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Review Article

SEVEN ARGUMENTS AGAINST STARTING WARFARIN ON THE FIRST DAY OF PULMONARY THROMBOEMBOLISM

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Abstract. *The aim is to analyze how the advances in pulmonary thromboembolism (PTE) may influence its therapeutic protocol, focusing on the anti-vitamin K (AVK) start. Narrative review (analyzing the most important Guidelines) was used for the synthesis of the improved approach regarding the time to start AVK in PTE. For PTE, it is crucial to instantly provide an optimal anticoagulant effect of both unfractionated heparin and AVK, a difficult task indeed. By delaying AVK we may avoid the AVK use (and thus the overlap); instead, following a parenteral anticoagulant, we may proceed with direct oral anticoagulant-DOAC (if the escalation therapy is not needed). There are seven new important arguments to postpone AVK commencement from the first day of PTE treatment (although recommended in contemporary guidelines for PTE patients who are not planned for thrombolysis). A more appropriate time to start the oral anticoagulant (preferably-DOAC) is when PTE comes under control and the need for escalation of fibirinolytic treatment is gone*.

Key words: *oral anticoagulants, warfarin, pulmonary thromboembolism.*

Introduction

We are witnesses to a rapid improvement of pharmacology in the field of pulmonary thromboembolism (PTE) [1]. It imposes a need to optimize utilization of new drugs together with the incorporation of clinical experience and current understandings of the disease into our contemporary approach to PTE patients [2–5]. Treatment of PTE has been complex due to a pronounced variability in the age, the number, and severity of comorbidities, thrombus burden and location, degree of cardiopulmonary reserve, variable response to therapy and treatment-related complications, etc. Nine years ago a number of reasons have been published to postpone anti-vitamin K (AVK) from the admission day [6]:

1. In PTE patients without shock and hypotension and therefore without the need for immediate „primary" fibrinolysis, the *escalation therapy* (*„secondary fibrinolysis"*) may be required on e.g., the fifth day. In such patients, AVK given on the first day will pose an unnecessary and avoidable risk of bleeding [6]. This is an important drawback of the protocol with AVK from the first day of admission because the prevalence of patients with PTE who need the escalation therapy (due to clinical markers of worse prognosis such as new-onset hemodynamic instability, worsening right ventricular dysfunction, or respiratory failure, or substantial myocardial necrosis), has not been low. In one study, cited in the 2014 European Society of Cardiology (ESC) guidelines, an escalation to the emergency treatment varied from 10.2% to 24.6% in PTE patients [7].

2. AVKs act *procoagulantly* for the first few days of being administered [8–10]. The worst time to expose PTE patients to the procoagulant effect of AVK, is exactly during the first days when the thrombus burden and the blood hypercoagulablility are maximal. Moreover, it is now easy to avoid the application of AVK from the first day because we have other, safer options – direct oral anticoagulants (DOACs), that do not act procoagulantly [6].

3. A later start of AVK makes the *vena cava filter* implantation less risky if indicated [2] e.g. when venous thromboembolism (VTE) had occurred despite the ongoing anticoagulation [11].

Materials and Methods

Narrative review (analyzing the important Guidelines) was used for the synthesis of the improved approach regarding the time to start AVK in PTE.

Results

The traditional beginning of the AVK treatment on admission day (as recommended by contemporary guidelines) [2, 7, 11, 12] is not imperative at all, because an AVK neither enhances thrombus degradation during the first critical days by itself nor allows the endogenous fibrinolytic system to do it. Actually, in addition to the three above-mentioned, one can list at least seven other shortcomings of the AVK commencing exactly on the day of admission.

