Diagnosis of recurrent deep vein thrombosis

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Summary
Deep vein thrombosis is a chronic disease with a continuing risk of recurrence. In a patient with recurrence long term prognosis and treatment are significantly altered both carrying their own risks not only in the acute phase but mainly in the long term perspective. Thus, accurate diagnosis of recurrence is of utmost importance for the fate of the patient. Diagnosis of a first DVT episode is well established and follows an algorithm including clinical prediction rules, D-Dimer testing and compression ultrasound. Due to the previous episode the efficiency of all three elements is impaired in a patient with suspected recurrence. This opens up areas of uncertainty which have to be filled by individual clinical judgement. Guidelines reflect this difficulty by providing mainly weak recommendations based on sparse data. The present review summarizes what is known about the performance of tools for DVT diagnosis, discusses recent guidelines, and finally gives personally weighed recommendations how to deal with this peculiar diagnostic situation. In conclusion, it will turn out that the well accepted diagnostic algorithm for a first DVT may be applied as well if the lower efficiency is regarded. Compression ultrasound largely benefits from a baseline assessment at the end of the previous episode. The order of tests may be discussed according to local and regional attitudes.

Schlüsselwörter
DVT-Diagnose, Rezidiv, klinische Vorentscheidung, D-Dimer-Test, Kompressionssonographie

Zusammenfassung

In many patients, venous thromboembolism (VTE) is rather a chronic relapsing disease than a once in life event (1). The frequency of recurrence depends on risk factors (2). In case of a transient surgical risk factor rates of recurrence are as low as 0% to 1% per year. With transient “soft” risk factors (e. g. immobilisation due to medical illness, hormonal contraceptive use, travellers thrombosis) the rates are 5% per year. Without any known risk factor (idiopathic or unprovoked VTE) the rate is 10% per year. With a known but permanent risk factor like cancer it may be even higher. Annual rates of recurrence decline over time but never become zero (3). A patient, who suffers from recurrence, in particular if the index event and the recurrence are unprovoked, has a high risk for even more episodes with their own morbidity and mortality. Therefore, indefinite duration anticoagulation will be indicated in most cases.

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On the other hand, post-thrombotic clinical signs and symptoms after a first episode of deep vein thrombosis (DVT) may mimic recurrence. Due to relapsing worsening of symptoms, the postthrombotic syndrome may have the same appearance as an acute episode but does not confer the same future risk. However, prescribing indefinite duration anticoagulation to a patient without proven risk of recurrence exposes him or her to an inappropriate risk of bleeding which may become disabling or even fatal. Therefore, accurate diagnosis of recurrence is at least as important for the fate of the patient as is the correct identification of a first episode.

In the past 20 years, diagnostic strategies have been developed to steer the diagnostic process in case of a suspected first episode of DVT. Supported by results of numerous prospective management studies we now have an efficient and safe diagnostic algorithm consisting of a small set of diagnostic tools, namely, clinical prediction rule (CPR), D-Dimer-test, and venous compression ultrasound. However, in case of suspected recurrent DVT, the functions of all three components of the algorithm are changed. Due to the impact of the previous episode their efficiency is impaired leading to a worsened functionality within the algorithm. The deviations from the situation in a first episode have been anticipated to have an extent which rendered it impossible to formally test this algorithm – or a modified one – in suspected recurrent disease. An additional obstacle to generate solid and reliable data for this particular diagnostic setting is the fact that there is no gold standard defining the diagnosis of recurrent DVT clear enough to use it as comparator in clinical studies.

In the following, based on the diagnostic algorithm for a first episode of DVT, the main diagnostic tools will be discussed. After that, two sets of recommendations by globally accepted scientific bodies will be presented: Finally, some clinical recommendations will be given with special regard to the readers of this journal, i.e. physicians in Germany, Austria and Switzerland.

### Clinical prediction rules

There are different clinical prediction rules for DVT (4). None of them has been specifically developed or investigated for patients with suspected recurrent DVT. *Sensus strictu*, they may not be used in the diagnostic process in those patients for this reason. The most widely used CPRs for DVT are the original (5) and the simplified Wells score (6). At least the simplified score includes the item of “previously documented episode of deep vein thrombosis” accounting for one out of nine positive scoring points. This means that patients with a previous DVT have been part of the derivation cohort for the simplified Wells score, and that the performance of the score has been evaluated in cohorts including those patients. Obviously, patients with a previous episode in general will score higher than patients without but when using the dichotomised version (< 2 versus ≥ 2) at least some patients will fall into the low probability group. The score in itself is not applicable but its efficiency will decrease.

