Extended secondary prophylaxis after venous thrombosis

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Summary
The drug therapy of thromboembolic diseases is considered standardized and effective in most cases. Recurrence has been known for years after discontinuing anticoagulation, both after DVT, after PE and also after SVT. Only recently has this particular patient clientele, the specific medical history and the potential triggering risk factors been dealt with in more detail. It became necessary to formulate a more precise differentiation of the risk factors and to specify in terms of the way and duration of secondary pharmacological prophylaxis. In addition to VKA, new registrations of NOAKs are helpful for this indication. ASS has no significance in this regard. Against this background, a „traffic light system" was developed, which should help the treating physicians in the estimation of the individual recurrence risk.

Zusammenfassung
Die medikamentöse Therapie thromboembolischer Erkrankungen gilt als standardisiert und effektiv in den meisten Fällen. Dass nach dem Absetzen der Antikoagulation Rezidive auftreten, ist seit Jahren bekannt und zwar sowohl nach TVT, nach LE und auch nach OVT. Erst seit kurzem hat man sich mit diesem speziellen Patientenklientel, dessen Anamnese und den möglichen auslösenden Risikofaktoren detaillierter beschäftigt. Es wurde notwendig, eine exaktere Differenzierung der Risikofaktoren zu formulieren und in Bezug darauf, die Art und Weise und die Dauer der medikamentösen Sekundärprophylaxe zu spezifizieren. Hierbei sind neben VKA auch die Neuzulassungen von NOAK`s für diese Indikation hilfreich. ASS hat in dieser Beziehung keinen Stellenwert mehr. Vor diesem Hintergrund wurde ein „Ampel-System" entwickelt, welches den behandelnden Ärzten bei der Abschätzung des individuellen Rezidivrisikos hilfreich sein soll.

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Introduction

Anticoagulation has proved to be the most important therapeutic measure to reduce acute mortality and morbidity, relieve symptoms, avoid recurrences and – as far as possible – prevent the occurrence of complications such as post-thrombotic syndrome (PTS) or chronic thromboembolic pulmonary hypertension (CTPH), in venous thromboembolism (VTE) – a term encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE).

It is only in recent years that consideration of the thromboembolic spectrum, including superficial vein thrombosis (SVT), as one entity in terms of the therapeutic approach, has become generally accepted. However, new concepts have also emerged in relation to the genesis of a thromboembolism. The trigger factor for a VTE becomes the decisive criterion for the duration of anticoagulant therapy. Detailed history-taking by the clinician and inclusion of the patient in the decision-making process are becoming important criteria for the primary therapy and for the sometimes complicated secondary prophylaxis of VTE.

The definition and classification of risk factors underlying the thromboembolic recurrences, recently published in a consensus document, together with studies on the extended use of DOACs (direct oral anticoagulants), require a differentiated therapeutic strategy, especially when specifying the duration of treatment. For all therapeutic considerations, efficient prophylaxis against recurrence is paramount.

The following aspects are new in this regard:

- Shortly after discontinuation of oral anticoagulation, there is a roughly 3-fold increase in VTE recurrences. The risk of recurrence is particularly high after a VTE that occurred without an identifiable trigger, or when only soft, uncertain triggering risk factors were present and where risk factors are ongoing, such as in a malignant disease.
- A reduced dose of DOACs enables an effective, extended secondary prophylaxis with a low risk of bleeding at the same time.
- Aspirin no longer has any place in the secondary prophylaxis of VTE, because the risk of bleeding is not lower, but efficacy considerably worse.
- For most patients, risk stratification into 3 groups permits a clear decision to stop

or continue the OAC; the use of a reduced DOAC for extended anticoagulation can be considered, weighing the benefits against the risks.

Current state of anticoagulation therapy

Anticoagulation is divided into three phases: the initial treatment, maintenance therapy and extended secondary prophylaxis (1,2) (▶ Table 1).

Initial treatment

The aim of acute treatment is to minimise the risk of a PE and to stop the thrombus growing. Therapeutic anticoagulation should therefore be initiated as soon as diagnosis is confirmed.

