Thrombosis Research 199 (2021) 85–96

Contents lists available at ScienceDirect

Thrombosis Research

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

Clinical Studies

Prediction models for recurrence and bleeding in patients with venous thromboembolism: A systematic review and critical appraisal☆

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ARTICLE INFO

Keywords:
Hemorrhage
Recurrence
Risk
Systematic review
Venous thromboembolism

ABSTRACT

Introduction: Prediction models for recurrence and bleeding are infrequently used when deciding on anticoagulant treatment duration after venous thromboembolism (VTE) due to concerns about performance and validity. Our aim was to critically appraise these models by systematically summarizing data from derivation and validation studies.

Materials and methods: MEDLINE and CENTRAL were searched until November 15th, 2019. Studies on prediction models for recurrence or bleeding after at least 3 months of anticoagulation in adult patients with VTE were included. The PROBAST, ROBINS-I and RoB2 tools were used to assess risk of bias and applicability.

Results: Selection yielded 18 studies evaluating 8 models for recurrence (7 on development; 9 on validation; 1 update). Generally, models for recurrent VTE appeared to perform poorly to moderately in external validation studies (C-statistics 0.39–0.66, one 0.83). However, impact studies show that HERDOO2 and Vienna prediction model may identify patients with unprovoked VTE at low recurrence risk. Sixteen studies evaluating 14 models for anticoagulation-related bleeding were identified (7 on development; 9 on validation). Although some models seemed promising in development studies, their predictive performance was poor to moderate in external validation (C-statistics 0.52–0.71). All but 3 studies were considered at high risk of bias, mainly due to limitations in the statistical analysis.

Conclusions: Prognostic models for recurrence and anticoagulation-related bleeding risk often have important methodological limitations and insufficient predictive accuracy. These findings do not support their use in clinical practice to weigh risks of recurrence and bleeding when deciding on continuing anticoagulation after initial treatment of VTE.

1. Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important cause of morbidity and mortality worldwide, affecting 1–2 per 1000 individuals annually [1,2]. Anticoagulation for at least 3 months is the mainstay of therapy [3,4]. Thereafter, a decision must be made to stop or continue anticoagulation. Although anticoagulation is highly effective in preventing recurrence, it carries a 1–2% annual risk of major bleeding, which can be debilitating and is associated with substantial healthcare utilization and costs [5,6]. A fixed treatment duration longer than 3 months (e.g. 6 or 12 months) only postpones recurrence until after cessation of treatment due to the so-called 'catch-up phenomenon', hence exposing patients to an unnecessary risk of bleeding [7]. Therefore, it is recommended to stop anticoagulation or continue indefinitely after 3 months of treatment [3,4,7]. International guidelines advise to decide on treatment duration by weighing an individual patient's risk of recurrence versus risk of bleeding, while taking into account patient preferences [3,4]. Anticoagulation may be stopped after 3 months when VTE is provoked by a major transient risk factor, whereas indefinite treatment should be considered in patients with unprovoked VTE as risk of recurrence is as high as 25% in 5 years [3,4,8].

☆ This paper (poster) was presented at the digital International Society on Thrombosis and Haemostasis (ISTH) Congress 2020, at July 12–14, 2020.

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https://doi.org/10.1016/j.thromres.2020.12.031
Received 13 October 2020; Received in revised form 7 December 2020; Accepted 31 December 2020
Available online 17 January 2021

Applying guidelines to decide on treatment duration for VTE in clinical practice poses a frequent dilemma. Risks of recurrence and bleeding differ strongly between patients. In some at high risk of recurrence, the benefit of extended treatment will not outweigh the associated bleeding risk and vice versa. Existing risk scores are not endorsed by guidelines as these scores may have methodological limitations and limited external validity [3,9]. Lack of proper risk assessment can lead to unfavorable treatment decisions, increasing risks of bleeding and recurrent VTE.

Several recent developments have the potential to change our current view on prediction tools for patients with VTE. First, new model derivation and validation studies for bleeding and recurrent VTE have been published. Second, PROBAST has been developed to assess risk of bias and applicability in prediction model studies, allowing for a systematic assessment of existing prediction models [10]. Finally, adequate risk assessment will become even more important in light of the new 2019 ESC guidelines for the treatment of VTE [3]. In addition to patients with unprovoked VTE, this guideline now also suggests indefinite treatment for those with VTE provoked by minor transient risk factors.

The objective of the present systematic review is to provide an overview of the strengths and limitations of currently available prediction models for recurrent VTE and bleeding risk using the PROBAST, ROBINS-I and RoB2 tools. We also highlight important considerations for developing robust and easily applicable clinical prediction models for patients with VTE.

2. Materials and methods

A review protocol was registered with PROSPERO (https://www.crd.york.ac.uk/prospero) on December 19, 2019 (CRD42020163076).

2.1. Data sources and searches

A systematic search was performed in MEDLINE and CENTRAL up to November 15th, 2019 (Appendix Table 1). Specific systematic review questions were prespecified (Appendix Table 2). We combined search terms for (i) VTE, DVT, or PE, (ii) prediction, risk, prognosis, or model, and (iii) recurrence or bleeding. The search was restricted to titles and MeSH terms, articles in English or Dutch, and studies published after 1985 as a preliminary search did not identify relevant articles prior to this year. Reference lists of all eligible articles and systematic reviews were hand-searched for additional studies. Furthermore, proceedings of the International Society on Thrombosis and Haemostasis (ISTH), American Society of Hematology (ASH), and European Society of Cardiology (ESC) conferences in 2018 and 2019 were searched to identify potentially relevant unpublished studies. Search and selection were conducted by 2 researchers independently (MN, MW). Any disagreement was resolved by discussion with the other authors.

2.2. Study selection

Studies were eligible if they had (i) included adult patients with DVT and/or PE, (ii) used any design for developing, updating, validating, or evaluating prediction models, scores, or other prognostic tools for bleeding during anticoagulant treatment or recurrent VTE after at least 3 months of anticoagulant treatment. Studies in which follow-up started within 3 months of treatment were included if the follow-up continued beyond 3 months. Studies describing model development in patients with VTE during initial treatment were only included if the model was subject of external validation in other included studies. Studies focusing on predicting risk of recurrence or bleeding in a selected study population with anticoagulation for indications other than VTE, patients with cancer, caval filters, or those having received thrombolytic treatment only, studies describing genetic risk factors only and predictor finding studies were excluded.

