Thrombosis Research 178 (2019) 59–62

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Measuring functional limitations after venous thromboembolism: A call to action

Frederikus A. Klok[a,b,*], Stefano Barco[b], Bob Siegerink[c]

[a] Department of Medicine – Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands
[b] Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[c] Center for Stroke Research Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany

ARTICLE INFO

Keywords:
Venous thromboembolism
Pulmonary embolism
Deep vein thrombosis
Classification
Postthrombotic syndrome
Activities of daily living, pulmonary hypertension
Mann Whitney *U* test
Value-based healthcare

ABSTRACT

The main objectives of therapeutic trials in venous thromboembolism (VTE) are to prevent recurrent VTE, major bleeding and death. While these outcomes are indeed highly relevant, they are also rare and do not fully capture the overall functional outcome of VTE patients. Importantly, functional limitations after VTE are prevalent after both deep vein thrombosis and pulmonary embolism occurring in up to 50% of patients. These post-VTE syndromes are associated with a decreased quality of life, higher risk of depressive disorders, unemployment and increased utilization of healthcare resources. Because of the major impact of functional limitations on individual patients and society as a whole, development of tools able to capture functional outcomes in clinical trials are urgently needed. We anticipate that a standardized post-VTE functional status scale will aid in demarcating effective and ineffective VTE therapies on functional outcomes in trials with appropriately powered sample sizes, as well as pave the road for value-based healthcare. The scale that we have in mind covers the entire spectrum of functional outcomes ranging from no symptoms to death. Moreover, it focuses on both limitations in usual activity as well as changes in lifestyle. The scale is not meant to replace current diagnostic or prognostic scores for post-VTE syndromes, but to be used as an outcome measure to evaluate the overall consequences of VTE on functional status. This review is a call for action to the VTE community to join forces and support further development of the proposed scale, a process of which we summarize the necessary steps.

1. Introduction

Where the post-thrombotic syndrome (PTS) has been long recognized as a relevant complication of deep vein thrombosis (DVT), the post-pulmonary embolism (post-PE) syndrome has been recognized as a potentially invalidating long-term consequence of acute PE only in recent years [1–8]. Both post-venous thromboembolism (VTE) syndromes have been reported to occur in up to 50% of patients despite adequate anticoagulation therapy, range from mild to severe symptoms, and involve a major impact on functional outcome, quality of life and health care costs [1–5,9–20]. Because of its relevance to the individual patient and society as a whole, prevention and treatment of post-VTE syndromes should be the object of focused interventional studies in VTE, whereas the occurrence of post-VTE syndromes can be included as an important outcome parameter in addition to ´standard´ ones, i.e. recurrent VTE, anticoagulant treatment-associated bleeding and death. Indeed, several recent trials have specifically focused on PTS prevention with varying degrees of success [21–24]. If chronic thromboembolic pulmonary hypertension (CTEPH) as rare and most extreme presentation is not taken into account, studies on the prevention or treatment of the post-PE syndrome are scarce [25–30]. One of the main reasons for this discrepancy is the relative unawareness of physicians and stakeholders for the post-PE syndrome, as well as the lack of a clear and widely accepted definition.

2. Measuring (the impact of) post-VTE syndromes

The essence of both PTS and post-PE syndrome is anxiety, pain, discomfort or exercise intolerance leading to functional limitations, decreased quality of life, and increased use of healthcare resources. Current diagnostic and prognostic tools for PTS are primarily oriented to measure or determine the presence of signs and symptoms of PTS rather than at establishing their impact on functional outcomes: therefore, they fall short to fully capture the heterogeneity of VTE consequences [31–33]. For post-PE syndrome, validated diagnostic tools are simply lacking. Quality of life questionnaires have been

* Corresponding author at: Department of Medicine – Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands.
E-mail address: f.a.klok@LUMC.nl (F.A. Klok).

https://doi.org/10.1016/j.thromres.2019.04.003
Received 26 February 2019; Received in revised form 2 April 2019; Accepted 4 April 2019
Available online 07 April 2019

developed for both DVT and PE, but while those were designed to provide an overall judgement on wellbeing, they do not target functional outcomes and were not designed to rank patients in meaningful categories [10,34–36]. The New York Heart Association (NYHA) functional classification measures the extent of heart failure and it is therefore not useful to study the impact of PTS. Moreover, functional limitations due to pain or anxiety can be hardly quantified. Finally, NYHA lacks a category for symptoms that exert an impact on patients´ life even in the absence of objective and measurable functional limitations. As such, there is great need of a new, robust and easy-to-assess objective measure of functional outcome that can be used to evaluate the impact of VTE in the setting of clinical trials as well as in clinical practice.

