# Breadth of complications of long-term oral anticoagulant care

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**The majority of patients with venous thromboembolism (VTE) have a considerable long-term risk of recurrence and may require extended duration of anticoagulant treatment after the initial 3 to 6 months. The decision to extend treatment is based not only on the individual risk of recurrence, but should also consider the potential complications associated with anticoagulation, taking into account that anticoagulant drugs are among the drugs most frequently associated with hospital admission due to adverse drug reactions. The most feared complication of oral anticoagulants is bleeding, which in some cases may be fatal or may affect critical organs. Case-fatality rates of bleeding have been reported to be ~3 times higher than case-fatality rates of recurrent VTE. Even when nonserious, bleeding may require medical intervention and/or may impact on patient quality of life or working activity. Factors associated with bleeding during anticoagulant treatment include, among others, advanced age, cancer, renal or liver insufficiency, or concomitant antithrombotic drugs, but no bleeding risk score is sufficiently accurate for use in clinical practice. Not uncommonly, bleeding occurs as a complication of trauma or medically invasive procedures. Nonbleeding complications associated with oral anticoagulants are unusual, and their relevance is extremely uncertain, and include vascular calcification, anticoagulation-related nephropathy, and osteoporosis. Finally, because VTE not uncommonly affects young individuals and the mean age of the population is ~60 years, the costs associated with extended anticoagulation should not be forgotten. The costs of the drugs need to be balanced against health outcome costs associated with both recurrent VTE and bleeding.**

**Learning Objectives**

- Provide an overview of all complications associated with the long-term use of oral anticoagulant drugs
- Assist clinicians when deciding the optimal duration of the secondary prevention of VTE

## Case 1

M.R. is a 31-year-old man with a recent diagnosis of proximal deep vein thrombosis (DVT) of the right lower limb. His previous medical history was unremarkable, he had a rather active life working as a tree climber and forest ranger and practicing several sports, including skiing and soccer. DVT had been defined as unprovoked because no major provoking factors (eg, surgery or trauma) could be identified. His family history was negative for thromboembolic diseases. M.R. was treated with a direct oral anticoagulant (DOAC) for ~4 months before being referred by his general practitioner to the anticoagulation clinic to discuss whether anticoagulant treatment should be continued or stopped. M.R. is currently asymptomatic. He gained weight due to a reduction of physical activity. A complete workup for thrombophilia was performed 3 months after the index event, and, to allow testing, the DOAC was temporarily replaced by low-molecular-weight heparin (LMWH). The results of the tests were negative. During the visit at the anticoagulation clinic, the doctor informed M.R. that his risk of recurrent DVT will probably be ~10% after 1 year, and will only slightly decrease thereafter. M.R. was informed that, according to the clinical prediction rule HERDOO2 (hyperpigmentation, edema, redness, D-dimer, obesity, and older than age 65), a score that aims to define the long-term risk of recurrent venous thromboembolism (VTE), he should continue on anticoagulant treatment. M.R. was concerned about the long-term effects of anticoagulation and by the possible limitations to his working activities, but the doctor reassured him about the safety of anticoagulation with the DOAC.

## Case 2

A.G. is a 76-year-old woman with a diagnosis of hemodynamically stable pulmonary embolism (PE) and proximal DVT of the left lower limb. She was on treatment with warfarin for 6 months with no complications. Her time in the therapeutic range was 62%. She was also on antihypertensive drugs (loop diuretics, ace inhibitors), statins, and metformin for type 2 diabetes, and had moderate renal insufficiency (her most recent glomerular filtration rate estimated using the Cockroft-Gault formula was 40 mL/min). However, during hospitalization for PE, her glomerular filtration rate went temporarily down to 26 mL/min. Her venous thromboembolic event was classified as unprovoked in the absence of major predisposing risk factors. After 3 months from the index event, she underwent echocardiography that showed normal pulmonary artery pressures. She also recently underwent compression ultrasonography of the lower limbs, with evidence of residual vein obstruction in

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the popliteal vein and complete recanalization of the femoral veins. A.G. presents some signs of postthrombotic syndrome with edema and hyperpigmentation in the left leg, although these signs are also moderately present in the contralateral leg suggesting chronic bilateral venous insufficiency. A.G. was referred to the anticoagulation clinic to discuss the duration of anticoagulant treatment. At the clinic, A.G. was told that her HERDOO2 score was 3 because of the presence of edema, hyperpigmentation, and age >65 years. D-Dimer levels on anticoagulant treatment were below the proposed threshold. Because the result of the score suggests a high risk of recurrence, and because PE is a potentially life-threatening disease, the doctor at the anticoagulation clinic recommended continuation of anticoagulant treatment with warfarin, given the good quality of international normalized ratio (INR) control.