2.3. Data extraction and quality assessment

Data extraction was performed according to the CHARMS checklist by one researcher (MW) using a predesigned data extraction form [11].

The Prediction model Risk Of Bias Assessment Tool (PROBAST) was used to critically appraise studies reporting on development or validation of prognostic models [10]. PROBAST contains signaling questions on risk of bias and applicability in the domains participants, predictors, outcome, and statistical analysis, answered with 'no', 'probably no', 'probably yes', 'yes', or 'no information'. If one or more questions in a domain were answered with '(probably) no', the study was considered at high risk of bias with regard to that domain. Studies were assumed to be at low risk of bias if none of the domains was considered at high risk of bias. Risk of bias in impact studies assessing the effect of using a prediction model for clinical decision-making was assessed using the RoB2 tool (randomized studies) or ROBINS-I tool (non-randomized studies), as PROBAST is not suitable for these studies [12,13]. In most studies, recurrent VTE was defined as any objectively confirmed symptomatic new PE or DVT. Most studies on predicting bleeding used definitions for major bleeding and clinically relevant, non-major bleeding (CRNMB) provided by the ISTH or related definitions [14,15]. For the present review, definitions of the included studies were adopted.

2.4. Data synthesis and analysis

Predictors, model performance (e.g. discrimination, goodness-of-fit) and risk of bias assessment were reported by tables and compared across different models for bleeding and recurrent VTE. A bar plot was used to illustrate the frequency with which predictors were included in models for recurrence or bleeding. Discrimination was considered poor with C-statistics of 0.50–0.69, moderate 0.70–0.79, good 0.80–0.89 and excellent 0.90–1.00. When multiple models were validated in a study, we investigated and reported risk of bias per model. If multiple models or scores are addressed, the word 'model' is used to refer to both for practical reasons.

2.5. Role of the funding source

This project was funded by ZonMw, (the Netherlands Organization for Health Research and Development), as part of their program "Goed Gebruik Geneesmiddelen", project number 848018012. ZonMw had no role in the conception, design, conduct, or interpretation of the study nor the decision to submit the manuscript for publication.

3. Results

3.1. Predicting risk of recurrent VTE

Eighteen eligible studies evaluating 8 prognostic models on recurrent VTE after cessation of anticoagulation were identified (Fig. 1): HERDOO2, Vienna, DASH, DAMOVES, Huang et al., pre D-dimer model, post D-dimer model and L-TRRiP. As shown in Appendix Table 3,7 studies reported on model development [17–23], 10 studies performed external validation of one or multiple models [20,23–31], one study reported on updating an existing model (Vienna prediction model) [32] and 2 prospective management studies were identified [16,33]. One study described external validation of a prognostic score for bleeding (VTE-BLEED) with recurrent VTE as outcome [29]. Study populations of the included studies comprised 121 to 2989 patients, with a median study follow-up ranging from 18 to 68 months. All studies were conducted in Europe or North America. All but one of the derivation studies included adult patients with first unprovoked VTE who discontinued anticoagulation after the initial treatment and aimed to stratify patients by their risk of (objectively confirmed) recurrent VTE. The most recent model derivation study on the L-TRRiP model included patients with any first VTE event and was developed to predict unprovoked recurrent