### D-dimer tests

D-dimer testing has been extensively studied as a very efficient step in the diagnostic algorithm for patients with a suspected first episode of DVT or PE. Due to its high sensitivity the negative predictive value of a D-dimer test allows for safe exclusion of the disease in negative patients who already had shown a low probability in the clinical prediction rule (7). There is no pathophysiologic reason to believe that sensitivity is lower in patients with a suspected recurrence. However, specificity may be lower, leading to a lower efficiency in these patients. Whereas D-dimer is decreasing to normal levels during a standard treatment period of an acute DVT episode (8) it has been shown that after stopping anticoagulation a significant proportion of patients, in particular those with idiopathic episodes, will have rising D-dimer levels after four weeks or three and more months (9).

There are four prospective cohort management studies investigating D-dimer testing in patients with suspected DVT recurrence (10–13) and one additional study which included patients with a previous episode (6). Two studies used D-dimer as a stand-alone test for exclusion (10, 11), resulting in diagnostic failure rates of 5% and 2%, respectively. When combined with a low probability clinical prediction rule (12) or a negative compression ultrasound (13), failure rates were zero. However, the latter two studies comprised less than 100 patients. In the Wells study (6), combining a clinical prediction rule with D-dimer testing, there were 102 out of 1096 patients with a previous episode; however, the results, which were favourable with a failure rate at three months of 0.9% (95% CI 0.3–3.3%) for the entire cohort, were not reported separately. Even if the safety of the combined approach CPR followed by D-dimer was high, which very likely is the case, its efficiency will be considerably lower. In the Auguilar study, in only 15% of patients recurrent DVT could be excluded by CPR and D-dimer alone, whereas this rate is estimated to be around 40% in patients with a first episode.

D-dimer tests have significantly different accuracy profiles. Quantitative ELISA or latex tests combine a very high or high sensitivity with a low or moderate specificity. By contrast, semiquantitative latex tests or bedside qualitative tests have a lower sensitivity and higher specificity (7, 14). In general, a high sensitivity should be preferred if a dichotomised CPR is used as compared to a three level CPR. Accordingly, if D-dimer testing is combined with ultrasound a highly sensitive ultrasound protocol may be combined with a slightly lower sensitive D-dimer test than with a less sensitive protocol. Whether D-dimer thresholds can be age-adjusted, as currently being discussed for suspicion of a first episode (15) will need more data evaluating this concept in different diagnostic settings.

### Compression ultrasound

For more than 15 years, lower extremity venous compression ultrasound is now regarded as the main diagnostic test for excluding or confirming acute DVT. At least two meta-analyses of external validation studies against venography as gold standard (16, 17) have established that compression ultrasound is sensitive and spe-
Specific enough to be a valid substitute to venography in diagnosing proximal DVT. Lower figures for distal DVT have been reported albeit some authors argued this might be due to the ultrasound protocol rather than to the method itself. Subsequent prospective cohort studies have transferred these result into the diagnostic management perspective, two main regimens are now well accepted. The first performs ultrasound on proximal veins only filling the diagnostic gap for overlooked but clinically important distal DVT by serial testing (18). The second relies on a single complete compression ultrasound strategy (19) which is at least as safe as the first one (20,21). Even if established in patients with a first DVT episode there are many situations in which these results may apply to patients with suspected recurrence. Obviously, this is the case if the side of the previous episode is known, and the current suspicion refers to the contralateral side. It occurs in approximately one third of all patients (13).

However, if an ipsilateral recurrence is suspected compression ultrasound may be severely confounded due to residual thrombus in veins which have not been fully recanalised after the previous episode. Overall, significant reduction of thrombus mass of about 50–60% occurs already within the first three months of treatment (22). Depending on the risk factor profile complete normalisation after 12 months is accomplished in 30%, 50% or 100% of patients with cancer, outpatients without cancer, or patients with post-surgical DVT, respectively (23). Albeit being a risk factor for recurrence in itself (24), residual thrombosis jeopardizes the very principle of compression ultrasound by preventing venous segments from collapse. Even if experienced sonographers in most cases have a clear conception as to whether a clot is "old" or "fresh" there are no validated criteria to distinguish residual from acute thrombosis. Wall adherence, echogenicity, and relative size compared to the expected vessel lumen are being assessed. However, finally any attempt for external validation fails due to the fact that there is no accepted gold standard defining thrombus age.