Such a measure should ideally: 1) target outcomes that are relevant for the individual patient surviving after an episode of acute VTE and its early complications (e.g. bleeding), i.e. capture the dimensions of daily living, 2) be designed as an ordinal, rather than binary, outcome to be able to assess the full range of limitations and thus better capture the heterogeneity of post VTE syndromes, 3) serve as a scale rather than a score to make sure there is only one way to be classified into a certain category (in contrast to a composite approach) making the interpretation of results unequivocal, 4) be equally meaningful for both PE and DVT patients, and 5) represent an easy and reproducible tool. Moreover, the measure should capture changes in or worsening of the functional state without overtly differentiating between the potential provoking causes, which may include post-VTE syndrome, physical deconditioning, anxiety or depressive disorder, or newly diagnosed concomitant diseases such as cancer. We postulate that the measure reflected by such scale should not be designed to screen for, diagnose, or grade the severity of post-VTE syndromes per se, nor to exclusively measure VTE-specific complications. The latter would rule out using the measure in patients with comorbidities as is often the case in non-selected VTE patients.

Major advantage of such a functional status scale would be the possibility to standardize evaluation of (new) treatment approaches by detecting more subtle, but clinically relevant, differences in patient-relevant outcomes. Moreover, it will likely reduce the number of patients needed in outcome studies, as more information is used to detect differences. However, considerations of power and sample size should not be the only drivers in the decision for dichotomized versus ordinal analyses, as the questions that are answered are substantially different. Ordinal analyses answers the clinically relevant question whether the treatment brings any meaningful improvement for the patient as measured by the scale, whereas dichotomized analyses answers whether treatment can prevent certain events from occurring. One additional advantage of an ordinal scale is that it can be linked to so called health–utilities, useful indicators of general health status, and thus providing more detailed information for the economic evaluations of new treatments [37]. Moreover, availability of such a tool is absolutely necessary for introducing value-based healthcare which will be the standard of care in the near future. Value-based healthcare is a healthcare delivery approach which aims to increase the value that is derived from the resources available for a population. Lastly, if the scale is sequentially applied in practice, it may even help to monitor persistence or worsening of poor functional status, which could be a way to detect severe VTE complications such as CTEPH earlier [38,39].

Disadvantages of the proposed approach are that the ratings of functional outcome are by definition subjective, at least to some extent. To limit interobserver variability, specific training to perform the interviews during which the functional status is assessed would be recommended or even necessary. Also, it may be impossible for some patients to go to a less severe functional class because of pre-existing morbidity, e.g. a wheelchair-bound patient who develops VTE is very unlikely to become fully independent for activities of daily living after VTE-specific treatment.

3. Lessons learned from stroke

The modified Rankin Scale (mRS) is a 7-level ordinal categorical scale capturing levels of patient functional independence following a stroke. The scale was initially described by Rankin in 1957 to assess the outcome of cerebrovascular accidents and slightly modified in 1988 [40]. Despite its subjective character, the mRS has a high interobserver agreement (weighted kappa between 0.8 and 0.9), especially when study personnel is trained and guided by structured interview questions [40–42].

The mRS has become the golden standard in seminal acute stroke trials like ECASS-III [43] and MR-CLEAN [44], despite the necessity of an interview (by telephone or in person) for a reliable assessment of the functional status. Although initially the mRS was often dichotomized in the primary outcome of clinical trials, the field has moved slowly to adopting ordinal analyses as the (co)primary endpoint in major trials. By adopting this approach, an interest in the specifics of ordinal data analyses in clinical studies grew over time in order to minimize the loss of information due to dichotomization and more sophisticated statistical approaches continue to be developed to this day [45–47]. The experiences in stroke research show that the use of an ordinal outcome in VTE, or more specifically the ordinal analyses of such a scale, is not necessarily a substitution for the more traditional approaches, but should be seen as useful and meaningful addition to the toolbox of a clinical researcher [48].