## Introduction

VTE affects ~500 000 individuals in the United States every year and is a leading cause of morbidity and mortality.[1] After a first episode of VTE, patients face a substantial risk of recurrence as well as long-term complications such as postthrombotic syndrome and chronic thromboembolic pulmonary hypertension. Overall, the incidence rate of recurrent VTE is ~5.0% patient-years, peaking during the first 6 months at 11.0% patient-years and then progressively decreasing, with a plateau at 2.2% patient-years between 4 and 10 years after the index event.[2] This rate almost doubles (9.6% patient-years) in patients with cancer,[3] whereas, in the absence of cancer, the risk of recurrence is lower if VTE is provoked by surgery and higher if VTE is unprovoked (ie, no major provoking factors identified).[4] Guidelines suggest that anticoagulation should be stopped after the initial 3 months of treatment of lower-risk patients (ie, patients with major, removable risk factors) and that indefinite treatment of higher-risk patients (including those with unprovoked VTE, who represent up to 47% of the whole population of VTE patients) should be considered.[2,4]

Therefore, based on current evidence and on available guidelines, the decision to continue anticoagulant treatment of M.R. and A.G., both having had unprovoked VTE, appears to be correct. This decision was also supported by the application of one of the validated clinical decisions rules, the HERDOO2, which identified both patients as having an increased risk of recurrence.[5] However, when deciding whether to continue anticoagulant therapy, the long-term risk of treatment-associated complications, as well as other factors, including patient preference and costs, should be considered. These factors are often difficult to quantify and this is why duration of anticoagulation in clinical practice remains heterogeneous and sometimes unpredictable, with high rates of discontinuation also in patients at high risk of recurrent VTE. In a large observational prospective study, the large majority of patients with unprovoked VTE continued anticoagulant treatment beyond 3 months (84%), but only 55% of patients remained on treatment at 1 year and 19% at 2 years.[6]

We will now review the breadth of complications related to long-term anticoagulation that clinicians need to consider when deciding treatment duration for the secondary prevention of VTE.

## Bleeding risk on extended oral anticoagulant treatment

Bleeding is the main complication of anticoagulant treatment and oral anticoagulants are among the drugs that are most frequently associated with hospital admission due to adverse drug reactions.[7] Correct knowledge of the burden of bleeding complications and on factors associated with the risk of bleeding is essential for all prescribing physicians.

### *Defining the severity of bleeding events*

Definitions of bleeding that occurs during anticoagulation have largely varied across studies in the past, thus making interstudy comparisons difficult. For this reason, a number of standardized definitions have been proposed for studies in acute coronary syndromes, atrial fibrillation (AF), and VTE. In the setting of VTE studies, the most widely used definition for major bleeding was proposed by the International Society on Thrombosis and Haemostasis (ISTH).[8] According to this definition, bleeding events are classified as major if they are fatal, are overt, and occur in a critical site (eg, intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intra-articular, or intramuscular with compartment syndrome), or if they cause a fall in hemoglobin level of 20 g/L or more or lead to transfusion of 2 or more units of blood.[8] Although the harmonization of the definition of major bleeding has represented an important step forward for clinical studies, work still needs to be done to standardize all of those events that do not fall in this category. Indeed, many bleeding episodes that are classified as nonmajor may have an important impact on patients and on subsequent therapeutic decisions. To distinguish such events from truly trivial bleeds, a new standardized definition has been recently proposed and includes any overt, actionable sign of bleeding not fitting the definition of major bleeding, but requiring medical intervention by a health care professional, or leading to hospitalization or increased level of care, or prompting evaluation.[9]