A solution to this dilemma is offered by the comparison of the current venous finding under suspicion with a previous state showing residual thrombus only (baseline test). If the diameter is significantly increased, acute recurrence may be regarded as proven. In comparative studies to venography different thresholds for "increase in diameter" have been investigated: 1–2 mm (25), ≥ 2 mm (22), and > 4 mm (22, 26). Taken together, these studies provide sufficient evidence that the increase in diameter approach might work. When incorporated into prospective management studies either alone or in combination with additional tests the diagnostic safety was favourable (27, 28). A post hoc randomized comparison between patients with and without baseline assessment demonstrated a significant clinical yield if a baseline assessment is available (29). This result is of course not entirely due to the increase in diameter criterion but also to the fact that the baseline assessment documents venous segments not affected by the previous episode. If such a segment is occluded in a patient with suspected ipsilateral recurrence the diagnosis is firmly proven.

Some doubts have arisen regarding the reliability of the residual thrombus baseline assessment. In a study of patients with previous DVT and high likelihood for residual abnormalities two independent sonographers assessed thrombus diameter, echogenicity, and Doppler flow. Interobserver agreement was found to be poor to moderate (30). When investigated in a better defined group of patients and analysed with a statistical analysis better adapted to clinical judgment requirements interobserver reliability was high. Variability introduced by interobserver reliability was stated to be of minimal clinical relevance (31).

As for suspicion of a first episode of DVT serial ultrasound examinations have been investigated for recurrent DVT. This approach is based on the assumption that, if the current situation is an active thrombotic process, an increase of thrombus burden must be detectable within days; the ambiguous finding of residual thrombus at day one can be cleared by a repeat ultrasound. The concept has been tested with a single repeat after seven days (6), and with a double repeat after two and seven days (32, 33) or of seven and ten days (11). Diagnostic failure rates defined as confirmed symptomatic disease within three or six months ranged from 1% to 5%.

It may be asked whether distal veins should be included into the ultrasound examination for recurrent disease. The pros and cons arguments will follow exactly the same lines as they do for the diagnosis of a first symptomatic episode (34–36). In addition to the feasibility argument of avoiding repeat examinations it may be argued that the deep calf veins are cleared more rapidly and more completely than the femoro-popliteal segments, offering many additional segments in which new thrombus may be detected. Obviously, the baseline assessment is a prerequisite.

Despite the obstacles formed by the nature of the disease, and despite conflicting or weak evidence, compression ultrasound is the central element in the diagnostic process of recurrent DVT. It should be kept in mind that the confounding factor of residual vein thrombosis decreases over time as the remaining clot keeps shrinking. Natural history of the disease suggests that with an interval of two years the diagnostic uncertainty has been overcome in almost every patient.

Other tests

Until the mid 1990ies, venography has been the gold standard not only for a first episode but also for recurrence. There are distinct venographic features differentiating acute thrombosis from postthrombotic findings. However, no formal investigation has been performed to evaluate the efficiency of venography in providing a clear-cut answer to the diagnostic question of recurrent DVT. The rate of uninterpretable findings is high as has been recognised 30 years ago (37). Today, there is virtually no training for venography in radiology departments. Thus, the test can only be recommended if a person with a continuous active experience over decades will perform it. Even then, it is painful, and it exposes the patient to radiation and contrast media both having their own risks.

As a contemporary variant of the Fibrinogen uptake test, 99mTc recombinant tissue
plasminogen activator (rtPA) scintigraphy has been developed. The radiotracer binds to C-terminal lysine residues on fibrin which are decreasingly exposed with increasing age of the clot. After 30 days no uptake was to be detected (38). Limited availability of the tracer and a potentially high interobserver variability may hamper the dissemination of the technique.

T1 weighted MRI images are able to reflect thrombus age due to the paramagnetic properties of methaemoglobin. Fresh thrombus with a high amount of methaemoglobin will give a high intensity signal whereas increasing transformation of the clot and scarring will decrease the intensity. Six months after the acute event no signal was to be detected in 39 patients with 14 of them still showing residual thrombus on compression ultrasound (39). No formal external evaluation of the method has been done so far.

Guidelines and recommendations

The most recent edition of the ACCP guidelines for the first time presents a separate chapter dedicated to the diagnosis of DVT (40). Chained by rigid methodological prompts like all other chapters, the result is a complex texture of if-then sentences definitely prohibiting implementation of the guideline into daily practice. However, thanks to the paucity of data, the few paragraphs on recurrent DVT provide at least some guidance. Due to methodological reasons, i.e. lack of formal validation in patients with suspected recurrence, the authors banned clinical decision rules. Instead, they placed D-Dimer-testing first line if no baseline ultrasound is available or compression ultrasound first line if baseline assessment is available. A negative single highly sensitive D-dimer test is deemed sufficient to rule out the diagnosis whereas a negative ultrasound (without examination of calf veins) needs confirmation by serial testing or D-dimer. A positive ultrasound allows for treatment. A non-diagnostic ultrasound needs repeat after one week or D-dimer. If negative, the diagnosis is refuted, if positive, a repeat ultrasound or venography is suggested. Definitions of positive or negative ultrasound depend on the result of prior testing (or contralateral leg involvement) whereas non-diagnostic ultrasound comprises equivocal changes in residual thrombus diameter or non-availability of baseline assessment.

