Novel imaging strategies in venous thromboembolism

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CHAPTER

Cost-effectiveness of magnetic resonance imaging for diagnosing recurrent ipsilateral deep vein thrombosis

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ABSTRACT

The diagnostic workup of recurrent ipsilateral deep vein thrombosis (DVT) using compression ultrasonography (CUS) can be complicated by persistent intravascular abnormalities after a previous DVT. We showed that magnetic resonance direct thrombus imaging (MRDTI) can exclude recurrent ipsilateral DVT. However, it is unknown whether the application of MRDTI in daily clinical practice is cost-effective. We aimed to evaluate the cost-effectiveness of MRDTI-based diagnosis for suspected recurrent ipsilateral DVT during first year of treatment and follow-up in the Dutch health care setting.

Patient-level data of the Theia study (NCT02262052), were analyzed in 10 diagnostic scenarios, including a clinical decision rule (CDR) and D-dimer test, and imaging with CUS and/or MRDTI. The total costs of diagnostic tests and treatment during 1-year follow-up, including costs of false-positive and false-negative diagnoses, were compared and related to the associated mortality. The 1-year health care costs with MRDTI (range, €1219 to €1296) were generally lower than strategies without MRDTI (range, €1278 to €1529). This was because of superior specificity, despite higher initial diagnostic costs. Diagnostic strategies including CUS alone and CUS followed by MRDTI in case of an inconclusive CUS were potential optimal cost-effective strategies, with estimated average costs of €1529 and €1263 per patient and predicted mortality of 1 per 737 patients and 1 per 609 patients, respectively. Our model shows that diagnostic strategies with MRDTI for suspected recurrent ipsilateral DVT have generally lower 1-year health care costs than strategies without MRDTI. Therefore, compared to CUS alone, applying MRDTI did not increase health care costs.

INTRODUCTION

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), poses a major health care burden.[1] In the Netherlands alone the costs for VTE management in 2015 was approximately 23 million euros for hospital treatment of almost 25,000 VTE patients, and 14.4 million euros for anticoagulants which increased to 38.2 million euros in 2017 because of the introduction of direct oral anticoagulants (DOACs).[2] The yearly total annual health care costs for VTE in the United States were estimated to be 2 to 10 billion dollars for 300,000-600,000 incident cases.[3] These costs were exclusive of costs for anticoagulant-related bleeding complications and thus true VTE costs are even higher. Therefore, an accurate VTE diagnosis to prevent false-positive diagnosis and subsequent mistreatment is crucial both for individual patients and society as a whole. Notably, the diagnostic management of suspected VTE is still complex in certain settings such as suspected recurrent DVT. The safety of using a clinical decision rule (CDR) in combination with D-dimer testing to rule out recurrent DVT is not established [4,5] and seems not as efficient as in patients with a suspected first DVT episode.[5,6] Moreover, ultrasonographic differentiation of acute recurrent ipsilateral DVT from chronic residual thrombi is difficult, with persisting thrombi being present in up to 50% of patients after 1 year despite adequate treatment.[6-8]

Magnetic resonance direct thrombus imaging (MRDTI) is a non-invasive magnetic resonance imaging technique that directly visualizes acute thrombi.[9] MRDTI has been shown to accurately distinguish acute recurrent DVT from chronic residual thrombotic abnormalities [10-12] and was proven to be an accurate, simple, feasible and reproducible diagnostic test for ruling out acute recurrent ipsilateral DVT.[13] Importantly, compression ultrasonography (CUS), which currently is the imaging test of choice in suspected recurrent DVT, was found to be associated with an excess of false-positive diagnoses of 19% compared to MRDTI [13]. Furthermore, in contrast to MRDTI, the CUS interpretation may vary greatly among radiologists.[14] As MRDTI is more expensive than CUS the cost aspect should also be taken into account when determining the optimal diagnostic strategy.

We set up to perform a 1-year cost-effectiveness analysis of different diagnostic scenarios with or without MRDTI for suspected recurrent ipsilateral DVT, specifically in the Dutch health care setting to better determine the potential role of MRDTI in daily clinical practice.