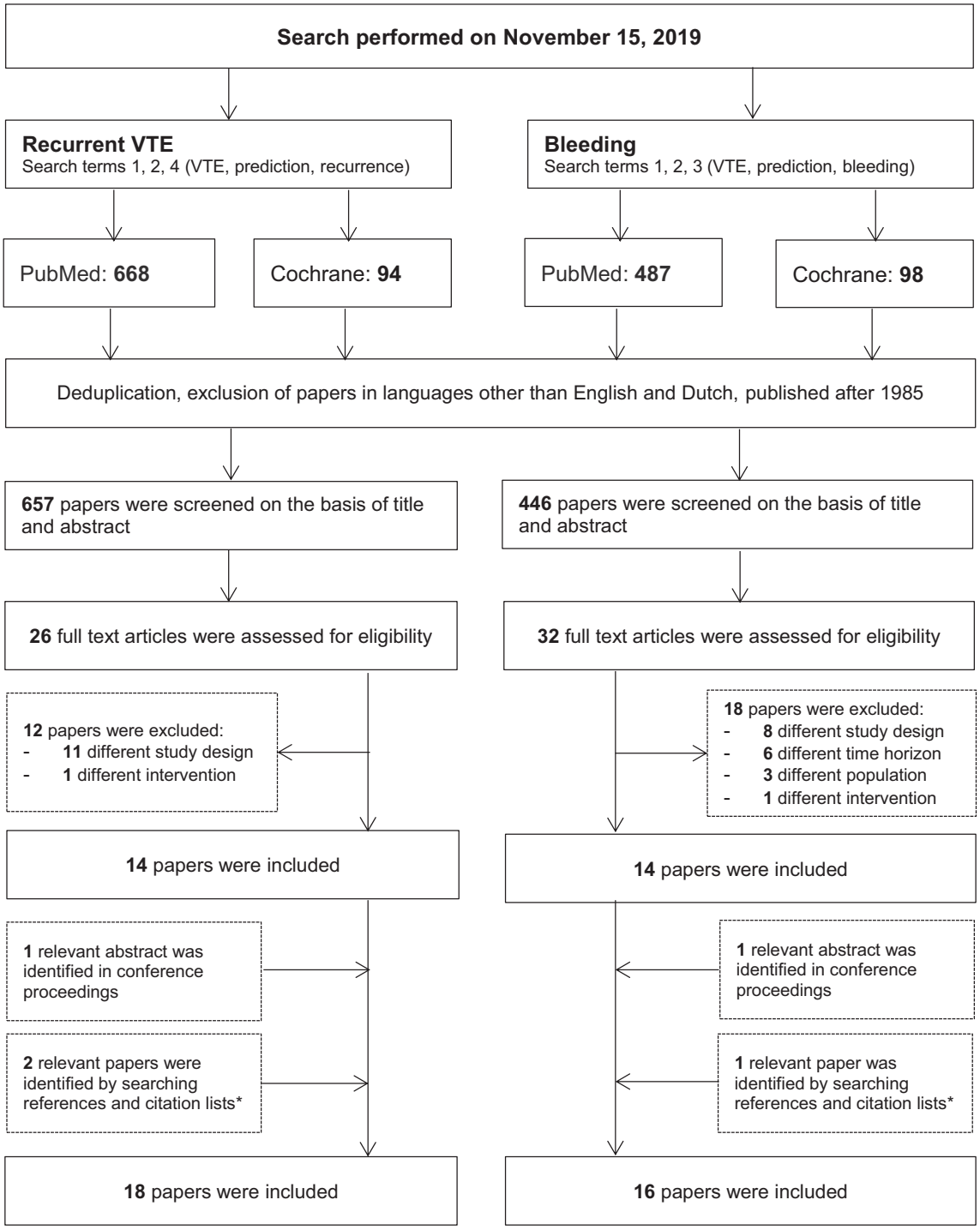

Fig. 1. Flow chart of search and study selection.
* Additional search terms on prediction (rule, score, validat*) and VTE (thromboembolism) were added when 3 relevant papers were identified from references and citation lists [4,16,17]. No additional missed papers were found.

VTE only [19]. All models except the one developed by Huang and colleagues and the post D-dimer model were externally validated in data that were not used for model development at least once.

3.2. Predictors in the models

Male sex, age, body mass index, D-dimer either while on anticoagulation or after cessation of treatment, and site of the index event are included in most identified models (Fig. 2). Some studies took into account the site of the index event, the presence of provoking factors and sex by including patients with proximal DVT or unprovoked VTE only [17,20,23] or developing a score to be used in women [17].

3.3. Performance of the prediction models

Discriminative accuracy of the included models varied from poor to excellent in model development studies, with C-statistics ranging from 0.56 to 0.91 (median 0.67, interquartile range(IQR) 0.60–0.71)