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Additional weaknesses of the current protocol with the early AVK treatment (from the admission day)

1. When we give AVK on the first day, together with a parenteral anticoagulant, in order to avoid complications (bleeding on one hand and thrombus propagation or re-embolization on the other), *it is crucial to instantly provide the optimal anticoagulant effect of both unfractionated heparin (UFH) and AVK, which is a very difficult task.* It is not easy at all to provide a stable adequate anticoagulant effect of an AVK (e.g., warfarin), during the first days and even weeks from the introduction [12]. For example, in one study the median time to reach a therapeutic international normalized ratio (INR) was 21 days in the genotype-guided group as compared to no less than 29 days in the usual care group [12]. Difficulties in the INR targeting (requiring frequent INR measurements and dose adjustments) are the consequences of warfarin's narrow therapeutic index and drug–to-drug interactions, as well as patient's health status, hepatic metabolism, and genotype, and diet [10]. It is also difficult to promptly provide the optimal anticoagulant effect of UFH, as measured by activated partial thromboplastin time (aPTT) or anti-Xa [3, 9]. Over 300 various reagent-coagulometer combinations are currently applied in the practice. As a result, therapeutic heparin concentration (0.3–0.7 anti-Xa u/ml) corresponds to wide aPTT ratios, from 1.6–2.7 to 3.7–6.2 times control [9]. The quality of UFH control also depends in practice on the capability of the local laboratory to measure aPTT or anti-Xa frequently, quickly, and 24 hours a day. According to the recommendations, the aPTT or anti-Xa levels ought to be checked every 6 hours until two consecutive therapeutic results are obtained [9, 10], which is not feasible in all hospitals. It was very important to obtain adequate aPTT during the first days of admission, as it considerably influenced the prognosis [8]. If PTE patients do not receive at least 30,000 UFH units a day, sub-therapeutic aPTTs within the first 24–48 hours will correlate with VTE recurrence [9]. The overactivity of each, and particularly of both UFH and AVK, substantially increases the risk of bleeding, while the insufficient anticoagulant effect can result in thrombosis extension in an already highly thrombogenic situation such as PTE.

2. Starting AVK on the first day, *precludes later in-hospital switching from a parenteral anticoagulant to a DOAC,* because it has been recommended not to change one oral anticoagulant (OAC) for another [2]. Each of the four approved DOACs has evidence of a better benefit /risk ratio in comparison with AVK [1, 3, 12]. DOACs have been shown to be safer than AVK, as they decrease the risk of bleeding [1]. Moreover, DOAC is much easier and quicker to introduce: there is no need to overlap DOAC with parenteral anticoagulant; we can simply administer DOAC 0–2 hours prior to and instead of the next scheduled regular dose of the original parenteral anticoagulant (low molecular weight heparin - LMWH or fondaparinoux in the majority of patients, as suggested by contemporary guidelines) [1, 7, 9, 12]. Thus, by introducing AVK on the first day we omit the possibility to choose in the hospital probably better option for prolonged treatment – DOAC [1]. Rivaroxaban was administered following LMWH/UFH, without introducing AVK on the first day in the important study of Sharifi et al. [13] Therefore, the decision which drug to administer during the coming months or even years (AVK or DOAC), is better not to make too early on the day of admission but once PTE gets under feasible control. Most physicians treating PTE patients have preferences regarding AVK or DOAC; therefore the intention to use one or another is present already at the patient's presentation. When this preference is DOAC, the agreement of a patient for financial participation is needed in many countries. In the absence of the patient's agreement for DOAC, we ought to proceed with LMWH and AVK combination. Admittedly, it is somewhat prematurely during the first day or two of hospital admission to explain to the patient with e.g. intermediate-high risk PTE the possible therapeutic options (and elaborate about their cost-effectiveness, LMWH, and AVK vs. DOAC). It seems more adequate to discuss post-acute treatment a couple of days before discharge, when PTE is under control and when the patient's confidence is obtained.