METHODS

Study population

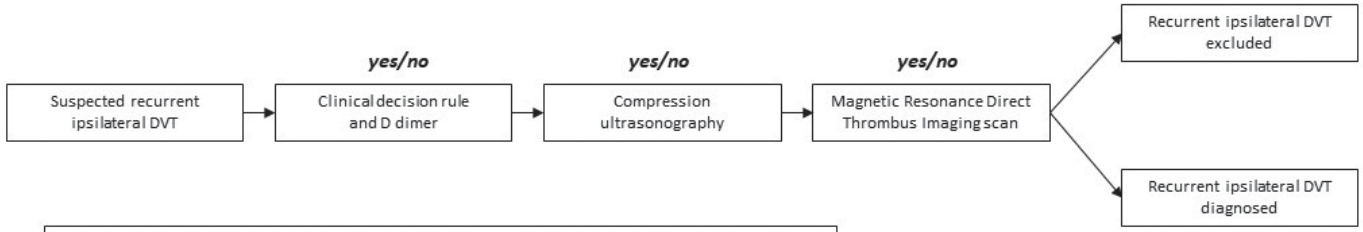
This study was a predefined secondary analysis of the Theia study (NCT02262052), a prospective international multicenter outcome study in which we evaluated the safety of excluding recurrent ipsilateral DVT with MRDTI. The full details of the study design and outcomes have been described previously.[13] In summary, between March 2015 to May 2019 adult patients with suspected recurrent ipsilateral proximal DVT of the lower extremity on or off anticoagulant treatment were managed according the result of the MRDTI scan. Main exclusion criteria were suspected concomitant acute PE, CUS-proven acute DVT within 6 months of presentation and general contra-indications for magnetic resonance imaging. CUS was performed as a reference examination in all patients with a MRDTI negative for DVT to guide diagnostic testing if suspected recurrence occurred during follow-up. Furthermore, the protocol dictated CDR assessment using the original Wells rule and D-dimer testing in all patients. Importantly, CUS, CDR assessment and D-dimer results did not influence management decisions. All included patients were followed for a 3-month period for the occurrence of recurrent VTE (DVT or PE), anticoagulation-associated major bleeding and all-cause mortality. For the current analysis, the results of the Theia study were extrapolated to the Dutch situation, excluding patients who were on anticoagulant treatment ≥48 hours prior to inclusion.

Study objectives and outcomes

The aim of this analysis was to compare the health care costs between 10 diagnostic scenarios for the diagnostic management of suspected recurrent ipsilateral DVT, in relation to the associated mortality. The scenarios included CDR assessment according to the Wells criteria in combination with D-dimer testing, and diagnostic imaging with CUS and/or MRDTI (**Figure 1**). In the scenarios including CUS, results were defined as either normal/abnormal or positive/negative/inconclusive; the latter is only applicable if a reference CUS was available.[15]

The first five scenarios included only diagnostic imaging tests. In the first scenario, MRDTI would have been performed in all patients and anticoagulant treatment

Figure 1. Ten diagnostic scenarios for the diagnostic workup of suspected recurrent ipsilateral deep vein thrombosis (DVT), applying various combinations of a clinical decision rule and D-dimer testing (CDR+DD) and diagnostic imaging with compression ultrasound (CUS) and/or magnetic resonance direct thrombus imaging (MRDTI).



10 diagnostic scenarios:

1. MRDTI only
2. CUS (normal/abnormal) only
3. CUS (positive/negative/inconclusive) only
4. Only CUS (normal/abnormal) in case of a likely CDR and/or abnormal DD
5. Only CUS (positive/negative/inconclusive) in case of a likely CDR and/or abnormal DD
6. Only MRDTI in case of an abnormal CUS
7. Only MRDTI in case of an inconclusive CUS
8. Only MRDTI in case of a likely CDR and/or abnormal DD
9. Only MRDTI in case of a likely CDR and/or abnormal DD and an abnormal CUS
10. Only MRDTI in case of a likely CDR and/or abnormal DD and an inconclusive CUS

would have been started in case of a MRDTI positive for DVT. In the second scenario, all patients would have been referred for CUS, which was either normal or abnormal, and anticoagulant treatment would have been started in case of an abnormal CUS. In the third scenario, CUS would have been performed in all patients, but the results were judged as positive/negative/inconclusive and anticoagulant treatment would have been started in patients with a positive or inconclusive CUS. In the fourth scenario, all patients would have been referred for CUS and MRDTI would be performed in case of an abnormal CUS. Anticoagulant treatment would have been started in patients with a MRDTI positive for recurrent DVT. In the fifth scenario, CUS would have been performed in all patients and only patients with an inconclusive CUS would have been referred for MRDTI. Anticoagulant treatment would have been started based on a positive MRDTI or positive CUS result. In scenario 6 to 10, the combination of CDR assessment and D-dimer testing was added as initial step to scenario 1 to 5. Diagnostic imaging (CUS and/or MRDTI) would only be performed in patients with a likely clinical probability and/or abnormal D-dimer result.

Definitions

A likely clinical probability according the Wells rule was defined as a Wells score of ≥2 points.[16] An abnormal D-dimer test was defined as abnormal according the assay dependent threshold, because this differed between the various assays used in the Theia study. An evaluation of the diagnostic performance of the Wells rule and D-dimer testing in the Theia study was recently published.[17] A normal CUS was defined as full compressibility along the venous system. An abnormal CUS was defined as 1 or more non-compressible venous segments. A positive CUS was defined as a new non-compressible segment or a ≥2-4 mm increase in vein diameter of a previously non-compressible venous segment when compared to a reference CUS. A negative CUS was defined as the absence of a non-compressible segment or the absence of a new non-compressible segment in comparison with a reference CUS and a <2 mm increase in vein diameter of a previously non-compressible vein. An inconclusive CUS was defined as 1 or more non-compressible venous segment(s) in the absence of a reference CUS for comparison. An MRDTI scan positive for acute DVT was defined as a high signal intensity in the location of a deep vein against the suppressed background greater than that observed in the contiguous segments or corresponding ipsilateral vein. Major bleeding

and clinically relevant non-major (CRNM) bleeding were defined according to the *International Society on Thrombosis and Haemostasis* (*ISTH*) criteria.[18,19]

Costs

One-year health care costs are reported in euros at price level of 2019 and included diagnostic, anticoagulant medication, management and bleeding complication costs (**Table 1**). The diagnostic costs included initial admission costs at the emergency department (ED) and costs for basic laboratory measurements for all patients. Depending on the diagnostic scenario, additional costs for the diagnostic tests (D-dimer, CUS and/or MRDTI) were included.

Anticoagulant medication costs for a 1-year period were calculated including the price of the medication itself (including value-added tax) and an additional €6 delivery costs of the medication per regular delivery.[20] Data from IQVIA, a global health care data source company, were used to estimate the proportions of the different types of anticoagulants, including DOACs, vitamin K antagonists (VKAs) and low-molecular weight heparins (LMWHs). For the estimation of the costs of LMWH, the price of Nadroparin was used, since it is the most prescribed LMWH in the Netherlands.[21] Since data of the average body weight in the Theia study population were not available, we used the mean body weight from a recent Dutch study, in which a CDR was evaluated in patients with suspected acute PE.[22]

For the estimation of the management costs, costs for hospital admission, outpatient visits and compression stockings for patients diagnosed with recurrent DVT were calculated. Data on hospital admission rate and duration were not available for the Theia study population. Therefore, hospital admission costs were estimated assuming that 14% of patients diagnosed with recurrent DVT would be hospitalized, for a mean duration of 7.2 days, based on available literature.[23,24] The outpatient visit costs included 2 routine visits which was in accordance with local hospital protocols. We estimated that all patients diagnosed with recurrent DVT (at baseline or during follow-up period) would be treated with (at least) 1 pair of class II compression stockings.