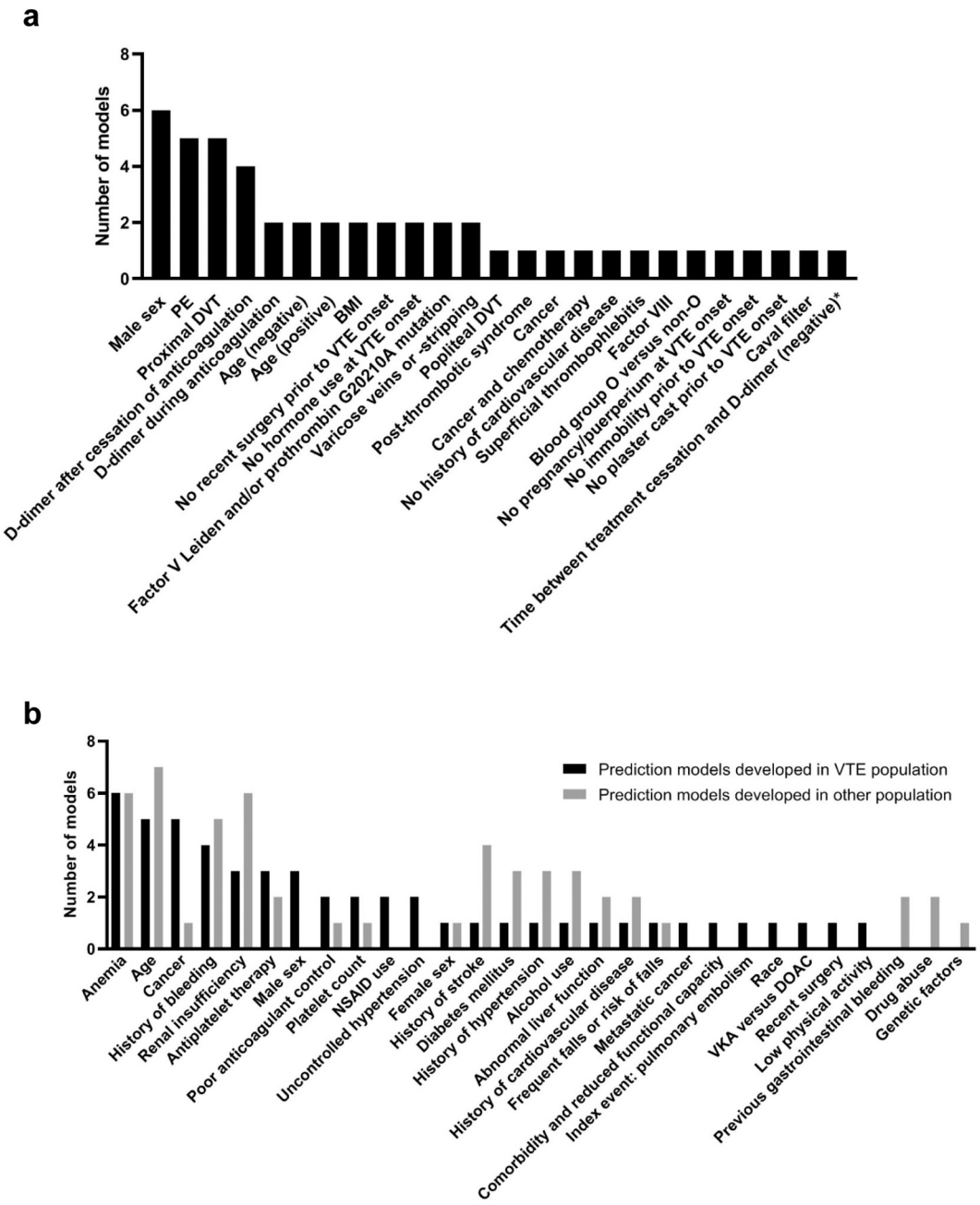

Fig. 2. a. Predictors included in models for recurrent venous thromboembolism after cessation of anticoagulation.
Predictors that are inversely associated with the outcome in the included models are oppositely described in this figure (e.g. "No plaster cast prior to VTE onset"), or the inverse association is indicated by adding '(negative)'. As VTE-BLEED was developed to predict risk of bleeding, its predictors are not included in the figure on prediction models for recurrent VTE.
* In conjunction with D-dimer after cessation of anticoagulation.
Abbreviations: DOAC direct oral anticoagulant; NSAID non-steroidal anti-inflammatory drugs; PE Pulmonary embolism; VKA vitamin K antagonist; VTE venous thromboembolism
b. Predictors included in models for bleeding during anticoagulation.
Predictors that are inversely associated with the outcome in the included models are oppositely described in this figure. Anemia may refer to hemoglobin (continuous) or anemia (dichotomous); thrombocytopenia may refer to platelet count (continuous) or thrombocytopenia (dichotomous).
Abbreviations: DOAC direct oral anticoagulant; NSAID non-steroidal anti-inflammatory drugs; VKA vitamin K antagonist.

(Table 1). In line with the ISTH recommendation, all models successfully identify a low risk group in whom anticoagulation may safely be excluded (annual risk of recurrent VTE below 5%) [34]. Discriminative performance was lower in external validation studies with C-statistics ranging from 0.39 to 0.83 (median 0.63, IQR 0.62–0.65). The higher C-statistic of 0.83 and good model calibration was observed in an external validation study on DAMOVES, which was conducted by the same research group that developed the model [28]. Similarly, the L-TRRiP model was found to be well calibrated [19]. Three other studies assessing calibration indicated either slightly overestimated risks especially in high risk categories or underestimated risks, respectively [23,26,30]. All but one of the models (Vienna prediction model in the validation study by Timp and colleagues) were able to identify a group with an annual risk of recurrence of below 5% in at least one external

Table 1
Characteristics of prognostic models for recurrent VTE and bleeding.

Model	Time horizon (months)[a]	Model derivation					External validation
		Predictors and assigned points (simple score) or coefficients[b,c]	Associated risks of recurrence (95% CI)	EPV (n events/ total)	Discrimination (C-statistic)[d] (95% CI)	Calibration	
Recurrent VTE							
L-TRRiP (model C) (Timp 2019-2 [19])	24	Male sex **0.63** Popliteal DVT **0.15** Proximal DVT **0.46** PE and DVT **0.47** Surgery prior to VTE onset **−0.51** VTE related to pregnancy/ puerperium **−1.49** Hormone use at VTE onset **−0.67** Plaster cast prior to VTE onset **−0.79** Immobility in bed prior to VTE onset **−0.31** History of CVD **−0.36** Blood group O vs non-O **0.24** Factor V Leiden **0.40**	2-year predicted risks of 0–32.0%	13 (507/ 3750)	0.70 (0.68–0.73)	Excellent; shrinkage slope 0.953	C-statistic 0.64; good calibration [19]
Pre D-dimer model (Ensor 2016 [23])	36	Male sex **0.58** Proximal DVT **1.82** PE **1.71**	3-year predicted risks of 1.5–12.9%	38 (230/ 1634)	0.56 (0.51–0.60)	Well calibrated; large heterogeneity between individual studies	C-statistic 0.56; reasonable calibration with underestimation of risks in lower (<3%) predicted risk categories (MEGA study) [23]
Post D-dimer model (Ensor 2016 [23])	36	Age **−0.01** Male sex **0.55** Proximal DVT **1.74** PE **1.76** D-dimer (log) **0.7** Lag time between cessation of anticoagulation and D-dimer measurement (log) **-0.29**	3-year predicted risks of 1.7–21.6%	29 (230/ 1634)	0.69 (0.63–0.75)	Excellent	N.a.
DAMOVES (Franco-Moreno 2016 [28])	12	**Nomogram (0–30 points)** Age (per 10 years) Male sex BMI > 30 kg/m^2 Abnormal D-dimer while anticoagulated Factor VIII Heterozygous factor V Leiden and/or prothrombin G20210A mutation Varicose veins	<11.5 points: 2.9%	5 (65/ 398)	0.91	Excellent	C-statistic 0.83; good calibration, Hosmer-Lemeshow *p*-value 0.125 [28]
Huang (Huang 2016 [22])	36	Active cancer receiving chemotherapy **HR 2.58** Active cancer not receiving chemotherapy **HR 1.59** Superficial thrombophlebitis **HR 1.69** Varicose vein stripping **HR 1.70** Caval filter placement **HR 2.06** Surgery prior to VTE onset **HR 0.73** **Risk score calculator only available for 3 month model**	Not reported	6 (329/ 2989)	0.62	Score versus observed risks and non-significant May-Hosmer test suggest good calibration	n.a.
Vienna (update) (Eichinger 2014 [32])	12, 60	Male sex PE vs distal DVT Proximal vs distal DVT D-dimer (after stopping anticoagulation) at different time points **Online calculator**	5-year predicted risks of 7–41%	17 (150/ 553)	0.61 (at 3 or 9 months); 0.58 (at 15 months)	Moderate calibration, slopes of 0.79 at 3 months, 0.81 at 9 months and 0.70 at 15 months	C-statistics 0.39 (12 months); 0.43 (24 months); Hosmer-Lemeshow p-value 0.03 and 0.06 respectively [31]
DASH (Tosetto 2012 [20])	12, 24, 60	Abnormal D-dimer (1 month after stopping anticoagulation) **2** Age ≤50 years **1** Male sex **1** Hormone use at VTE onset **−2**	≤1 point: 3.1%; ≥2 points: 9.3%	17 (239/ 1818)	0.71	Calibration slope of 0.97 indicates strong performance	C-statistic 0.63 [25]; 0.66 [24]; C-statistic 0.65 and calibration slope 0.71, suggesting overfitting [26]; No information on

(*continued on next page*)

Table 1 (*continued*)