Since the risk of recurrence is initially especially high both with classical treatment with heparin and vitamin K antagonists (VKA) as well as with non-VKA oral anticoagulants (NOACs), a more intensive anticoagulation – either through an increased dose of a NOAC for one to three weeks or through prior parenteral anticoagulant treatment for at least 5 days is required. Even under adequate anticoagulation, the risk of recurrence is increased in the first four weeks, so that care must be taken here that the anticoagulation is effective and continuous (3).

After initiation of treatment, a control investigation is recommended in the first 5 to 21 days of treatment. The time of switching from subcutaneous treatment to an oral anticoagulant, or a dose reduction in the case of apixaban or rivaroxaban, is particularly suitable for such a check. Ultrasonography is generally not necessary (1).

Maintenance therapy (3–6 months)

Maintenance therapy follows the initial anticoagulation, in order to consolidate the thrombus and prevent an early recurrence. It is generally continued for a period of 3–6 months and is usually given with VKA or NOACs.

Ultrasonography to investigate possible residual thrombi should be performed after 3–6 months and always at the end of anticoagulation (1), also to enable results to be compared in the case of a suspected recurrence.

Extended maintenance therapy (>6 months)

Efficacy (the prevention of a potentially fatal recurrence) and safety (especially the risk of bleeding) should be reviewed after 3–6 months. Principal criteria, in addition to patient preference, are unprovoked (without identifiable trigger) versus provoked event (with trigger, e.g. OP, immobilisation etc.), proximal DVT versus calf DVT (for the latter, 3 months anticoagulation suffice), thrombosis recurrence, severe thrombophilia (e.g. antithrombin deficiency, Lupus anticoagulant, homozygous factor V Leiden mutation, prothrombin mutations or combination thrombophilia). Together with the patient, these aspects must be weighed up against the risk of bleeding in order to reach a joint decision on the ending or continuation of anticoagulant therapy. In the case of long-term extension, the current therapeutic options are to be reviewed from time to time, as they may change.

For a long time, VKA was the sole standard medication for extended maintenance therapy >6 months and for life-long secondary prophylaxis. Of the DOACs, rivaroxaban, apixaban and dabigatran have been investigated with regard to extended secondary prophylaxis. Recurrences could be reduced by 70–90% without increasing major bleeds. However the number of clinically relevant non-major bleeds increased with rivaroxaban and dabigatran. Aspirin has also been tested in this regard in comparison with placebo (5); the effectiveness in terms of reduction in recurrences was lower and the rate of bleeds was comparable with placebo (see below).

EINSTEIN CHOICE: Reduced dose of rivaroxaban in extended secondary prophylaxis

Based on this – admittedly moderate, but significant efficacy of aspirin, with no increase in the risk of bleeding, in the EINSTEIN-CHOICE study (10) aspirin was chosen as the comparator arm – in contrast to placebo in the AMPLIFY-EXTENSION study (4). The prophylactic dose of rivaroxaban (1 x 10 mg) was used alongside the therapeutic dose (1 x 20 mg). VTE patients who had completed 6 to 12 months of treatment with an oral anticoagulant and who showed no indication for therapeutic anticoagulation were enrolled. Exclusion criteria included the need for extended anticoagulation at a therapeutic dosage or a platelet aggregation inhibitor, contraindications for extended anticoagulation, creatinine clearance < 30 ml/min.

In contrast to the AMPLIFY-EXTENSION and the long-term studies on aspirin, a higher percentage (57–60%) of patients with a previous provoked event were enrolled. Few patients had an active malignant disease also in this study (▶ Table 2).

It is important that only patients for whom extended therapeutic anticoagulation after VTE > 6–12 months was not regarded as necessary, were enrolled in the study. Both rivaroxaban arms (10 mg/20 mg) showed superiority over aspirin 100 in relation to recurrence prophylaxis. Therefore, according to EINSTEIN-CHOICE aspirin, with the same rate of bleeding but lower efficacy, has no place in extended prophylaxis against recurrence.