Finally, costs caused by bleeding complications were calculated by multiplying the costs per complication with the estimated risk for bleeding in VKA and DOAC treatment and the estimated number of VKA and DOAC users (**Table 1**). The risk for bleeding in VKA versus DOAC treatment was obtained from previous publications

and was set at 1.7% versus 1.1% for non-intracranial major bleeding, 0.25% versus 0.09% for intracranial bleeding and 8.4% versus 6.6% for CRNM bleeding.[25]

For this analysis, initial diagnostic costs were defined as diagnostic costs including ED admission, and both laboratory and imaging costs for the first hospital presentation. Return diagnostic costs included the costs for ED readmission, and both laboratory and imaging costs for patients returning for repeated diagnostic imaging after a missed DVT diagnosis. The treatment costs were defined as anticoagulant medication costs, management costs and costs for bleeding complications for all patients with recurrent DVT. The overtreatment costs included the anticoagulant medication costs, management costs and costs for bleeding complications for patients who were falsely diagnosed with recurrent DVT.

Decision analytic model

From patient-level data of the Theia study, the prevalence of recurrent ipsilateral DVT was calculated as was the diagnostic accuracy of each test, conditional to the outcome of preceding tests and disease prevalence (**Figure 1**). From these, the true-positive, false-negative, true-negative, and false-positive rates of each of the 10 diagnostic scenarios were estimated. False negative diagnoses (also referred to as misdiagnosis in this analysis) were defined as 1) patients in whom recurrent DVT was excluded based on an unlikely CDR in combination with a normal D-dimer or based on a negative CUS but with a positive MRDTI for recurrent DVT or 2) patients in whom recurrent DVT was excluded based on a negative MRDTI but with recurrent VTE during 3 months of follow-up. False positive diagnoses were defined as patients with a positive or inconclusive CUS, but negative MRDTI for recurrent DVT. For reference, we also assessed scenarios that treat all patients, treat no patients and treat only those patients with a likely CDR and/or abnormal D-dimer (i.e. scenarios without imaging tests). These reference scenarios are hypothetical and do not serve as a realistic or ethically defendable scenarios for clinical practice.

For each scenario, costs of diagnostic tests were counted for the number of patients undergoing the tests. For each true-negative outcome, only the initial diagnostic costs were counted (**Figure 2**). For each true-positive and false-positive outcome additional treatment and overtreatment costs, respectively were counted. For false-negative outcomes, we conservatively made the following three assumptions. First, we assumed that all patients with a false-negative diagnosis would return to the ED for repeated diagnostic testing. Second, the costs of the

Table 1. The total 1-year health care costs, including diagnostic, anticoagulant medication, management and bleeding complication costs

Resources		Specification	Prices, € (2019)	Volume	Percentage	Average costs per patient per year	Source
Diagnostic costs	ED admission		276.61	1.00	100%	276.61	Kanters et al, 2017[40]
	Laboratory test*	Without D-dimer	24.84	1.00	100%	24.84	Kosteninkaart, 2018[41]
		Including D-dimer	34.54	1.00	100%	34.54	Kosteninkaart, 2018[41]
	Radiologic imaging	CUS	107.60	1.00	100%	107.60	Kosteninkaart, 2018[41]
		MRDTI	237.87	1.00	100%	237.87	Kosteninkaart, 2018[41]
Anticoagulant medication costs	DOACS (day)	Apixaban	4.49 the first 7 days, 2.25 thereafter	1.00	17.2%	143.95	Zorginstituut N.[20]
		Rivaroxaban	4.71 the first 21 days, 2.35 thereafter for 6 months, 2.50 thereafter	1.00	53.6%	501.19	Zorginstituut N.[20]
		Dabigatran	2.44, prior 5 day LMWH use	1.00	4.8%	45.23	Zorginstituut N.[20]
		Edoxaban	2.44, prior 5 day LMWH use	1.00	4.8%	45.23	Zorginstituut N.[20]
	VKA (day)		0.09, prior 7-day LMWH use	1.00	17%	17.89	Zorginstituut N.[20]
	LMWH (day)		10.34	1.0	2.6%	0.27	Zorginstituut N.[20]
Management costs	Hospital admission (day)		512.44	7.2	14%	512.44	Kanters et al, 2017[40]
	Outpatient visit		97.19	2.0	100%	194.38	Kanters et al, 2017[40]
	Compression stockings		71.45	1.0	100%	71.45	Steunkousen.nl[42]
Bleeding costs	Non-intracranial major bleeding		5,348.23	1.0	1.14%	60.93	De Jong et al, 2017[43]
	Intracranial bleeding (acute care)		21,759.32	1.0	0.10%	21.87	De Jong et al, 2017[43]
	Intracranial bleeding (long-term care)		62,838.54	1.0	0.10%	63.17	De Jong et al, 2017[43]
	CRNM bleeding		32.62	1.0	6.72%	2.19	De Jong et al, 2017[43]

