGREL: withhold 7 days). Restart the day after the procedure. In patients at high thrombotic risk, consider postponing the procedure until the risk is low/intermediate (1 month or more) and do instead a procedure with lower invasiveness.

As regards DOAC suspension according to renal function, see Table 1.

Conclusions

The goal of the present consensus document is to offer a systematic set of recommendations on the management of antithrombotic treatment and bleeding disorders in patients requiring venous access devices. Though hard evidence from the literature is missing on many topics, the panel has fully agreed on several statements based on expert's opinion, on low quality clinical studies, and on a few good quality clinical studies conducted on invasive procedures at low bleeding risk (CIED implantation) not related to VADs, but similar to VAD insertion.

The recommendations of the panel have been structured in three sets of questions. In the first set of questions, the panel has differentiated three different groups of VADs, with different invasiveness. In the second set of questions, the panel has developed recommendations about the management of patients with bleeding disorders associated with low platelet count or high PT/INR. The third set of questions includes recommendations about the opportunity to withhold antithrombotic treatment, based on the type of drug and on the specific thrombotic risk of the patient. The final recommendations of the panel are summarized in Table 2.

Table 1. Recommended interruption of DOACs, based on renal function, for procedures with low bleeding risk*. Bridging with LMWH or UFH is not recommended.

CrCl	Dabigatran	Apixaban–edoxaban–rivaroxaban
>80 mL/min	24 h	24 h
50–79 mL/min	36 h	
30–49 mL/min	48 h	
15–29 mL/min	**	

*All vascular access procedures are considered as low bleeding risk procedures (see text).
**dabigatran is not recommended in patients with CrCl < 30 mL/min.
Table modified from Steffel et al.[6]

Table 2. Summary of the panel recommendations.

	Type of venous access procedure		
	Minimally invasive (*all peripheral VADs, nontunneled PICCs, nontunneled FICCs at mid-thigh*)	**Moderately invasive** (*nontunneled CICCs, nontunneled FICCs at the groin, tunneled PICCs, nontunneled dialysis catheters*)	**Highly invasive** (*tunneled CICCs, tunneled FICCs, tunneled-cuffed dialysis catheters, ports and PICC-ports*)
Bleeding disorder			
PT/INR > 1.5 and/or aPTT ratio > 1.3	No contraindication	Relative contraindication (see text)	Absolute contraindication
Platelet $<50 \times 10^9$/L	No contraindication	Relative contraindication	Absolute contraindication (see text)
Antithrombotic treatment			
VKA	Do not withhold	Aim for PT/INR < 3 (see text)	Maintain PT/INR in the low therapeutic range (see text)

(Continued)

Table 2. (Continued)

	Type of venous access procedure		
	Minimally invasive (*all peripheral VADs, nontunneled PICCs, nontunneled FICCs at mid-thigh*)	**Moderately invasive** (*nontunneled CICCs, nontunneled FICCs at the groin, tunneled PICCs, nontunneled dialysis catheters*)	**Highly invasive** (*tunneled CICCs, tunneled FICCs, tunneled-cuffed dialysis catheters, ports and PICC-ports*)
DOAC	Do not withhold	Wait 12 h after last dose	Withhold 24–48 h, depending on the type of drug and on renal function (see text)
UFH	Do not withhold	Withhold 4 h	Withhold 4–6 h
LMWH	Do not withhold	Withhold one dose	Withhold 8–12 h (prophylactic dose) or 24 h (therapeutic dose)
Fondaparinux	Do not withhold	Withhold one dose	Withhold 24 h (prophylactic dose) or 36 h (therapeutic dose)
SAPT	Do not withhold	Do not withhold	Do not withhold
DAPT	Do not withhold	In emergency, do not withhold; in elective procedure, withhold one drug (see text)	Withhold one drug (see details in the text)

aPTT: activated partial thromboplastin time; DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulant; LMWH: low molecular weight heparin; PT/INR: international normalized ratio of prothrombin time; SAPT: single antiplatelet therapy; UFH: unfractionated heparin; VKA: vitamin K antagonist. See additional details of each recommendation in the text.

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