AMPLIFY extension: reduced dose of apixaban in extended secondary prophylaxis

This study enrolled patients who had completed 6 to 12 months anticoagulation

Tab. 1 Three phases of anticoagulation

Initial	Maintenance therapy	Extended secondary prophylaxis
0 – 10 days	Up to ~ 3 – 6 months	~ 3 – 6 months to unlimited

treatment and in whom it was unclear whether the anticoagulation should be ended or continued. The patients were randomly assigned to placebo, 2 x 5 mg apixaban daily or 2 x 2.5 mg, the high-risk prophylactic dose. The extended therapy lasted 12 months (4).

Symptomatic recurrent VTE or fatal VTE occurred in 8.8% of placebo patients compared with 1.7% under 2 x 2.5 mg apixaban and 1.7% under 2 x 5 mg apixaban (P<0.001 for both comparisons). The rates of major bleeds were 0.5% under placebo, 0.2% with 2 x 2.5 mg apixaban and 0.1% under 2 x 5 mg apixaban. The results are summarised in ▶ Table 2.

Apixaban also led to a marked reduction in recurrences. In addition, the prophylactic dose showed an effect as adequate as the treatment dose without significantly increasing the rate of bleeding. Apixaban in the prophylactic dose is therefore an additional option for secondary prophylaxis.

Aspirin for extended secondary prophylaxis

WARFASA (6) and ASPIRE (7) were double-blind, randomised, placebo-controlled studies in patients after a first-ever, unprovoked VTE and 6–12 months of VKA treatment. Patients were randomised to either 100 mg aspirin or placebo and treated for up to 4 years (7). The recurrence rate in the ASPIRE study was 4.8%/year under aspirin compared with 6.5%/year under placebo (HR 0.74 (0.52–1.05)). The incidence rates for severe or clinically relevant non-major bleeds did not differ (▶ Table 2.).

In both studies (7), although a reduction in VTE recurrence of 32% was demonstrated, this reduction rate did not reach the 70–90% as described under DOAC or VKA. In addition, studies on atrial fibrillation have allowed a similar rate of bleeding with aspirin as the DOACs. Aspirin is therefore only suitable for secondary prophylaxis in a group of patients with a very low risk of recurrence or particular cardiovascular risks.

Risk factors (RF) for VTE recurrence

The differentiated classification of a provoked and unprovoked VTE (Scientific and Standardization Committee ISTH) (8) (p.[9]) and the strong and weak risk factors on which the recurrence prognosis and option of a full therapeutic or reduced extended secondary prophylaxis depend, are new (▶ Table 3).

Tab. 2 AMPLIFY-Extension, ASPIRE and EINSTEIN-CHOICE

	AMPLIFY EXTENSION			ASPIRE		EINSTEIN CHOICE		
	2.5 mg Apixaban	5 mg Apixaban	Placebo	Placebo	Aspirin 100	Aspirin 100	Rivaroxaban 20 mg	Rivaroxaban 10 mg
n	840	813	829	411	411	1131	1107	1127
Duration	Active study period: one year			37.2 months		Median 350 days	Median 349 days	Median 353 days
Unprovoked index VTE (%)	93.2	90.7	91.1	100	100	41.4	39.8	42.6
Provoked index-VTE (%)	6.7	9.3	8.7			58.6	60.2	57.4
Recurrence VTE and fatal VTE (%)	1.7	1.7	8.8	1st year: 10.6 6.5/yr	1st year: 4.9 4.8/yr	4.4	1.5	1.2
Major bleed	0.2	0.1	0.5	0.3/yr	0.3/yr	0.3	0.5	0.4
Clinically relevant major bleed	3.2	4.3	2.7	0.6/yr	1.1/yr	2.0	3.3	2.4
Malignant disease (%)	1.8	1.1	2.2			3.3	2.3	2.4
VTE, fatal VTE, AMI, stroke, fatal CV, major bleed	2.4	2.5	10.4	9.0	6.0	5.6	2.0	1.9

Tab. 3 Classification of risk factors for the occurrence of VTE: Provoked VTE, especially with strong transient risk factors have a low risk of recurrence after discontinuation of OAK; unprovoked VTE or VTE with persistent risk factors such as cancer have a high risk of recurrence (according to (12)). The term "idiopathic" is now preferred to "unprovoked".