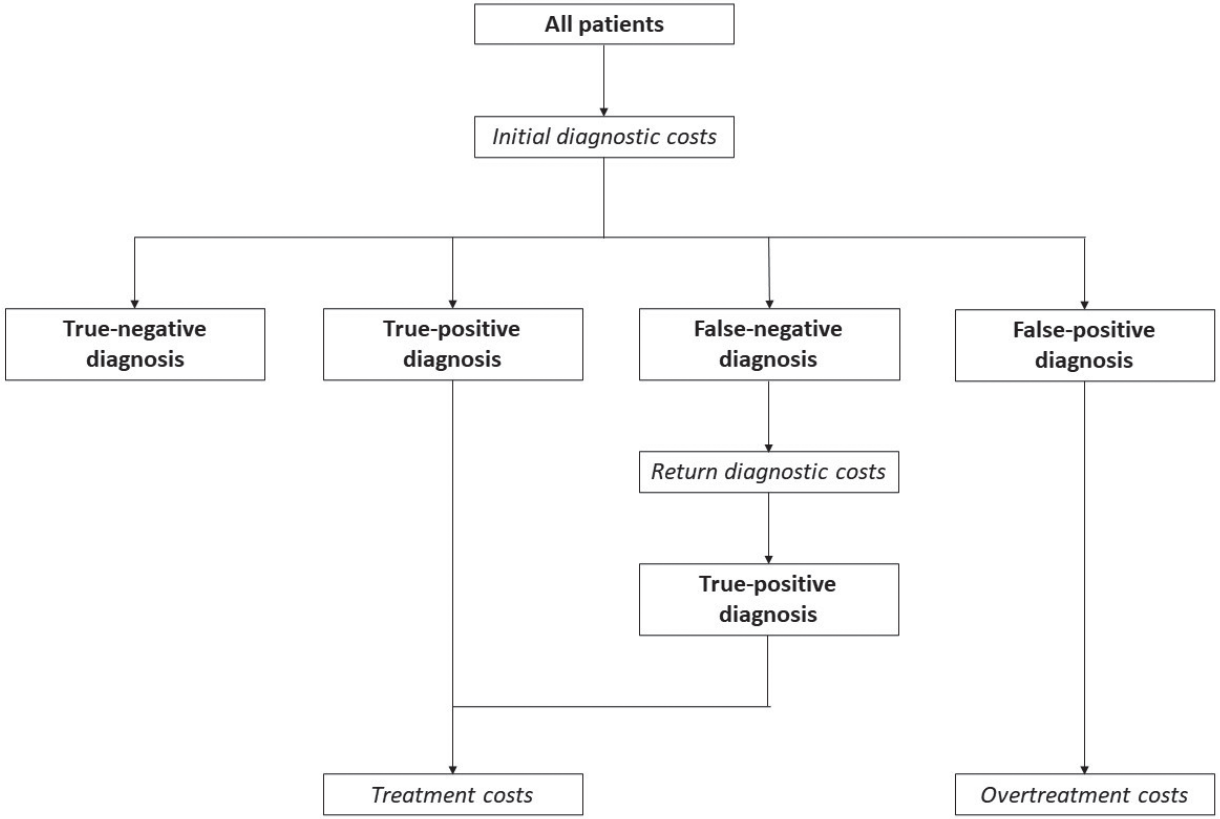
**Laboratory costs included order for collection of blood, hemoglobin/hematocrit and cell indices, leukocytes, thrombocytes, creatine (and estimated glomerular filtration rate), urea, sodium and potassium levels, and bleeding time tests.*