### *Major bleeding rates in clinical trials*

In the main clinical trials comparing extended duration of treatment with vitamin K antagonists (VKAs) with no extended treatment (or with an active comparator) for the secondary prevention of VTE, cumulative rates of major bleeding ranged from 0.4% to 3.0% after 1 year[10-15] (Table 1). In studies with the DOACs, major bleeding rates ranged between 0.1% and 0.9% after ~12 to 15 months of treatment[12,13,16,17] (Table 2). A caveat for the readers is that these rates do not reflect the overall cumulative risk of bleeding associated with anticoagulation, as patients at higher hemorrhagic risk may bleed early after starting treatment and were possibly excluded from these studies. It must also be noted that the duration of exposure to anticoagulant treatment prior to enrollment in the study differed across the trials and this may have affected the observed rates (Tables 1 and 2).

In principle, bleeding rates must be interpreted in the context of the clinical characteristics of the population studied and should not be extrapolated from randomized controlled trials to everyday clinical practice because high-risk patients may be excluded from the trials and because monitoring of anticoagulation and patient management are of better quality in clinical studies than in clinical practice. Therefore, data from noninterventional studies are necessary to complement this information.

### *Major bleeding rates in observational studies*

Long-term rates of major bleeding in observational studies appear to be highly variable, depending on the setting of the study and on the characteristics of the included population. Usually, patients on VKAs followed by anticoagulation clinics have better quality of control (ie, time in therapeutic range) and fewer adverse events than patients not followed by anticoagulation clinics.[18] In the Worcester Venous Thromboembolism study, the cumulative incidence rates of major

**Table 1. Major bleeding rates with extended treatment duration of at least 1 year in clinical trials with VKAs**

| Study | Reference | Duration of treatment, mo | Patients, n | Events, n | % |
|---|---|---|---|---|---|
| WODIT | 10 | 12 | 134 | 4 | 3.0* |
| WODIT PE | 11 | 12 | 165 | 3 | 1.8* |
| HOKUSAI VTE | 12 | 12 | 1659 | 6 | 0.4* |
| REMEDY | 13 | ≅15 | 1426 | 25 | 1.8† |
| PADIS | 14 | 18 | 184 | 4 | 2.2‡ |
| LAFIT | 15 | 24 | 79 | 3 | 3.8* |

*Observation started at 3 mo from the index event.
†Observation started after ~6 mo from the index event.
‡Observation started at 6 mo from the index event.

bleeding after VTE ranged between 6.5% and 9.4% after 1 month in patients with DVT or PE, respectively, between 10.3% and 11.6% at 1 year, and 12.4% and 15.6% at 3 years.[19] Thus, although the risk of bleeding complications was highest during the first weeks of anticoagulant treatment, event rates continued to increase over time. These rates were much lower in a recent prospective cohort study on 1593 VTE patients on VKA treatment regularly followed by anticoagulation clinics, with an annualized rate of 1.0%.[20]

Only a few noninterventional studies were published after the approval of the DOACs; they reported major bleeding rates after the first 3 months of treatment. In the XA Inhibition with Rivaroxaban for Long-Term and Initial Anticoagulation in Venous Thromboembolism (XALIA) study, the annual event rate for major bleeding in patients treated with rivaroxaban was 1.2%.[21] In the control arm of patients receiving standard anticoagulation with LMWH and/or VKAs, the annual event rate was 3.4%.[21] This difference in the rates of events was mainly explained by the different baseline characteristics of the 2 populations, with the latter group being older and more frequently affected by renal impairment, cancer, or PE at baseline than the former. In a large retrospective cohort study from the United States, of the 1764 patients who continued rivaroxaban for at least 12 months, the incidence of major bleeding at 1 year was 1.5%.[22] In the Dresden registry, the incidence of major bleeding in patients treated for VTE with the DOACs was 4.1% patient-years.[23]