3. If one or two INR values >2 have been achieved relatively rapidly, e.g., in 5 days (which is the minimum allowed by actual guidelines) [7, 9, 11, 12], the overlap is finished and the *period of the administration of stronger anticoagulant* (*the parenteral one*) [14] *may be too short* to help to obtain successful thrombus dissolving. An insufficiently long administration of more efficient, parenteral anticoagulant is probably one of the important reasons why (with classic PTE protocol) residual thrombosis in pulmonary arteries has been found after 6 or 12 months of follow-up in a disturbing number of patients, e.g., 50% [8, 15] or 70% [16]. This residual thrombosis in VTE may increase the probability of re-thrombosis [3, 7, 8]. Therefore, it is better to cease more efficient parenteral anticoagulant treatment when we judge that it is the right time (once when we have objective evidence of improvement of patients' findings, such as respiration rate, hemoglobin oxygen saturation, electrocardiogram - ECG, echocardiogram, computer tomography pulmonary angiography - CTPA, D-dimer, etc.) than when it happens that the patient achieves INR >2 once [5] or two times, 24 hours apart (indicating the end of the overlap) [2, 3, 7, 11].

4. Starting AVK may turn out to be *a mistake for* approximately 10% of the patients with unprovoked PTE, in whom we find *cancer later* during hospitalization (in the quick examination of all patients aged over 40 years with a first unprovoked PTE or deep venous thrombosis - DVT, searching for the cause of VTE, using e.g., basal clinical investigation, laboratory, and chest X-ray, plus an abdomino-pelvic CT scan - and a mammogram for women) [11]. Since Traussaud described the temporal re-

lation between cancer and VTE in 1865 [17], it is wise to have it in mind. This relation is named "metachronous" because each of the two may come first or they can be present simultaneously. Therefore, cancer screening is recommended [18]. It is particularly important to search for cancer in patients with "unprovoked" PTE, because as many as 10% may have a diagnosis of cancer during the first year of follow-up [19]. The reasons are numerous; cancer increases mortality rates in VTE and the other way round; cancer presence influences to a great deal the estimation of both re-thrombosis and bleeding; there are several specificities in VTE treatment in patients with cancer, etc. The optimal thoroughness of the cancer screening is a matter of long-standing debate. On the one hand, it is not sound to spend a lot of time, effort, hospital capacities, and resources as the probability of positive finding is not high; on the other hand, it is a mistake to miss cancer in a patient with VTE and jeopardize his/her prognosis, particularly because this relationship is known for >150 years. Therefore, a balance is needed. The 2019 ESC and National Institute for Health and Care Excellence (NICE) Guideline recommend careful medical history taking and a physical examination, together with baseline laboratory findings, such as complete blood count (CBC), parameters of hepatic and renal function, as well as PT and aPTT [20, 21]. Other investigations are not necessary and they can be invasive, time-consuming, costly, stressogenic, and represent a radiation risk [20]. Starting AVK on the admission day is a mistake for cancer patients with PTE because LMWH has been recommended (provided patient agrees) for 6 months or as long as the cancer is present / under treatment, without the usage of AVK at al [2, 3, 11]. The more comfortable post-acute anticoagulant treatment in VTE patients with cancer is DOAC [21], except for gastrointestinal tumors [21]. Therefore, AVKs are currently regarded insufficient for the majority of patients with VTE and cancer.