4. A new scale to quantify functional outcome in VTE patients

The scale that we have in mind closely resembles the mRS used in stroke research and contains several elements of and integrates the main concepts of the NYHA functional classification scale, as applying experiences from the mRS and NYHA will jump start our efforts to have a clinical meaningful scale for VTE studies. In fact, only some minor changes that shift the focus from limitations in motor function of mRS to a focus on cardiorespiratory function are necessary. We have provided a first suggestion of such a scale in Table 1 that focuses on relevant aspects of daily life related to the consequences of VTE or its complications (e.g. discomfort, breathing problems and/or pain). This post-VTE functional status scale is to be assessed during a short structured interview with the patient, either by phone or in the office, and categorizes the level of physical functioning with reference to pre-VTE activities. Our first draft of a post-VTE functional status scale has a couple of underlying characteristics, i.e. the scale is ordinal, has 7 steps with 0 indicating no symptoms and 6 being death, and covers the entire range of functional outcomes and focuses on both limitations in usual activity and changes in lifestyle. Its categories are intuitive and can be easily grasped by clinicians and patients. Classes 1 and 2 are reserved for patients with nuisance symptoms or slight functional limitations, which, however, do no prohibit or limit doing all usual activities either at work or at home; the same are performed at a lower intensity in class 2. Importantly, it is intended to assess whether usual activities *could* be carried out, preventing overestimation of the severity of symptoms in patients who have chosen to abandon certain activities in the course of a VTE diagnosis or simply never performed certain activities. Class 3 involves moderate functional limitations relevant for patients who were forced to modify usual duties at work or at home as a consequence of the VTE, VTE-related complications, or VTE treatment. Class 4 and 5 describe patients with moderate to severe functional limitations that necessitate assistance with some (class 4) or most (class 5) activities of daily living, e.g. preparing a meal, personal/toilet hygiene, functional mobility or basic household chores. We suggest that -after further development- the post-VTE functional status scale is assessed at the moment of hospital discharge and after 90 days following a VTE diagnosis. This later timepoint is chosen as the functional status has stabilised in most patients. Also, it corresponds with a routine visit to the treating physician for determination of the duration of anticoagulant treatment.

Table 1
Post-VTE functional status scale.

Scale category		Description
0	No functional limitations	No symptoms/discomfort.
1	No significant functional limitations	Able to carry out all usual activities at the same level of intensity, despite some symptoms/discomfort.
2	Slight functional limitations	Some usual activities are carried out at a lower level of intensity due to symptoms/discomfort.
3	Moderate functional limitations	Able take care of activities of daily living unassisted, but with modified duties at work/activities at home.
4	Moderate to severe functional limitations	Requires help for activities of daily living or cannot work; breathlessness at rest.
5	Severe functional limitations	Unable to carry on activities of daily living without assistance, breathlessness at rest. Requires nursing care and attention.
6	Dead	Dead

Note: The Post-VTE functional status scale is assessed during a short structured interview with the patient, either by phone or in the office. Breathlessness at rest is comparable to NYHA class IV and differentiates between classes 1–3 and class 4–5. For class 1 and 2, it is intended to assess whether usual activities *could* be carried out and refers to "usual activities" as any activity that patients used to undertake on a monthly basis or more frequently. Class 3 is intended to capture *any* VTE-associated reason for modification of the usual duties at work/at home. For class 4, it should be indicated that assistance with some activities of daily living, e.g. preparing a meal, personal/toilet hygiene, functional mobility or basic household chores, is *absolutely essential*. For class 5, it should be indicated that assistance with *most/all* activities of daily living is *absolutely essential*. Nursing care here not necessarily administrated by a certified nurse, but indicates that patients cannot be left alone for longer period of times. *When in doubt between two adjacent alternatives on the scale even despite that both appearing equally valid, the worse option should be chosen.*

Table 2
Proposed steps of development of performance outcome instruments, and current status of the Post-VTE functional status scale.