Model	Time horizon (months)[a]	Model derivation					External validation
		Predictors and assigned points (simple score) or coefficients[b,c]	Associated risks of recurrence (95% CI)	EPV (n events/ total)	Discrimination (C-statistic)[d] (95% CI)	Calibration	
							discrimination or calibration [27]
Vienna (Eichinger 2010 [18])	12, 60	Male sex **HR 1.90** PE vs distal DVT **HR 2.60** Proximal vs distal DVT **HR 2.08** D-dimer per doubling (after stopping anticoagulation) **HR 1.27**	≤180 points: 4.4%	12 (176/ 929)	0.67 (at 12 months); 0.65 (at 60 months)	Goodness-of-fit test p-value 0.54	C-statistics 0.63 [25]; 0.62 [24]; C-statistic 0.62 and calibration slope 1.17 [30]
HERDOO2 (Rodger 2008 [17])	12	*All men are considered at high risk. Criteria for women*: Post-thrombotic signs **1** D-dimer while anticoagulated ≥250 μ/L **1** BMI ≥30 kg/m^2 **1** Age ≥65 years **1**	≤1 point: 3.1%; 2–4 points: 7.4%	3 (91/ 646)	Not reported	Not reported	N.a.
VTE-BLEED (Klok 2019 [29])	18	As in original model	Low risk: 15.0%; high risk: 16.0% HR 1.16 (0.6–2.2) for high vs low risk	44/308	Not reported	Not reported	*External validation only*
Bleeding							
Seiler (Seiler 2017 [39])	36	Previous major bleeding **1** Active cancer **1** Low physical activity **2** Anemia **1** Thrombocytopenia **1** Antiplatelet drugs or NSAIDs **1** Poor INR control **1**	0–1 points: 1.4 per 100 patient-years 2–3 points: 5.0 per 100 patient-years >3 points: 122 per 100 patient-years	4 (66/ 743)	0.68 (0.61–0.74)	Goodness-of-fit test p-value 0.93	N.a.
Hokusai (Di Nisio 2017 [37])	12 (from 3rd month onwards)	Female sex **1** Antiplatelet therapy **1** Hb ≤10 g/dL **1** History of hypertension **1** SBP >160 mmHg **1**	*Edoxaban arm; warfarin arm* 0 points: 1.4%; 1.1% 1 point: 1.0%; 1.4% 2 points: 2.1%; 2.1% ≥3 points: 5.4%; 3.7%	2 (56/ 4118)	Edoxaban 0.65 (0.50–0.79); Warfarin 0.57 (0.54–0.60)	Hosmer-Lemeshow goodness-of-fit test p-value 0.976	N.a.
EINSTEIN (Di Nisio 2016 [38])	±6.8 months (from 5th week onwards)	Rivaroxaban vs enoxaparin/VKA **HR 0.60** Age per 10 years **HR 1.45** Hb (mg/dL) **HR 0.66** Male sex if Hb <12 mg/dL **HR 1.40** Hb in males (mg/dL) **HR 1.31** Race (vs caucasian)- black **HR 3.93** Asian **HR 1.11** Other **HR 1.74** History of CVD **HR 1.74**	Not reported	3 (112/ 8060)	0.68 (0.60–0.76)	Not reported	N.a.
VTE-BLEED (Klok 2016 [35])	6 (from 2nd month onwards)	Active cancer **2** Male and uncontrolled hypertension **1** Anemia **1.5** History of bleeding **1.5** Renal dysfunction (creatinine clearance 30–60 mL/min) **1.5** Age ≥60 years **1**	0–1 point: 2.8% ≥2 points: 12.6%	11 (138/ 2553)	0.75	Not reported	C-statistics 0.67 [41]; 0.71 [51]; 0.66 [47]; no discrimination or calibration reported [48]
ACCP[e] (Kearon 2016 [4])	12 (from 4th month onwards)	Age >65 years, age >75, previous bleeding, cancer, metastatic cancer, renal failure, liver failure, thrombocytopenia, previous stroke, diabetes, anemia, antiplatelet therapy, NSAIDs, poor anticoagulant	0 points: 0.8% 1 point: 1.6% ≥2 points: ≥6.5%	n.a.	Not reported	Not reported	C-statistic 0.56, calibration fairly well for 1st-3rd decile, overestimated risks in high scoring patients [49]; C-statistics 0.55 with continuous and 0.52 with

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Table 1 (*continued*)