## The clinical effects of bleeding events

### *Case-fatality rates associated with major bleeding events*

When assessing the risks and benefits of anticoagulant treatment on the extended secondary prevention of VTE, the estimated incidence of recurrence is conventionally balanced against the estimated incidence of major bleeding events. In patients for whom an extended duration of anticoagulation is suggested, such as those with unprovoked VTE, expected recurrence rates should exceed expected major bleeding rates. However, this comparison is of little value if the severity and potential consequences of clinical events are not taken into account. On the one hand, a recurrent DVT in a lower limb is probably associated with less severe consequences (and with less concerns) than recurrent PE. On the other hand, a drop in hemoglobin of 20 g/L due to a large subcutaneous hematoma is likely associated with less severe consequences (and certainly creates less concerns) than intracranial hemorrhage. Yet, both recurrent events are counted as recurrent VTE and both bleeding events are counted as major hemorrhages. To help better discriminate the severity of events, estimation of case-fatality rates associated with recurrent VTE or with major bleeding (defined as the proportion of patients who die as a consequence of these conditions) may provide strong, additional information. A pooled analysis of randomized controlled trials and prospective cohort studies reported a case-fatality rate for major bleeding of 9.1% in patients taking warfarin for >3 months.[24] As expected, case-fatality with intracranial hemorrhage was almost fivefold higher than with major extracranial bleeds. Of interest, although major bleeding rates were higher during the first 3 months of therapy, case-fatality rates were similar during the acute and long-term phase. This was confirmed by the results of a large observational study that reported a case-fatality rate for major bleeding of 20% during the first 3 months and 18.2% thereafter.[25] These findings are relevant because the case-fatality rate for recurrent VTE after discontinuation of anticoagulant treatment was reported to be 3.6% in another systematic review of randomized clinical trials and prospective cohort studies.[26] Thus, although major bleeding during anticoagulant treatment is less common than recurrent VTE after treatment withdrawal, bleeding events cause at least a threefold higher risk of mortality, which needs to be carefully taken into account when deciding treatment duration.

Fewer data are available on case-fatality rates during extended anticoagulant treatment with DOACs. In the randomized controlled trials, 1 of 5 major bleeding events that occurred in patients treated with rivaroxaban 20 mg in the EINSTEIN CHOICE study was fatal, whereas no fatal events were reported with the 10-mg dose of rivaroxaban in the same study, or with edoxaban or dabigatran.[12,13,16] In the Dresden registry, the case-fatality rate for major bleeding was 6.3% in the whole cohort of patients with AF and DVT.[23] In the XALIA study, none of the bleeding events on rivaroxaban was fatal.[21]

**Table 2. Major bleeding rates with extended treatment duration of at least 1 year in clinical trials with DOACs**

| Study | Ref | Drug | Duration of treatment, mo | Patients, n | Events, n | % |
|---|---|---|---|---|---|---|
| EINSTEIN CHOICE | 16 | Rivaroxaban | | | | |
| | | 10 mg daily | 12 | 1107 | 6 | 0.5* |
| | | 20 mg daily | 12 | 1127 | 5 | 0.4* |
| AMPLIFY EXTENSION | 17 | Apixaban | | | | |
| | | 2.5 mg twice daily | 12 | 840 | 2 | 0.2* |
| | | 5.0 mg twice daily | 12 | 813 | 1 | 0.1* |
| HOKUSAI VTE | 12 | Edoxaban | 12 | 1661 | 5 | 0.3† |
| REMEDY | 13 | Dabigatran | ≅15 | 1430 | 13 | 0.9‡ |

Ref, reference.
*Observation started after 6 to 12 months from the index event.
†Observation started at 3 months from the index event.
‡Observation started after ~6 months from the index event.

Although the DOACs appear to cause fewer life-threatening events than VKAs, more information from noninterventional studies in high-risk populations is needed.

### *The clinical impact of nonmajor bleeding events*

Although less important than major bleeding, clinically relevant nonmajor bleeding should not be neglected when deciding on anticoagulation because of its impact on therapeutic decision, costs, and patient quality of life. These events are at least twice as frequent as major bleeding events, raise concerns, and not uncommonly tend to recur after resumption of treatment. For example, women of childbearing potential requiring oral anticoagulant treatment may experience abnormal uterine bleeding that leads to anemia and often requires iron supplementation. The impact on women's quality of life and loss of working hours is not negligible. Of note, this risk appears to be higher in patients treated with DOACs than in patients treated with warfarin.[27] Higher rates of gastrointestinal bleeding with the DOACs were reported in studies in AF patients, but not in the pivotal trials on VTE patients.[18] However, this difference may be explained by the higher mean age and by the higher prevalence of comorbidities in AF patients; similar trends toward increased mucosal bleeding from the gastrointestinal tract, or the genitourinary tract, in elderly or sicker VTE patients cannot be excluded. This is also suggested by the results of recent trials carried out in patients with cancer-associated VTE, where increased rates of gastrointestinal bleeding with the DOACs were observed.[28,29]