5. Keeping in mind the importance of bleeding in PTE [2], it is particularly *important to avoid or postpone procedures and drugs* (*such as AVKs*), *which increase bleeding risk, until patient's clinical state becomes far better*. For example, an eventual major bleed may further deteriorate the already bad condition and may limit the use of otherwise needed anticoagulants in the next period. Thus, eventual major hemorrhage would cause less harm if it occurs on day nine (when thrombus burden, symptoms, and risk are smaller) than on day three of hospitalization (when thrombus burden is still prominent). Therefore, it makes sense to postpone AVK from the first day in order to delay eventual bleeding in an already dangerous disease. It is important to postpone AVK particularly in numerous patients with recent bleeding or high risk of bleeding, such as listed in *Hestia criteria*, e.g., gastrointestinal (GI) bleed within 14 days, recent stroke (within 4 weeks), recent surgery (within 2 weeks), platelets <75,000/μl, uncontrolled arterial hypertension (systolic blood pressure, BP>180 mmHg, diastolic BP>110 mmHg) [3]. It is wise to postpone AVK commencement in PTE patients with a high risk of bleeding, which can be recognized by *RIETE* (Registro Informatizado de la Enfermedad Thomboembolica venosa) Bleeding Score: recent major bleed (1 month), creatinine >1.2 mg/dl, anemia, cancer, clinical presentation as PTE (vs. DVT) and age >75 years [8]. Moreover, *ACCP* (*American College of Chest Physicians*) *Score for Bleeding Risk* also suggests who is on the elevated bleeding risk: age >65 years / >75 years, previous bleed, cancer / with metastasis, renal insufficiency, liver failure, thrombocytopenia, previous stroke, diabetes mellitus, anemia, anti-platelet drugs, poorly controlled anticoagulation, comorbidity, and reduced functional capacity, recent surgery, frequent falls, and alcohol abuse [8]. According to the ESC 2014 PTE guidelines, in the absence of properly evaluated bleeding risk scores for VTE patients, high risk for hemorrhage represents old age (especially >75 years), previous GI bleeding (particularly if the cause is not reversible), any type of the previous stroke, chronic illness of kidney or liver, parallel antiplatelet treatment, other serious diseases, and poor anticoagulation control [7]. Therefore, it is logical to avoid commencing AVK on the first day(s), particularly in the following categories of PTE patients A) with the high thrombus burden, B) with the more central thrombus location, C) with the worse the patients' cardiopulmonary reserve and symptoms (suggesting a severe form of intermediate-risk PTE, and thus life-threatening situation if bleeding occurs), and D) with the higher risk of bleeding. Moreover, high bleeding risk implies that the proper choice of peroral anticoagulant for post-hospital treatment would be one of the DOACs (due to their safer profile) [1, 3, 12]. Therefore, as far as OACs are concerned, if a PTE patient has a high risk for hemorrhage, it is better to decrease it a) by introducing OAC later during the hospitalization and b) by choosing a DOAC instead of AVK.

6. By starting AVK from the beginning of the hospitalization, there is a risk for *AVK hyper-responders* that they may bleed at the worst time possible – when PTE is not under acceptable control. Postponing the overlap (e.g., UFH and AVK) may allow time for a parenteral anticoagulant to clear an important part of thrombus before eventual bleeding may compromise the effects of therapy. We may search for AVK hyper-responders by pharmacogenomic study because variations in two genes correspond to >30% of the dosing variability of warfarin. One gene determines the activity of cytochrome P2C9 that inactivates warfarin's S-enantiomer, and the other regulates the activity of vitamin K epoxide reductase, which produces the active form of vitamin K [7, 12].

7. Starting AVK on the first day exposes patients too early to bleeding risk, before the main job is mostly finished – getting the disease (PTE) under control. An additional risk is imposed by drugs, capable of inducing hemorrhage directly by themselves or indirectly, by influencing AVK. For example, *dual antiplatelet therapy* (*DAPT*) may be necessary (because of e.g., recent coronary artery stent implantation), and the early AVK

Table 1 Important arguments to postpone AVK commencement from the first day of PTE treatment

Number[a]	Reason[b]	References supporting the case
1	AVK given from the day of admission may increase the risk of bleeding in case that *thrombolysis* becomes needed due to eventual deterioration of the patient's hemodynamics.	6, 7
2	AVKs act *procoagulantly* for the first few days of being administered.	8, 9, 10
3	It also makes the *vena cava filter* implantation more risky (if an indication arises).	6, 11
4	It is *challenging to obtain adequate INR during the first week* of AVK and *under-anticoagulation increases the risk of rethrombosis* following the cease of the parenteral anticoagulant.	10, 12
5	Starting AVK on the first day, *precludes later in-hospital switching from a parenteral anticoagulant to a DOAC.*	2
6	If target INR is obtained too soon (before day 5), it may *preclude the full duration of a parenteral anticoagulant* (recommended in PTE Guidelines)	7, 9, 11, 12
7	Starting AVK may be *a mistake for* approximately 10% of the patients with unprovoked PTE, in whom we find *cancer later* during hospitalization because LMWH (and not AVK) has been recommended for cancer patients with PTE.	2, 11, 13
8	*If INR raises too much hemorrhage may occur*. Such a scenario is real and *it is better to postpone AVK in order to have the patient stabilized before starting AVK.*	2, 8
9	It is particularly true if the patient is a *hyper-responder to AVK* and the worst time for very high INR is during the first days of treatment.	7, 12
10	AVK from the day of admission overlapped with LMWH is also a premature approach for *patients with recent coronary artery stent implantation who have an indication for DAPT*, as the bleeding risk is unacceptably high.	23