Model	Time horizon (months)[a]	Model derivation					External validation
		Predictors and assigned points (simple score) or coefficients[b,c]	Associated risks of recurrence (95% CI)	EPV (n events/ total)	Discrimination (C-statistic)[d] (95% CI)	Calibration	
		control, comorbidity and reduced functional capacity, recent surgery, frequent falls, alcohol abuse**: all 1 point**					categorized variables [44]; 0.61 [45]
RIETE (Ruiz-Giménez 2008 [40])	3	Recent major bleeding **2** Creatinine levels >1.2 mg/dL **1.5** Anemia **1.5** Cancer **1** Clinically overt PE **1** Age >75 years **1**	0 points: 0.3% 1–4 points: 2.6% >4 points: 7.3%	29 (314/ 13,057)	Not reported	Not reported	C-statistics 0.60 [39]; 0.55 [45]; 0.61 for continuous and 0.51 for categorical variables [44]
Kuijer (Kuijer 1999 [36])	3	Age ≥60 years **1.6** Male sex **1.3** Malignancy **2.2**	0 points: 0.0%; 1–3 points: 6.0%; >3 points: 26.0%	4 (22/ 241)	0.75 (0.64–0.83)	Not reported	C-statistics 0.55 [41]; 0.55 [45]
ORBIT		Age ≥75 years **1** Reduced Hb, Ht or history of anemia **2** Bleeding history **2** Insufficient kidney function (eGFR <60 mL/min/1.73 m2) **1** Antiplatelet therapy **1**					C-statistics 0.65 [41]
ATRIA		Anemia **1** Severe renal disease **3** Age ≥75 years **2** Previous hemorrhage **1** Diagnosed hypertension **1**					C-statistics 0.62 [41]; 0.52 [45]; 0.58 for continuous and 0.56 for categorical variables [44];
HAS-BLED		Hypertension **1** Abnormal liver function **1** Abnormal renal function **1** Stroke **1** Bleeding history or predisposition **1** Labile INR **1** Age ≥65 years **1** Drug abuse **1** Alcohol abuse **1**					C-statistics 0.55 [41]; 0.69 [42]; 0.58 [45]; 0.55 for continuous and 0.58 for categorized variables [44]; No discrimination and calibration reported [46,48]
HEMORR2HAGES		Hepatic or renal disease **1** Ethanol abuse **1** Malignancy **1** Age ≥75 years **1** Reduced platelet count or functioning **1** Prior bleeding **2** Hypertension **1** Anemia **1** Genetic factors **1** Excessive fall risk **1** Prior stroke **1**					C-statistics 0.57 [45]; 0.60 for continuous and 0.60 for categorized variables [44]
Shireman		Age ≥70 years **0.49** Female gender **0.32** Remote bleeding **0.58** Recent bleeding **0.62** Alcohol/drug abuse **0.71** Diabetes **0.27** Anemia (Ht <30%) **0.86** Antiplatelet use **0.32**					C-statistic 0.53 [45]
mOBRI		Age ≥65 years **1** History of stroke **1** History of gastrointestinal bleeding **1** Recent myocardial infarction, renal insufficiency, diabetes mellitus or anemia (Ht <30%) **1**					C-statistic 0.55 [45]
OBRI		Age ≥65 years **1** Either current or past stroke **1** Both current and past stroke **1** History of gastrointestinal bleeding <2 weeks **1** Atrial fibrillation **1**					C-statistics 0.58 for continuous and 0.51 for categorized variables [44]

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Table 1 (*continued*)

Model	Time horizon (months)[a]	Model derivation					External validation
		Predictors and assigned points (simple score) or coefficients[b,c]	Associated risks of recurrence (95% CI)	EPV (n events/ total)	Discrimination (C-statistic)[d] (95% CI)	Calibration	
		Recent myocardial infarction; Ht <30%; creatinine >1.5 mg/dL, diabetes mellitus **1**					

Abbreviations: CI confidence interval; CRNMB clinically relevant, non-major bleeding; CVD cardiovascular disease; DVT deep venous thrombosis; EPV events per variable; Hb hemoglobin; Ht hematocrit; HR hazard ratio; INR international normalized ratio; IQR interquartile range; NSAID non-steroidal anti-inflammatory drugs; PE pulmonary embolism; RCT randomized controlled trial; RR risk ratio; VTE venous thromboembolism.

[a] If separate models are derived or validated at different time points, the model most closely resembling our systematic review question is reported (underlined). Time horizon reported in this column indicates the model discussed in this table.

[b] If coefficients or assigned points were unavailable, hazard ratios are shown.

[c] If both coefficients and assigned points as used in simple scores are available, points are reported to represent the model as it is recommended for clinical practice.

[d] For internal validation studies, if available, optimism corrected C-statistic from internal validation is reported. For external validation studies, C-statistic for the main model is reported.

[e] The 2012 and 2016 versions of the ACCP bleeding risk score were analyzed together as these differed by one predictor only (use of NSAIDs in the 2016 version) and estimated risks were equal.

validation study [24].

3.4. Risk of bias and applicability

The model derivation studies on the updated Vienna prediction model, pre D-dimer model and post D-dimer model and L-TRRiP model were judged to be at an overall low risk of bias (Appendix Table 4) [19,23,32]. All other studies were scored as high risk of bias, predominantly because of bias in the domain of statistical analysis. Main concerns were handling of missing data (83%), univariable predictor selection (83%), too few outcome events per variable (50%), and not accounting for overfitting (50%). All of the included model validation studies were also judged to be at high risk of bias, again mainly due to concerns regarding the statistical analysis. Similarly, this mainly concerned handling of missing data (88%) and an insufficient number of outcome events (50%).

Applicability to our research question was considered low in all studies except for the score by Huang and colleagues and validation studies of the DASH score and Vienna prediction model by Timp and colleagues, the main reason being that only patients with unprovoked VTE were included rather than a broader population of VTE patients.

3.5. Impact studies

Geersing and colleagues randomized 441 patients with unprovoked VTE to management guided by the Vienna prediction model or usual care (i.e. treatment duration was left at the physician's discretion) [33]. In patients with a predicted annual recurrence risk of below 5% according to the model, the observed annual incidence was 4.4% (95% CI, 2.7–6.9) during a total follow-up of 24 months. The risk of recurrent VTE was comparable between the groups (RR, 0.92; 95% CI, 0.36–1.25), which was consistent when restricting the analysis to compliant patients. Risk of bias assessment (data not shown) indicated concerns regarding possible deviations from the intended intervention as physicians were aware of the assigned intervention. Rodger and colleagues validated the HERDOO2 score in a prospective cohort management study in which 3155 patients with unprovoked VTE were managed based on their HERDOO2 risk score [16]. Observed incidence of recurrence in women at low risk who discontinued anticoagulation according to HERDOO2 (predicted annual risk of <5%) was 3.0% (95% CI, 1.8–4.8), compared to 8.1% (95% CI, 5.2–11.9) in women at high risk and men who discontinued anticoagulation and 1.6% (95% CI 1.1–2.3) in women at high risk and men who continued anticoagulation. This study was scored as low risk of bias according to the ROBINS-I tool (data not shown).

3.6. Prediction of risk of bleeding during anticoagulant treatment

Sixteen studies on predicting bleeding during extended oral anticoagulation for VTE were identified (Fig. 1). As shown in Appendix Table 3, 7 studies reported on model development [4,35–40] and 9 studies performed external validation of one or multiple models [41–49]. The included studies involved 7 prognostic models derived in or developed for patients with VTE (Kuijer et al., RIETE, VTE-BLEED, Hokusai, ACCP, EINSTEIN and Seiler et al.) and 7 models that were validated in a VTE population but derived in a population of patients with anticoagulation for atrial fibrillation or other indications (OBRI, mOBRI, Shireman, HEMORR2HAGES, HAS-BLED, ATRIA and ORBIT). Study populations of the included studies comprised 111 to 132,280 patients with a median study follow-up of 3 to 33 months (Appendix Table 3). Most studies were conducted in Europe or North America, although trials generally included patients from all geographic regions. The majority of the models were developed (5/7 studies) and validated (6/9 studies) to predict major bleeding during oral anticoagulation.