repeated diagnostic testing (i.e. return diagnostic costs) would be the same as at initial presentation, except for the following scenarios: a) in scenarios including CDR assessment and D-dimer testing and radiologic imaging (CUS and/or MRDTI) were only repeated radiological testing would be performed and b) in scenarios including MRDTI after CUS were only repeated CUS would be performed. And thirdly, we assumed that all patients with an initial false-negative diagnosis would have a true-positive diagnosis at the repeated diagnostic testing and thus included treatment costs as for models were a true-positive diagnosis was made.

The mortality risk included three types of mortality: 1) mortality from misdiagnosis, 2) from recurrent fatal PE and 3) from anticoagulant-related bleeding.1) For the mortality risk associated with misdiagnoses, we considered the probability of death for the time period between the false-negative diagnosis and the moment of the true-positive diagnosis, using the exact timelines observed in the Theia study. This was estimated as a fixed 2.05% of the number of false-negative diagnoses, i.e. obtained from previous publications that 50% of the patients with DVT would have asymptomatic PE and 4.1% of all PEs is fatal [26-30]. 2) The mortality risk as a result of recurrent fatal PE during 1-year follow-up period was calculated for patients with a false-positive, true-positive or initial false-negative and true-negative diagnosis. 2a) The risk for mortality from recurrent fatal PE in patients with a false-positive diagnosis was set as 0.0%, as the risk for fatal PE in patients with no recurrent DVT at baseline, but who were falsely treated with anticoagulants is estimated to be negligible. 2b) The risk for mortality from recurrent fatal PE during anticoagulant treatment in patients with a true-positive diagnosis and an initially false-negative diagnosis was set at 0.07%, which was obtained from previous publications.[25] 2c) Mortality as result of recurrent fatal PE in true-negative patients without anticoagulant treatment was estimated as 0.18%, also obtained from previous studies.[31,32] 3) The mortality risk as a result of bleeding related to anticoagulant treatment was estimated as 0.07% of the number of those treated with anticoagulants (i.e. true-positives, false-negatives and false-positives), including 0.06% among DOAC users versus 0.17% among VKA users.[25]

For each diagnostic scenario, the estimated 1-year health care costs were plotted against the estimated mortality. Diagnostic scenarios with costs and mortality equal or higher than other scenarios were not considered cost-effective.[33] The remaining scenarios constitute the efficient frontier, i.e. the set of potentially most cost-effective strategies. For these scenarios incremental cost-effectiveness ratios (ICERs) were calculated, defined by the difference in costs divided by the difference in mortality. The estimated costs per-prevented-death ratios were used

Figure 2. Flowchart of diagnostic and (over)treatment costs for each diagnosis



to select the optimal scenario. In the Netherlands, interventions are considered cost-effective up to 20,000 to 80,000 euros per quality-adjusted life years (QALY).[34] Assuming a quality-adjusted life expectancy of about 25 years in our population, these thresholds translates to 0.5 to 2 million euros per prevented death.[35,36] Microsoft Excel (2016) was used to perform all analyses.

RESULTS

Study patients

The Theia study flowchart was described in previous publications from the Theia study.[13,17] A total of 234 patients were included in this analysis, excluding 71 patients for the following reasons: therapeutic anticoagulant treatment ≥48 hours prior to presentation (n=68), inconclusive MRDTI because of artefacts (n=1), MRDTI not performed because of claustrophobia (n=1) and protocol deviation (n=1). The baseline characteristics of the study population are shown in **Table 2**. The DVT prevalence (baseline and 3-months follow-up combined) was 43% (100/234). The diagnostic accuracy of each test, depending on preceding tests, are reported in **Table 3**.