I. Provoked VTE with transient trigger factor	**II. Unprovoked VTE** (no trigger factor)	**Provoked VTE** with persistent trigger factor
Examples of strong triggers: OP > 30 min; bed-ridden inpatient treatment, Caesarean section. Somewhat weaker triggers are, for example, short OP; < 3 days of inpatient treatment; oestrogen, pregnancy, post-partum, leg injury with reduced mobility >3 days	**No transient or persistent risk factors**	**Active cancer** Continuing, non-malignant disease, e.g. chronic inflammatory bowel diseases

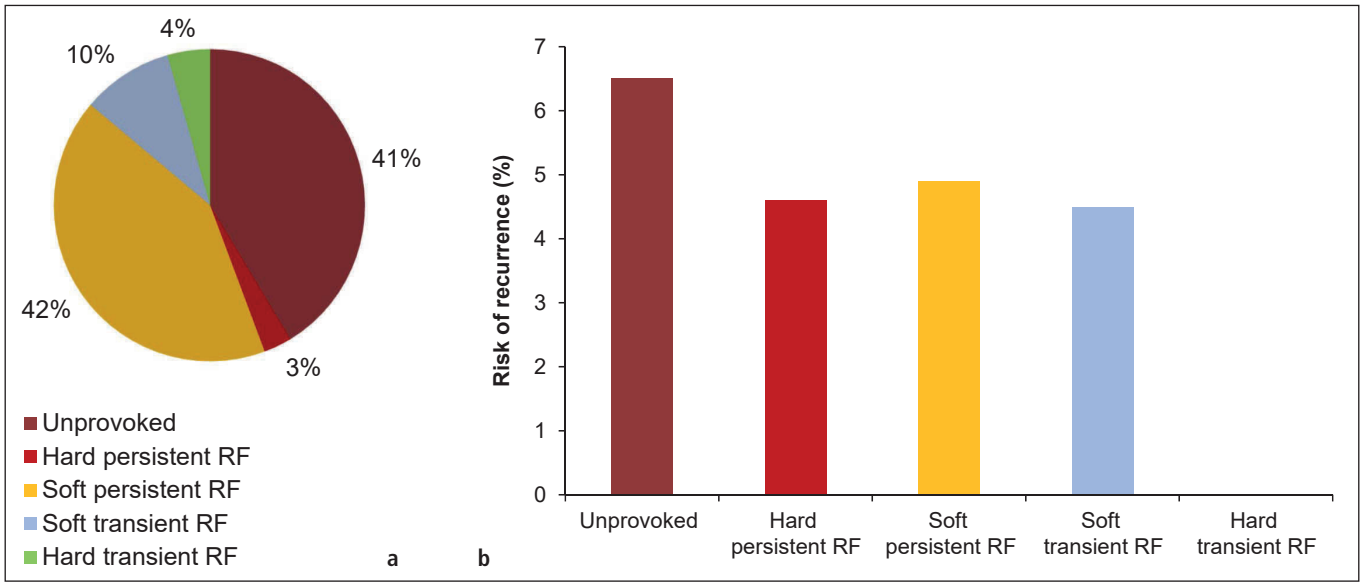

Fig. 1 a) Percentage distribution of underlying risk factors in the EINSTEIN Extension study and in EINSTEIN-CHOICE. Modified from Prins et al., Thromb Haemost 2017; 1:187 (23). b) VTE recurrence rates depending on the underlying risk factors (RF) under placebo or aspirin 100 from EINSTEIN Extension and EINSTEIN-CHOICE. Modified from Prins et al., Thromb Haemost 2017; 1:187 (23).

Tab. 4 12 criteria as decision aids for the duration of anticoagulation

	Shorter	Longer
Risk factor	transient	ongoing
Genesis	trigger	unclear
Recurrence	no	recurrence
Sex	female	male
Thrombosis	distal	proximal
Thrombus extent	short	extensive/PE
Residual thrombus	no residual thrombus	+
D-dimers (after end of treatment)	normal	increased
Severe thrombophilia	no thrombophilia	+
Patient preference	against it	for it
Quality of OAC	poor	good
Risk of bleeding	high	low

According to these criteria, the risk of recurrence after strong and weak RF could be measured in the EINSTEIN-CHOICE (10) and EINSTEIN-EXTENSION studies.