## Predictors of bleeding and factors to consider when bleeding occurs

History of bleeding is the most important factor associated with major bleeding events in patients on anticoagulant therapy. Other major risk factors include advanced age, renal insufficiency, liver disease, cancer, thrombocytopenia, and the concomitant use of antiplatelet drugs.[4,18] Excessive anticoagulation due to poor INR control or to inappropriately high doses of DOACs is also associated with an increased incidence of bleeding complications.[18,30] Finally, history of frequent falls or alcohol abuse should also be considered. Kearon et al have estimated that the presence of 1 risk factor for bleeding is associated with an annual incidence of major bleeding of 1.6%, and that 2 or more risk factors increase this risk to an annual incidence of 6.5%.[4] In a large Swedish cohort of patients with VTE treated with warfarin, the rate of major bleeding increased from 1.25 per 100 treatment-years in patients under 60 years to 4.33 per 100 treatment-years in patients over 80 years of age.[31] Factors independently associated with bleeding complications were increasing age, history of major bleeding, comorbidities such as cardiac failure, chronic pulmonary disease, anemia, or hypertension, and alcohol abuse.

It is important to remember that when bleeding occurs, in particular from the gastrointestinal or the urinary tract, the presence of underlying occult lesions should always be considered. Studies have reported that ~10% of bleeds in patients on warfarin are associated with previously unsuspected lesions.[18]

## Can we predict bleeding events? Performance of bleeding risk scores

A number of bleeding risk scores have been proposed for patients on VKAs, but only a few were assessed in patients with VTE and none is sufficiently validated.[4,32-34] Furthermore, 2 of these scores were derived in patients with acute VTE, whereas their true goal should be to support the decision on the optimal duration of anticoagulant treatment after the first 3 months of treatment.[32,33] We carried out an external validation of all of these scores in a retrospective cohort of 681 patients on secondary prevention of VTE with VKAs.[35] The incidence of events in this cohort was 2.60% patient-years for major bleeding and 7.39% patient-years for clinically relevant nonmajor bleeding. None of the scores predicted major bleeding better than chance, and only the score proposed by Kearon et al[4] showed a modest predictive value after the initial 3 months of treatment, with an area under the curve of 0.61.[35]

More recently, a new predictive score was derived in both patients on VKAs and DOACs, the VTE BLEED score.[36,37] With the use of this score, high-risk patients had a threefold to sixfold increased risk of major bleeding. However, the VTE BLEED score was only validated in patients enrolled in randomized clinical trials, and its performance in "real-world" patients is currently under way. Table 3 summarizes the characteristics of all bleeding risk scores available for VTE patients.

## Nonhemorrhagic adverse events associated with oral anticoagulants

Nonhemorrhagic adverse events on VKAs are uncommon and are usually observed during the initiation phase of therapy. These include skin necrosis, limb gangrene, and purple toe syndrome.[18] Adverse events that have been reported to be associated with the long-term administration of VKAs include vascular calcification, anticoagulation-related nephropathy, and osteoporosis. However, the true clinical relevance of these events has never been proven. Vascular calcification is supposed to be caused by the preventive effect of VKAs on the activation of Gla proteins and growth arrest–specific gene 6.[38] It has been hypothesized that such an effect may be clinically relevant in patients on chronic hemodialysis who suffer from extensive vascular calcifications, which could be worsened by the use of VKAs.[39] Ongoing studies are comparing the effects of warfarin and DOACs on the progression of arterial calcification in this population.[39] Anticoagulation-related nephropathy is an acute kidney injury possibly related to thrombin depletion or reductions in activated protein C in patients with high INR values, but recent evidence suggests that it may also occur with DOAC treatment.[40] Biopsy findings suggest that acute kidney injury may result from severe glomerular hemorrhage, with subsequent renal tubular obstruction from red blood cell casts and consequent acute tubular necrosis.[41] Unfortunately, information on the true incidence of anticoagulation-related nephropathy is scant and only based on the results of retrospective studies in which the role of other confounding factors cannot be reliably excluded. Furthermore, very few cases have been confirmed by biopsy. Finally, VKAs may have an impact on bone metabolism by inhibiting the carboxylation of osteocalcin, but there is conflicting evidence on the risk of osteoporosis and bone fractures in long-term warfarin users[42,43] and no specific measures are currently recommended.