Legend: AVK anti-vitamin K; INR international normalized ratio; DOAC direct oral anticoagulant; PTE pulmonary thromboembolism; LMWH low-molecular-weight-heparin; DAPT dual antiplatelet therapy.
[a] Serial number of an argument.
[b] Reason to postpone AVK commencement from the first day of PTE.

commencement (on the first day), overlapped with LMWH is not the best approach - due to safety reasons [22].

To sum up, in addition to three already published, there are seven new important arguments (making a total of ten) to postpone AVK commencement from the first day of PTE diagnosis (as recommended in all the contemporary guidelines for PTE patients who are not planned for thrombolysis) (Table 1). On the other hand, why should we introduce AVK on the day of admission? Both obvious reasons to do it are outdated. Firstly, the risk of heparin-induced thrombocytopenia (HIT) with prolonged UHF or LMWH therapy can be avoided by choosing the parenteral anticoagulant which does not induce HIT (fondaparinoux). Secondly, the potential increased cost of prolonged hospitalization due to the postponement of AVK, can be easily outbalanced by avoiding the time-consuming overlap of parenteral anticoagulant and AVK by introducing DOAC without overlap (instead of AVK with overlap), once PTE patient is stabilized. Such an approach has already been tested [13, 23].

Discussion

PTE is very important due to its high incidence, prevalence, morbidity, and mortality. Considering global mortality, PTE is the second most important cardiologic and the third most important cardiovascular disease (after myocardial infarction and stroke). Even a small improvement in the therapy of PTE may result in thousands of lives saved worldwide annually.

The review attempts to analyze if there is room for improvement of the current protocol for PTE treatment. AVK has been the standard of care in PTE therapy for decades; AVK has been recommended to start with on the day of diagnosis, together with UFH/LMWH, overlapping them for at least five days. Nevertheless, up to half of PTE patients who survived a year following hospitalization, have in pulmonary artery/arteries residual thrombosis; this worsens the symptoms and prognosis and proves that the before-mentioned standard PTE protocol is far from being optimal. On the other hand, all historical reasons to introduce AVK from the first day (e.g., 1. risk of HIT with prolonged UHF or LMWH therapy, or 2. increased cost of prolonged hospitalization) can be easily solved by contemporary evidence-based treatment (e.g., 1. by choosing the parenteral anticoagulant which does not induce HIT and 2. by avoiding the time-consuming overlap of parenteral anticoagulant and AVK in this way that we simply introduce DOAC without overlap, once when a PTE patient is stabilized).

Aiming to obviate the complications (bleeding on one hand and thrombus propagation or re-embolization on the other), it is crucial to instantly provide an optimal anticoagulant effect of both UFH and AVK, which is a very difficult task. For intermediate-risk, PTE patients who obtain INR >2 in e.g., five days, the administration of parenteral anticoagulant (which is evidence-based stronger than AVK) may be too short for the efficient thrombus removal and starting AVK early would not allow the individualization of stronger parenteral anticoagulation. Starting AVK may turn out to be a mistake for approximately 10% of the patients with unprovoked PTE in whom we find cancer later during hospitalization. Furthermore, we identified numerous PTE patients who may benefit from postponing AVK from the first day of treatment, for example, patients at high bleeding risk.