▶ Figure 1a shows the distribution of the underlying RF, ▶ Figure 1b summarises the recurrence rates under aspirin or placebo.

Patients with an unprovoked VTE continue to have the highest risk of a recurrence. But patients with weak persistent or weak transient RF also suffer recurrences, which must lead to a reconsideration of the therapeutic consequences. As hardly any patients with hard RF (cancer) were enrolled, evaluations for these patients are therefore not necessarily relevant.

Duration of anticoagulation

Setting the duration of anticoagulation and of an extended secondary prophylaxis is becoming increasingly complex. The risk of recurrence is highest in the acute phase of VTE. The scheme for initial treatment – applicable to all anticoagulants – covers this period. The risk of recurrence of an unprovoked VTE is highest at 10% in the first 2 years and is then 30–40% for at least another 8 years (1). The treatment scheme given in the guidelines (1,2) covers this problem, taking efficacy and safety into account. The German guidelines expressly point out the need to adjust treatment on an individual basis, with consideration of patient preference (1). Aids to decision-making are provided, amongst other things, by 12 criteria (▶ Table 4).

As this deliberately intended flexibility and individualisation can, however, mean some degree of uncertainty for clinicians (and patients), an attempt is made below to give a pragmatic decision-making aid for the most common cases encountered in everyday practice, based on current study results and a recent statement of the ISTH-Standardisation Committee (14).

Tab. 5 Traffic light principle to assess the risk of recurrences: High risk of recurrence (red light): Anticoagulation should not be ended provided there are no contraindications. Low risk of recurrence (green light): Anticoagulation can be ended after 3–6 months (with calf vein thrombosis after 3 months). Intermediate risk (amber light): in these, roughly 20% of patients, additional aspects and findings need to be considered; if there is uncertainty regarding the further procedure, refer to a specialist. [1]Severe thrombophilia: e.g. AT deficiency, APS, homozygous disorders. Modified from Bauersachs et al., Dtsch Med Wochenschr 2018; 143: 1–6 (13)

Red light	Long-term anticoagulation, if no contraindication	Active cancer, persistent risk factor Severe thrombophilia[1]
Amber light	Extended secondary prophylaxis? => if necessary clarify with specialist	Recurrent VTE Unprovoked event Soft, uncertain and transient risk factor, e.g. travel
Green light	End (3–6 months) (3 months)	Clear, hard risk factor (e.g. OP, leg injury with reduced mobility, confined to bed) contraceptive pill or hormone therapy (now ended) pregnancy, post-partum Calf DVT

The traffic light decision-making aid for the duration of anticoagulation

The aim of the "traffic light principle" (13) and its interpretation is to classify patients into a group with a very high risk of recurrence in whom the anticoagulation should not be ended (red light) and those in whom the risk of recurrence is estimated as low and therefore the anticoagulation can be discontinued after 3–6 months (green light) (▶ Table 5).

These two groups cover about ¾ of cases encountered in practice; in the other patients, the decision concerning continuation of anticoagulation is to be made according to additional individual factors, in particular by also taking patient preference into account (amber light). If applicable, it is worthwhile referring these patients to a specialist regarding the question of extended anticoagulation.

The aim of the "traffic lights" is to facilitate the therapeutic decision of the treating physician. Above all, the option remains to include the patient in the decision about the duration of anticoagulation, which can be necessary for a shorter or longer period or even for life. One of the potentials of the "traffic lights" is, in difficult cases, to optimise the cooperation between the family doctor as attendant physician and the specialist as decision-maker.

Conclusion

In summary, clear treatment schemes for the therapy of thromboembolism have been established which grant patients a high degree of certainty with regard to their treatment; on the other hand, there are calls for even more individualised therapy, which would place high demands on the clinician, but which would also guarantee tailored treatment for patients at risk. Once again, patient history is central to successful therapy.

Conflict of interests

The authors state that there is no conflict of interests.

Ethical guidelines

Preparation of the manuscript did not involve any studies on humans or animals.

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