Steps of development		Status of the scale
1	Review of evidence for functional scales and tools assessing functional status in patients with VTE (*current manuscript*)	✓
2	Identification of the key characteristics of the modified Rankin Scale for patients with stroke in order to draft measure and item specifications, and fields of applicability which may be relevant for patients with venous thromboembolism (*current manuscript*)	✓
3	Assemble a dedicated multidisciplinary work group (including patients, and physicians, nurses, and representatives of major societies) to achieve consensus on the instrument (*aim of current manuscript*)	
4	Formal rounds of review of the proposed categories of the ordinal scale from the dedicated multidisciplinary work group (*Delphi analysis*)	
5	Formal assessment of reliability and validity of the scale in different settings and patient populations	
6	Formal assessment of feasibility (e.g. logistics and costs) of the scale in a major trial	
7	Dissemination and implementation	

Despite having a strong similarity to the well-studied and widely implemented mRS, our first draft of a post-VTE functional status scale should only be used in the context of studying the scale itself. It is only after formal evaluation that our score could be used as the primary outcome of clinical studies. The steps of this evaluation are described in Table 2.

5. Conclusion

We propose a first draft of a post-VTE functional status scale to assess VTE-associated functional limitations in a standardized manner. The scale is still in a preliminary stage and not meant to replace current diagnostic or prognostic scores for PTS or post-PE syndrome, but to be used as an outcome measure to evaluate the overall consequences of VTE on functional status. After further development, it could be used to test new treatment strategies on patient relevant outcomes beyond bleeding and recurrent VTE, to increase awareness of PTS and the post-PE syndrome and possibly to identify patients that benefit from targeted interventions such as cardiopulmonary rehabilitation programs or endovascular procedures to restore venous outflow of the extremities. Considering how the introduction of the mRS has demarcated effective and ineffective acute stroke therapies in trials with appropriately powered sample sizes, we anticipate that a formally developed and validated post-VTE functional status scale will help refining the designs of trials in the VTE field with a more prominent focus on patient-relevant functional outcome, and ultimately improve prognosis. By this review, we call upon the VTE community to join forces and support completing the necessary steps of development of this VTE performance outcome instrument.

Acknowledgements

The work of Frederikus A. Klok and Stefano Barco is supported by the German Federal Ministry of Education and Research (BMBF 01EO1003 and 01EO1503). The work of Bob Siegerink is supported by the German Federal Ministry of Education and Research (BMBF 01EO0801).

Disclosures

Frederikus Klok reports research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi-Sankyo, MSD and Actelion, the Dutch Heart foundation and the Dutch Thrombosis association. Stefano Barco received congress and travel payments from Daiichi-Sankyo and Bayer HealthCare, and personal fee from BTG/EKOS, outside the submitted work. Bob Siegerink has no disclosures.

Authorship statement

All authors have contributed significantly to this manuscript and approve of its final version.

References

[1] S.R. Kahn, A.J. Comerota, M. Cushman, et al., The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association, Circulation 130 (2014) 1636–1661.
[2] A. Rabinovich, S.R. Kahn, How I treat the postthrombotic syndrome, Blood 131 (2018) 2215–2222.
[3] F.A. Klok, T. van der Hulle, P.L. den Exter, et al., The post-PE syndrome: a new concept for chronic complications of pulmonary embolism, Blood Rev. 28 (2014) 221–226.
[4] F.A. Klok, S. Barco, Follow-up after acute pulmonary embolism, Hamostaseologie 38 (2018) 22–32.
[5] A.K. Sista, F.A. Klok, Late outcomes of pulmonary embolism: the post-PE syndrome, Thromb. Res. 164 (2018) 157–162.
[6] A.S. Wolberg, F.R. Rosendaal, J.I. Weitz, et al., Venous thrombosis, Nat. Rev. Dis. Primers 1 (2015) 15006.
[7] M.V. Huisman, S. Barco, S.C. Cannegieter, et al., Pulmonary embolism, Nat. Rev. Dis. Primers 4 (2018) 18028.