3.7. Predictors in the models

Fig. 2b shows the predictors included in the models for bleeding, stratified by type of population in the derivation study. Overall, anemia (86%), age (86%), history of bleeding (64%) and renal insufficiency (64%) were included in the most models. Selection of predictors was comparable in models developed in patients with VTE or other populations.

3.8. Performance of the prediction models

Model discrimination in development studies was poor to moderate (median C-statistic 0.68; range 0.65–0.75) (Table 1). As expected, discriminative value was lower in external validation (median C-statistic 0.59; range 0.52–0.71). The agreement between predicted and observed risks (calibration) was reported in only one model validation study. The models derived in an atrial fibrillation or mixed anticoagulated population (various indications, including a small proportion of patients with VTE) appeared to discriminate poorly in a VTE population, as demonstrated by C-statistics ranging from 0.52 to 0.71 (median 0.57). Only for the recalibrated HAS-BLED model, discriminative performance was moderate [42]. However, this updated version has not been subject of external validation. Similarly, no external validation studies were identified for the Hokusai and EINSTEIN models [37,38]. Decision analyses were only reported by 2 external validation studies on VTE-BLEED, indicating that management based on VTE-BLEED may be

beneficial compared with current treatment strategies up to a threshold probability of 3–4% (Klok 2017) or 0.5–1.5% (Klok 2018) for major bleeding after day 30 of anticoagulation [43,47]. In model derivation studies as well as most derivation studies, all models were able to identify a group of patients with a high annual risk of bleeding of >6.5%, as suggested by guidelines [4]. A high risk group could not be identified in any of the validation studies for ACCP, OBRI and Shireman.

3.9. Risk of bias and applicability

The included model derivation studies generally had a low risk of bias regarding 'participants', 'predictors', and 'outcome' (Appendix Table 5). With respect to the domain 'statistical analysis', all included derivation studies were judged to be at high risk of bias. In particular 6 (86%) model derivation studies did not appropriately handle continuous predictors, 5 (71%) did not have a sufficient number of outcome events per variable, and 5 (71%) did not account for overfitting. Only one study (ACCP guideline) was considered of low concern regarding applicability to our systematic review question [4]. Other models were derived in a selected trial population in which patients with a high risk of bleeding were generally not included, or during the first 3 months of treatment rather than during extended treatment.

The 9 external validation studies also scored well in the domains 'participants', 'predictors', and 'outcome', but poor in the domain 'statistical analysis'; 8 (89%) studies had an insufficient number of events per variable. Only one external validation study assessed both discrimination and goodness-of-fit [49]. Six external validation studies were considered of low concern regarding applicability [4,41,43,45,46,48–50]. The other studies included a (highly selected) population consisting of trial patients or employed persons only. Therefore, their results may be less applicable when deciding on treatment duration after the initial treatment.

4. Discussion

Eight models for recurrent VTE and 14 models for bleeding developed or validated in patients with VTE after at least 3 months of anticoagulant treatment were identified. None were judged to be at low risk of bias and to have a satisfactory predictive performance in independent external validation. In addition, the majority of the models did not align with the aim of the present investigation by including a selected group of VTE patients. Hence, these findings do not support the use of currently available prediction models to guide duration of anticoagulant treatment.

Three models for recurrent VTE seem promising. L-TRRiP was considered to be at low risk of bias, applicable to the clinical question, and performed well in the development data [19]. DAMOVES performed well in both derivation and validation studies, although there are important concerns regarding risk of bias with respect to the statistical analysis and applicability (i.e. unprovoked VTE only) [21,28]. The post D-dimer model had low risk of bias as well as adequate predictive performance in internal-external cross-validation, but lacks independent external validation and applies to patients with unprovoked VTE only [23]. To assess the potential value of these models for clinical practice, external validation in a population with a sufficient number of outcome events is warranted. Moreover, the included impact studies suggest that, despite risk of bias in model development studies and unsatisfactory performance in external validation, HERDOO2 as well as the Vienna prediction model may be used to identify patients at low risk of recurrence [16,33]. However, this only applies to patients with first unprovoked VTE.

Two previous systematic reviews on prediction models in VTE were identified [52,53]. Being conducted before the new ESC 2019 guideline, both reviews focused on patients with first unprovoked VTE only. One identified all but one of the bleeding models included in the present review (Seiler et al.) [39]. The systematic review by Ensor and colleagues was conducted before publication of L-TRRiP and DAMOVES and used a pilot version of PROBAST [19,21]. Both reviews came to similar conclusions with respect to model performance and risk of bias, although their conclusions were restricted to unprovoked VTE only.

Unlike previous systematic reviews, we evaluated prediction models for patients with VTE using the final version of PROBAST to assess risk of bias and applicability [10]. The identified methodological shortcomings may have contributed to the unsatisfactory model performance. For example, most models did not report how missing data was handled or performed complete case analysis, potentially resulting in biased estimates [10]. Continuous predictors were often dichotomized, which reduces the performance of models [54]. Variables were often selected based on univariate analysis, which does not account for interaction [55]. Most included models did not apply shrinkage to reduce overfitting, resulting in too optimistic results. In addition, differences in study population, eligibility criteria, setting, outcome definitions, and use of predictor substitutions compared to the model development population may be responsible for the reduced discrimination and calibration in external validation studies [56]. This is particularly relevant for models developed in a non-VTE population as well as for validation studies enrolling a selected study population (e.g. elderly or trial patients). Regarding model validation studies, calibration was rarely reported while knowing whether the predicted risk corresponds to the actual risk is essential in practice [57]. C-statistics alone do not provide information on systematic bias in risk predictions. Even when discriminative ability is moderate, a well calibrated model is still useful to identify patients at high or low risk for treatment decisions. A potential explanation is that external validation can only be adequately performed when the prediction model is reported appropriately (e.g. including baseline hazard and range of continuous predictors) which was infrequently the case [58]. Furthermore, decision analysis is warranted to investigate whether implementing a model in clinical practice would positively impact decision-making in clinical practice [59]. Subsequently, an impact study may be conducted to assess whether this leads to improved clinical outcomes. As these studies generally cost substantial time and resources, prediction models should be adequately developed and externally validated, subsequent treatment decisions should have a solid scientific base and the model should be tailored to the new setting if required [60]. Yet, it is important to acknowledge that the true impact of a model is likely to be underestimated by impact studies. A double-blind design is hampered as soon as the prediction model has been published and physicians consciously or subconsciously take the included predictors into consideration in subsequent treatment decisions.