Less information is currently available on the occurrence of other nonhemorrhagic adverse events associated with DOACs. Dyspepsia is consistently reported by patients treated with dabigatran, although the rates reported in clinical trials on VTE treatment were lower than in trials on stroke prevention in AF patients.[18]

In women of childbearing potential, adequate contraceptive strategies are warranted as both VKAs and DOACs cross the placenta. In the first trimester of pregnancy (in particular between the sixth and 12th week of gestation), VKA-related embryopathy is caused by the induction of vitamin K deficiency in the fetus and results in nasal

**Table 3. Bleeding prediction scores for patients with VTE**

| Ref | Variables | Attributed points | Risk categories |
|---|---|---|---|
| 34 | **mOBRI score** | | |
| | Age ≥65 y | 1 | Low: 0 point |
| | History stroke | 1 | |
| | History GI bleeding | 1 | |
| | Recent MI | 1 | |
| | Renal insufficiency | 1 | |
| | Diabetes | 1 | |
| | Anemia | 1 | |
| 32 | **Kuijer score** | | |
| | Age ≥60 y | 1.6 | Low: 0 point |
| | Female sex | 1.3 | Moderate: >0 and <3 |
| | Malignancy | 2.2 | High: ≥3 |
| 33 | **RIETE score** | | |
| | Age >75 y | 1 | Low: 0 point |
| | Recent bleeding | 2 | Moderate: 1-4 points |
| | Cancer | 1 | High: >4 points |
| | Creatinine >1.2 mg/dL | 1.5 | |
| | Anemia | 1.5 | |
| | PE at baseline | 1 | |
| 4 | **ACCP score** | | |
| | Age >65 y | 1 | Low: 0 point |
| | Age >75 y | 1 | Moderate: 1 point |
| | Previous bleeding | 1 | High: ≥2 points |
| | Cancer | 1 | |
| | Metastatic cancer | 1 | |
| | Renal failure | 1 | |
| | Liver failure | 1 | |
| | Thrombocytopenia | 1 | |
| | Previous stroke | 1 | |
| | Diabetes | 1 | |
| | Anemia | 1 | |
| | Antiplatelets | 1 | |
| | Poor anticoagulation | 1 | |
| | Comorbidity/reduced functional capacity | 1 | |
| | Recent surgery | 1 | |
| | Frequent falls | 1 | |
| | Alcohol abuse | 1 | |
| 36 | **VTE-Bleed score** | | |
| | Cancer | 2 | Low: <2 point |
| | Uncontrolled hypertension in men | 1 | High: ≥2 |
| | Anemia | 1.5 | |
| | History of bleeding | 1.5 | |
| | Age ≥60 y | 1.5 | |
| | Renal dysfunction | 1.5 | |

ACCP, American College of Chest Physicians; GI, gastrointestinal; MI, myocardial infarction; mOBRI, Modified Outpatient Bleeding Risk Index; Ref, reference; RIETE, Registro Informatizado Enfermedad Trombo Embólica.

hypoplasia and stippled epiphyses.[18] In the second and third trimesters, the use of VKAs is associated with not only an increased risk of bleeding for the fetus, but also of minor neurologic dysfunction.[18] The adverse effects of the DOACs on fetal development remain unknown.