[8] S.V. Konstantinides, S. Barco, S. Rosenkranz, et al., Late outcomes after acute pulmonary embolism: rationale and design of FOCUS, a prospective observational multicenter cohort study, J. Thromb. Thrombolysis 42 (2016) 600–609.
[9] S.D. Grosse, R.E. Nelson, K.A. Nyarko, et al., The economic burden of incident venous thromboembolism in the United States: a review of estimated attributable healthcare costs, Thromb. Res. 137 (2016) 3–10.
[10] S.R. Kahn, T. Ducruet, D.L. Lamping, et al., Prospective evaluation of health-related quality of life in patients with deep venous thrombosis, Arch. Intern. Med. 165 (2005) 1173–1178.
[11] F.A. Klok, K.W. van Kralingen, A.P. van Dijk, et al., Quality of life in long-term survivors of acute pulmonary embolism, Chest 138 (2010) 1432–1440.
[12] F.A. Klok, J.E. Tijmensen, M.L. Haeck, et al., Persistent dyspnea complaints at long-term follow-up after an episode of acute pulmonary embolism: results of a questionnaire, Eur. J. Intern. Med. 19 (2008) 625–629.
[13] F.A. Klok, K.W. van Kralingen, A.P. van Dijk, et al., Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism, Respir. Med. 104 (2010) 1744–1749.
[14] M. Tavoly, H.S. Wik, P.A. Sirnes, et al., The impact of post-pulmonary embolism syndrome and its possible determinants, Thromb. Res. 171 (2018) 84–91.
[15] S.R. Kahn, A. Akaberi, J.T. Granton, et al., Quality of life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: results of the ELOPE cohort study, Am. J. Med. 130 (2017) (990 e999-990 e921).
[16] B.G. Stevinson, J. Hernandez-Nino, G. Rose, J.A. Kline, Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients, Eur. Heart J. 28 (2007) 2517–2524.
[17] J.A. Kline, M.T. Steuerwald, M.R. Marchick, et al., Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure, Chest 136 (2009) 1202–1210.
[18] M. Tavoly, K.K. Utne, L.P. Jelsness-Jorgensen, et al., Health-related quality of life after pulmonary embolism: a cross-sectional study, BMJ Open 6 (2016) e013086.
[19] A.K. Sista, L.E. Miller, S.R. Kahn, J.A. Kline, Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: systematic review with meta-analysis, Vasc. Med. 22 (2017) 37–43.
[20] R. Hunter, S. Noble, S. Lewis, P. Bennett, Long-term psychosocial impact of venous thromboembolism: a qualitative study in the community, BMJ Open 9 (2019) e024805.
[21] S.R. Kahn, S. Shapiro, P.S. Wells, et al., Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial, Lancet 383 (2014) 880–888.
[22] G.C. Mol, M.A. van de Ree, F.A. Klok, et al., One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial, BMJ 353 (2016) i2691.
[23] S. Vedantham, S.Z. Goldhaber, J.A. Julian, et al., Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis, N. Engl. J. Med. 377 (2017) 2240–2252.
[24] A.J. Ten Cate-Hoek, E.E. Amin, A.C. Bouman, et al., Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial, Lancet Haematol 5 (2018) e25–e33.
[25] S.V. Konstantinides, E. Vicaut, T. Danays, et al., Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism, J. Am. Coll. Cardiol. 69 (2017) 1536–1544.
[26] F. Noack, B. Schmidt, M. Amoury, et al., Feasibility and safety of rehabilitation after venous thromboembolism, Vasc. Health Risk Manag. 11 (2015) 397–401.
[27] S.G. Lakoski, P.D. Savage, A.M. Berkman, et al., The safety and efficacy of early-initiation exercise training after acute venous thromboembolism: a randomized clinical trial, J. Thromb. Haemost. 13 (2015) 1238–1244.
[28] D. Taboada, J. Pepke-Zaba, D.P. Jenkins, et al., Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease, Eur. Respir. J. 44 (2014) 1635–1645.