Another concern regards the applicability of the models in clinical practice. To guide decisions on treatment duration, a prediction model should ideally be developed and validated in patients after the initial treatment. However, many studies evaluating risk of bleeding had a follow-up duration of <3 months after the index event. We excluded these studies as the decision to stop or continue anticoagulation is completely different in patients who developed major bleeding early after treatment initiation. In addition, according to the new ESC guideline the decision to stop or continue anticoagulation after the initial 3 months should be made not only in patients with unprovoked VTE but also in those with VTE provoked by minor risk factors [3]. Our findings show that suitable tools are not yet available to follow this recommendation. All but one of the models for recurrent VTE are applicable to patients with unprovoked VTE only, with a variety of definitions.

In line with the ESC guidelines, weighing risks of recurrence and bleeding is essential in (shared) decision-making for all patients. Yet most studies, except for those on L-TRRiP and the models by Ensor and colleagues, developed or validated risk scores to stratify patients into low or high risk rather than predicting actual risks [19,23]. According to impact studies, HERDOO2 and the Vienna prediction model may be useful to identify patients with a low risk of recurrence among those

with unprovoked VTE in whom extended treatment does not need to be considered further. However, this does not provide further guidance for patients at high risk of recurrence. Risk stratification neglects heterogeneity in risks between patients in the same risk category and does not allow to actually weigh risks. A clinical dilemma arises when a patient is considered to be at high risk of both bleeding and recurrent VTE; a likely scenario given the overlap in risk factors (e.g. older age and male sex).

Patients are considered to be at high risk of recurrence when the annual risk of recurrent VTE is 5% or higher based on the ISTH recommendation [34]. However, an annual risk just below 5% may still be considered high, especially when extrapolated to a lifetime. In addition, this threshold should probably be lowered now that DOACs are recommended for treatment of VTE, as these drugs are associated with a significant 40% lower risk of major bleeding and the dose can be reduced after 6 months [5]. Furthermore, a single cut-off to decide about continuation or discontinuation of anticoagulation does not provide enough nuance.

Recently, significant developments have taken place in cardiovascular research with the potential to change the view on risk assessment in patients with VTE. The increasing attention for individualized prediction has resulted in models to estimate absolute effects of cardiovascular preventive treatment for individual patients, allowing for more personalized care [61–63]. The focus is shifting from treating all patients at high risk of an outcome to benefit-based treatment, in which only those who benefit from treatment in absolute terms will be treated [64]. This approach reflects the principle that absolute risk reduction not only depends on relative risks, but even more on baseline risk defined by individual patient characteristics. Along this line, individualized decision-making in patients with VTE is just as important. Clinical decision-making may improve when treatment duration is decided based on an individualized trade-off between absolute recurrence risk reduction and the absolute increase of bleeding risk, which should be the focus of future development studies.

4.1. Limitations

By focusing on methodology and applicability using a structured approach, the present systematic review adds information on the clinical usefulness of currently available prediction models for recurrence and bleeding. It has to be taken into account that PROBAST reflects a new standard for prediction model studies based on the most recent developments in this research field. Many older models therefore were not able to comply with this standard. In addition, PROBAST does not take dependencies between questions into account (e.g. applying shrinkage to reduce potential bias caused by not adhering to other PROBAST items), although considering dependencies would not have altered our final conclusions. Also, PROBAST could not be used to evaluate risk of bias and applicability in the 2 included impact studies. Furthermore, the included studies were heterogeneous regarding study population and follow-up duration. There was considerable heterogeneity across the included studies with respect to reported model performance measures, which complicated data synthesis and precluded meta-analysis. As major bleeding was the primary outcome of most included studies, we were unable to draw conclusions about the performance of the models for CRNMB, which can also be burdensome. For pragmatic reasons, we limited our systematic search to title and keywords only. However, a thorough exploration of references of the included studies only resulted in 3 additional eligible papers. After adjusting the database search to include apparently missing relevant search terms, no other papers were identified.

5. Conclusions

Currently available prediction models for recurrent VTE and bleeding during anticoagulant treatment after VTE often have important methodological limitations and insufficient predictive accuracy, or lack independent external validation. In line with current guidelines, the present findings do not support the use of these models to inform the decision to stop or continue anticoagulant treatment after an initial treatment of at least 3 months in the total VTE population. However, a group at low risk of recurrence may be identified among patients with unprovoked VTE. Future prediction model studies should focus on all patients with VTE beyond the first 3 months of treatment, including those with events provoked by minor risk factors, and adhere to methodological recommendations and reporting guidelines on model development and validation [65].

Addendum

All authors contributed to study conception and design. M.A. de Winter and M. Nijkeuter conducted the search, screened search results and assessed papers for inclusion. M.A. de Winter performed risk of bias assessment and data extraction. All authors interpreted the results. M.A. de Winter drafted the manuscript in close collaboration with N. van Es and M. Nijkeuter. H. R. Büller and F.L.J. Visseren critically revised the manuscript. All authors were responsible for and approved the final version of the manuscript.

Declaration of competing interest

For this activity, the authors have no conflicts to declare.

Appendix A. Supplementary tables

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.12.031.

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