Table 2. Baseline characteristics of 234 patients with suspected recurrent ipsilateral deep vein thrombosis included in this analysis.

Characteristics	*Data*
Mean age (+/- SD) – years	56 (16)
Male – no (%)	110 (47)
Median duration of complaints (IQR) – days	4 (2-7)
More than 1 prior VTE episode – no (%)	50 (21)
Mean time since the last DVT episode (+/- SD) – years	6.9 (9.2)
Active malignancy – no (%)	10 (4.3)
Immobility for >3 days or recent long travel >6 hours in the past 4 weeks – no (%)	15 (6.4)
Trauma/surgery during the past 4 weeks – no (%)	9 (3.8)
Hormone (replacement) therapy – no (%)	5 (2.1)
Known genetic thrombophilia – no (%)	19 (8.1)

Table 3. Average 1-year health care costs and mortality for 10(+3) diagnostic scenarios for the diagnostic workup of suspected recurrent ipsilateral deep vein thrombosis (DVT).

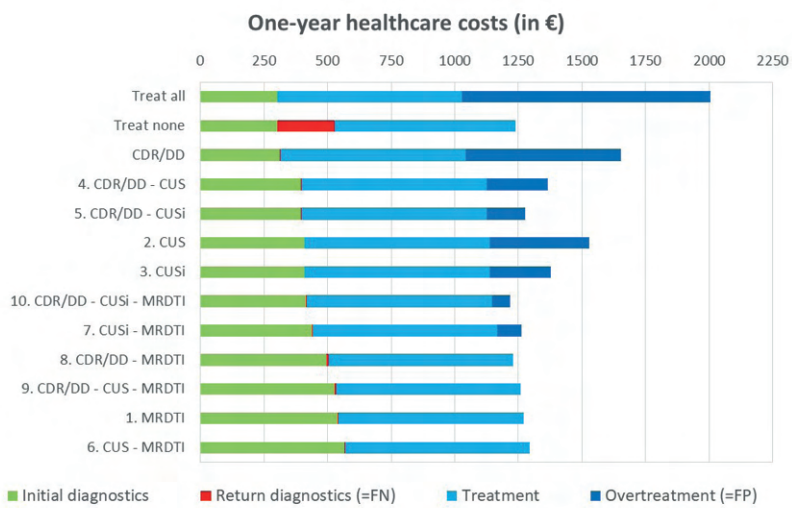
Diagnostic scenario	Sensitivity (%)	Specificity (%)	Initial diagnostics costs (€) (All patients)	Return diagnostic costs (€) (For FN)	Treatment costs (€) (For TP+FN)	Overtreatment costs (€) (For FP)	Total 1-year healthcare costs (€)	Mortality due to misdiagnosis per 10,000	Mortality recurrent fatal PE per 10,000	Mortality due to bleeding per 10,000	Total mortality per 10,000 patients
Treat all	100	0	301	0	727	975	2004	0	3	7	10
Treat none	0	100	301	225	727	0	1239	88	13	3	104
CDR+DD	98	37	311	5	727	611	1654	2	7	5	14
1. MRDTI	98	100	539	5	727	0	1271	2	13	3	18
2. CUS	100	60	409	0	727	393	1529	0	9	4	14
3. CUSi	99	75	409	2	727	240	1378	1	11	4	15
4. CDR+DD-CUS	98	75	395	3	727	240	1365	2	11	4	16
5. CDR+DD-CUSi	98	84	395	3	727	153	1278	2	12	3	17
6. CUS-MRDTI	98	100	566	3	727	0	1296	2	13	3	18
7. CUSi-MRDTI	99	90	440	2	727	95	1263	1	12	3	16
8. CDR+DD-MRDTI	97	100	496	7	727	0	1230	3	13	3	19
9. CDR+DD-CUS-MRDTI	97	100	528	5	727	0	1260	3	13	3	19
10. CDR+DD-CUSi-MRDTI	98	93	415	3	727	73	1219	2	13	3	17

CDR+DD, clinical decision rule + D-dimer testing; CUSi, compression ultrasonography is positive, negative, or inconclusive; FN, false negatives; TP, true positive; FP, false positive.