[29] S.R. Kahn, A.M. Hirsch, A. Akaberi, et al., Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study, Chest 151 (2017) 1058–1068.
[30] F.A. Klok, M. Delcroix, H.J. Bogaard, Chronic thromboembolic pulmonary hypertension from the perspective of patients with pulmonary embolism, J. Thromb. Haemost. 16 (2018) 1040–1051.
[31] H.S. Wik, T.R. Enden, W. Ghanima, et al., Diagnostic scales for the post-thrombotic syndrome, Thromb. Res. 164 (2018) 110–115.
[32] A. Rabinovich, T. Ducruet, S.R. Kahn, investigators SOXT, Development of a clinical prediction model for the postthrombotic syndrome in a prospective cohort of patients with proximal deep vein thrombosis, J. Thromb. Haemost. 16 (2018) 262–270.
[33] G.C. Mol, C.E.A. Dronkers, M.A. van de Ree, et al., Elastic compression stockings one year after DVT diagnosis: who might discontinue? Thromb. Res. 173 (2019) 35–41.
[34] F.A. Klok, D.M. Cohn, S. Middeldorp, et al., Quality of life after pulmonary embolism: validation of the PEmb-QoL questionnaire, J. Thromb. Haemost. 8 (2010) 523–532.
[35] A. Akaberi, F.A. Klok, D.M. Cohn, et al., Determining the minimal clinically important difference for the PEmbQoL questionnaire, a measure of pulmonary embolism-specific quality of life, J. Thromb. Haemost. 16 (2018) 2454–2461.
[36] B. Lubberts, N.R. Paulino Pereira, C. Kabrhel, et al., What is the effect of venous thromboembolism and related complications on patient reported health-related quality of life? A meta-analysis, Thromb. Haemost. 116 (2016) 417–431.
[37] M. Ali, R. MacIsaac, T.J. Quinn, et al., Dependency and health utilities in stroke: data to inform cost-effectiveness analyses, Eur Stroke J 2 (2017) 70–76.
[38] F.A. Klok, S. Barco, S.V. Konstantinides, et al., Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH Registry, Eur. Respir. J. 52 (2018).
[39] Y.M. Ende-Verhaar, W.B. van den Hout, H.J. Bogaard, et al., Healthcare utilization in chronic thromboembolic pulmonary hypertension after acute pulmonary embolism, J. Thromb. Haemost. 16 (2018) 2168–2174.
[40] J.C. van Swieten, P.J. Koudstaal, M.C. Visser, et al., Interobserver agreement for the assessment of handicap in stroke patients, Stroke 19 (1988) 604–607.
[41] E. Lopez-Cancio, M. Salvat, N. Cerda, et al., Phone and video-based modalities of central blinded adjudication of modified Rankin scores in an endovascular stroke trial, Stroke 46 (2015) 3405–3410.
[42] J.T. Wilson, A. Hareendran, A. Hendry, et al., Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview, Stroke 36 (2005) 777–781.
[43] W. Hacke, M. Kaste, E. Bluhmki, et al., Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke, N. Engl. J. Med. 359 (2008) 1317–1329.
[44] O.A. Berkhemer, P.S. Fransen, D. Beumer, et al., A randomized trial of intraarterial treatment for acute ischemic stroke, N. Engl. J. Med. 372 (2015) 11–20.
[45] G. Howard, J.L. Waller, J.H. Voeks, et al., A simple, assumption-free, and clinically interpretable approach for analysis of modified Rankin outcomes, Stroke 43 (2012) 664–669.
[46] V.W. Rahlfs, H. Zimmermann, K.R. Lees, Effect size measures and their relationships in stroke studies, Stroke 45 (2014) 627–633.
[47] S.A. Dijkland, D.C. Voormolen, E. Venema, et al., Utility-weighted modified Rankin scale as primary outcome in stroke trials: a simulation study, Stroke 49 (2018) 965–971.
[48] B. Siegerink, J.L. Rohmann, Impact of your results: beyond the relative risk, Res Pract Thromb Haemost 2 (2018) 653–657.