It is astonishing that the ACCP 2012 guidelines, first, have strong confidence that a single D-dimer test, even if a highly sensitive one, is deemed able to rule out the diagnosis; and second, have the confidence that in cases where both ultrasound and D-dimer are inconclusive, venography will make it. Both measures, at the very beginning and the very end of the diagnostic process, are not supported by firm data – as is explained in the text. On the other hand, it is of great practical value that in these guidelines the sequence of ultrasound first followed by D-dimer if inconclusive is recommended here. It is the inverse order compared to the first episode test sequence but it is plausible and supports what many physicians are doing in daily practice.

Very recently, a new document has been released by a subcommittee of standardisation of the ISTH (41). It does not aim to install new evidence based guidelines but “outlines factors that may influence decision-making in the diagnostic process with reference to published evidence-based guidelines”. Significant differences to the ACCP guidelines can be noticed.

1. The usual order of tests: CPR, D-dimer, ultrasound is recommended even for suspicion of recurrence. The lower efficiency of both CRP and D-dimer is appreciated. However, the remaining fraction of cases which can be decided by these two tests is deemed to be worth it.

2. Venography is further downgraded. Like CT venography or MRI it should only be used in cases where no ultrasound is available or the results remain inconclusive even after repeat testing.

In full concordance with ACCP, compression ultrasound plays a pivotal role with its highest value if a baseline assessment is available. Thus, baseline assessment in every patient is suggested at the time of stopping standard duration anticoagulation. Surprisingly, whole leg ultrasound is suggested in patients with recurrent distal DVT, preferably if a baseline whole leg ultrasound has been performed.

In Germany, diagnostic algorithms putting CRP and D-dimer first line, are widely disregarded (42). The same seems to hold true for Austria and Switzerland as well as for parts of Italy and France. These countries have a strong affinity to the ultrasound first and only strategy. In the guess of the author this is unlikely to change within the next years. Thus, in order to be helpful for daily practice in these countries, recommendations should refer to this attitude. For the case of suspected recurrent DVT this means that ultrasound first leads into three different situations:

1. Ultrasound is unequivocally positive: This is the case if the usual ultrasound criteria for DVT are met in a leg contralateral to the previous event. This is also the case if a baseline assessment is available and the criteria for acute recurrence are met (new segment involved, increase in diameter of residual thrombus ≥ 4 mm). Depending of the experience of the sonographer, this may also be the case if the previous event occurred long time ago (e.g. two years and more), and the clot appearance is not compatible at all with that a long history. A positive CUS will establish the indication for treatment – possibly long term.

2. Ultrasound is unequivocally negative: This is the case if all venous segments are fully compressible (contralateral or ipsilateral to the previous episode). This is also the case if a baseline assessment is available and there is no change or improvement. A negative CUS will allow withholding anticoagulation and considering any other diagnosis than recurrent DVT.

3. Ultrasound is inconclusive: This is the case if an ipsilateral leg with no baseline assessment available any clot can be detected, regardless of intuitive age estimate. This is also the case if a baseline assessment is available and the increase of diameter is more than 1 but less than 4 mm. An inconclusive ultrasound should be followed by a highly sensitive D-dimer. If negative, the diagnosis can be refuted. If positive, a repeat ultrasound should be scheduled, preferably at day 2 and day 7. If no further increase
of thrombus diameter is noted without anticoagulation the diagnosis can be refuted. If there is an increase of ≥ 4 mm, the patient should be treated for recurrent DVT. The remaining grey zone has to be filled by individual judgement and cannot be covered by general recommendations.

For the countries mentioned there is, in the opinion of the author, no high priority need to implement the CRP / D-dimer first strategy for suspected recurrent DVT. It would be much more helpful to implement this strategy for suspicion of a first episode. This will only be accomplished with implementation of reimbursement for CRP / D-dimer at the general practitioner level.

Conflict of interest

The author declared that there is no conflict of interest.

References

23. Piovella F, Crippa L, Barone M et al. Normalization of D-dimer at the general practitioner level. This will only be accomplished with implementation of reimbursement for CPR / D-dimer at the general practitioner level.