## Other factors to consider when extending oral anticoagulation

Patients receiving extended-duration anticoagulant therapy are not only exposed to an increased risk of "spontaneous" bleeding, but also to several intercurrent situations that may be complicated by bleeding. For example, traumatic brain injury is a major health problem and one of the leading causes of visits to emergency departments.[44] Traumatic brain injury may occur not only in elderly subjects as a consequence of falls, but also in younger individuals, for example, after road accidents or during physical activities. Most commonly, patients present with mild or minor injuries and a Glasgow Coma Scale of 13 or more. Although most injuries have a favorable clinical course, intracerebral bleeding is a feared complication and this risk is expected to increase in patients receiving anticoagulant therapies. In a study on patients older than 65 years of age hospitalized after a fall, 8% of those on anticoagulant treatment had intracranial hemorrhage as compared with 5.3% in non-anticoagulated patients, and the case-fatality rate of posttraumatic intracranial bleeding was 21.9%.[45] Posttraumatic hemorrhages may occur in other critical sites with potentially serious consequences. Due to the increased risk conferred by the use of anticoagulant drugs, patients may require restrictions or changes in their working activities in particular for some jobs (or sports) at higher risk for trauma.

It has been estimated that ~10% of patients treated with anticoagulants undergo surgical or invasive procedures each year, which means ~250 000 patients/year in the United States.[46] Patients on anticoagulant treatment are exposed to an increased risk of bleeding during these procedures, in particular when performed in urgent conditions.[46] Also hospitalization per se represent a risk factor for bleeding complications in anticoagulated patients. A recent study has reported hospital admission or discharge and surgery as the most important causes of bleeding complications due to medication errors in patients on anticoagulant therapy, both with VKAs and DOACs.[47]

## The economic burden of extended anticoagulation

The decision to extend or to stop anticoagulant treatment in a patient with previous VTE will also have an economic impact. On the one hand, the costs of the drugs can be highly relevant in particular in young patients with an expected treatment duration of several years. On the other hand, health outcomes associated with the management of recurrent VTE or bleeding complications need to be taken into account. VKAs are relatively inexpensive drugs, and the cost of treatment is mainly related to the cost of INR monitoring, which greatly varies across countries. The cost of INR monitoring includes laboratory testing, nurse or doctor visits, and loss of working hours for the patients. The use of DOACs has substantially reduced the number of visits required for the patients, but the cost of the drugs is higher than the cost of VKAs and ranges between 300 and 600 US dollars per month.[48] The costs associated with recurrent VTE or with the occurrence of major bleeding have been estimated to range from 11 000 to 15 000 US dollars and from 11 000 to 22 000 US dollars, respectively.[49] The results of economic analyses suggest that DOAC use is cost-saving compared with warfarin, but these results may not apply to all countries.[50] Furthermore, DOACs may not be accessible to all patients based on insurance coverage or national health plans.

## What about M.R. and A.G.?

Both M.R. and A.G. initially continued on oral anticoagulant treatment. For safety reasons and to his great regret, M.R. could no longer work as a tree climber and was moved to an in-office activity. After few months, though, he suffered intra-articular bleeding after a skiing accident. After few additional months, he finally decided to stop anticoagulation and to return to his previous activities. He was instructed to immediately refer to the anticoagulation clinic in case of occurrence of signs or symptoms suggesting the recurrence of DVT.

A.G. was concerned about new episodes of accidental falls and sought a second opinion. She was initially convinced to continue on VKAs, and was then switched to a DOAC in light of a possibly lower risk of bleeding and her stable renal function. Two years later, after a new fall with traumatic brain injury, she developed subdural hematoma. She recovered well, but anticoagulant treatment was finally stopped.

## Conclusions

The decision to continue anticoagulant treatment of the secondary prevention of VTE is based on several factors and must be tailored on the individual patient. The burden of VTE recurrence must be carefully balanced against the breadth of complications of anticoagulant treatment. Our task is to identify all relevant factors associated with recurrence, bleeding, and any other treatment-related effect as well as to consider all currently available therapeutic options, and to share our knowledge with the patient who needs to be deeply involved in the therapeutic decision. In particular, the patient must be informed about all risks associated with treatment and adequate follow-up strategies must be planned. The choice made after the initial course of anticoagulation needs to be reconsidered over time, as individual factors and preferences may change. Ideally, all patients should have a team of specialists (eg, anticoagulation clinic, thrombosis center) to whom they can refer for any need or advice. Among all variables, costs associated with long-term anticoagulation should always be taken into account.

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