Several benefits may be expected for PTE patients: avoiding the procoagulant effect of AVK during the first critical days of the hospitalization, the decrease of the bleeding risk of concomitant therapy (overlap) using difficult-to-control anticoagulant AVK, particularly with another anticoagulant with low bioavailability and predictability of effect (UFH). Furthermore, eventual escalation of therapy (due to hemodynamic compromise, absent at admission, that appeared later during the course of PTE, and required fibrinolysis) would result in less bleeding if the patient is without AVK.

Thus, a patient with a previously unrecognized cancer may get a chance to avoid unnecessary AVK therapy. Additionally, all PTE patients with high bleeding risk and this is a large group, will benefit from the later introduction of OAC (preferably DOAC) because the overlap, i.e., administration of two anticoagulants (parenteral one and AVK) is risky, particularly due to the difficulties to obtain the target INR range for AVK. Thus, it is better to start OAC when the thrombus burden is diminished and the patient is out of a life- threatening situation. It is because should a major bleed eventually occur, we might be forced to temporarily withdraw the anticoagulant; indeed, to temporarily cease the anticoagulant, would result in less harm when thrombosis is under control and critical days for the patient are gone.

Final Remarks

From the aforementioned, the following recommendation can be stated: *Starting LMWH as the only anticoagulant in intermediate-risk PTE patients* has several advantages. One of them is the possibility to individualize treatment in terms of A) *leaving all therapeutic options open*, i.e. being prepared for an escalation of treatment or to –to the contrary- to decrease the intensity and proceed to peroral anticoagulation; and B) tailoring *duration* of LMWH administration according to the improvements in patient's clinical picture (symptoms and signs), as well as in oxygen saturation (or arterial blood gasses), ECG, echocardiography, D dimer, etc. This watchful waiting and re-examination of a need to thrombolyse can help us avoid unnecessarily thrombolysis (on the one hand, with its imminent bleeding risk) and enable full preparedness to escalate treatment (including rescue thrombolysis – if needed, on the other hand). The second advantage of LMWH (as the only anticoagulant treatment from the hospital admission – without AVK) is an *easy and quick transition to DOAC* as soon as aforementioned numerous PTE parameters indicate that the risk of sudden hemodynamic worsening/compromise is over (it became very low). No overlap is needed for LMWH and DOAC (as it is for LMWH and AVK), which may substantially reduce hospital stay and costs. The most recent guideline on PTE recommends direct oral anticoagulants (DOACs) over AVK; therefore, the smooth transition from LMWH to DOAC is warranted [24]. An argument for DOAC is about 30% lower risk of major bleeding (as compared to AVK) [24]. The third advantage of "LMWH only" approach to intermediate-risk PTE patients is the *avoiding premature AVK inclusion, which may almost preclude later switch to DOAC* in case of newly diagnosed cancer. The fourth advantage of "LMWH only" pathway is the *avoiding of premature DOAC initiation* in case of e.g. triple-positive antiphospholipid syndrome (APS) [25], because it will be necessary to switch to AVK later on (and any switch from one oral anticoagulant to the other has to be avoided); this 4th advantage can be obtained by providing enough time to diagnose APS. Therefore, "LMWH only" in intermediate-risk PTE patients is a valid option, with numerous advantages over the early introduction of AVK (on the first or second day); it enables us to avoid the premature introduction of each of the following drugs: thrombolytic, AVK, and DOAC.

The other subset of PTE patients (low-risk subset) inclines to the home-treatment or toward an early discharge and the majority of such patients are candidates for a DOAC, preferably one that does not require prior parenteral anticoagulation.

Conclusion

The prevalence of patients with PTE and at least one of ten listed reasons to postpone AVK is high – the majority of PTE patients are concerned. A better time to start OAC (either AVK or -preferably- DOAC) is when PTE comes under control, and the need for the escalation fibirnolytic treatment is gone (i.e. when clinical condition, ECG, echocardiogram and eventually CTPA findings become correct). Moreover, we have got nothing to lose, because even the hospital stay will become shorter due to the lack of days needed to overlap if we proceed from UFH or LMWH/fondaparinoux (and eventual escalation treatment – secondary fibrinolysis if necessary) to DOAC.

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