Costs

The estimated total 1-year health care costs per patient for all diagnostic scenarios are shown in **Figure 3** and **Table 3**. Although MRDTI itself is more expensive than CUS, health care costs of diagnostic management strategies including MRDTI (range €1219 to €1296) were calculated to be comparable or lower than diagnostic strategies without MRDTI (range €1278 to €1529) because of superior specificity (sensitivity, 97-99% vs 98-100%; specificity, 90-100% vs 60-84%).

Figure 3. One-year health care costs per patient for the 10 diagnostic scenarios, and a scenario to treat all, treat none and treat those with a likely clinical probability and/or abnormal D-dimer without diagnostic imaging.



CDR+DD, clinical decision rule + D-dimer testing; CUSi, compression ultrasonography is positive, negative, or inconclusive; FN, false negatives; FP, false positives.

When CDR and D-dimer testing were applied as initial diagnostic tests, health care costs were lower, even considering the higher false negative rate. This could be explained by the lower initial diagnostic costs, because of decreased imaging costs, and the lower false-positive rate. The diagnostic strategy including CDR and D-dimer testing, CUS and subsequent MRDTI in case of an inconclusive CUS was associated with the lowest 1-year health care costs of €1219 (scenario 10). The diagnostic strategy including CUS (normal/abnormal) and treatment in all patients

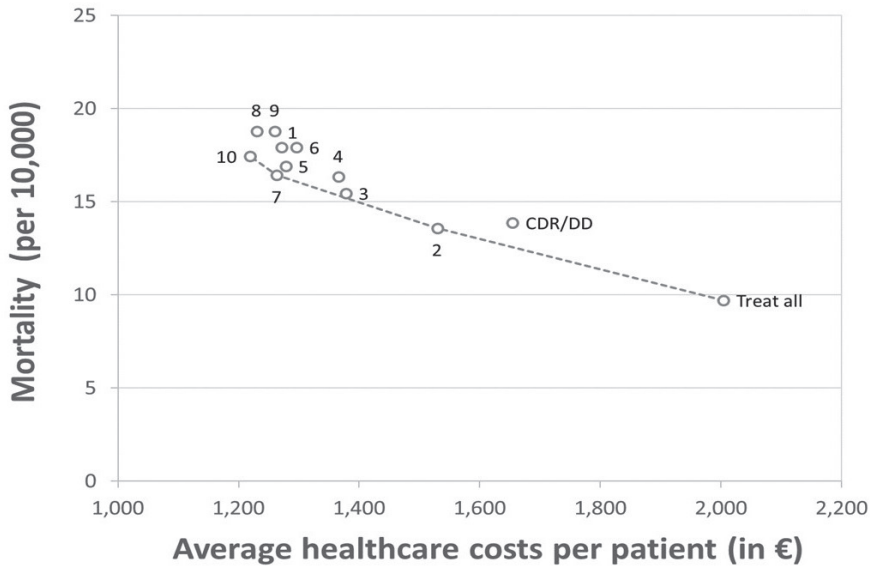
with an abnormal CUS (scenario 2) would be the most expensive strategy (1-year health care costs of €1529), because of high false-positive rates. Notably, the most and least expensive strategy differed for only €320, which is a relatively limited difference.

Cost-effectiveness

The estimated total 1-year health care costs of each diagnostic scenario were plotted against the predicted mortality per 10,000 patients (**Figure 4** and **Table 3**). Strategies at the bottom left of the figure are optimal, with low costs and low mortality. The diagnostic strategy that treats all patients had the lowest predicted mortality (1 per 1029 patients), but with highest estimated total health care costs. Four diagnostic scenarios were on the efficient frontier and thus potentially the most cost-effective strategies: CDR and D-dimer testing followed by CUS (positive/negative/inconclusive) and MRDTI (scenario 10), CUS (positive/negative/inconclusive) followed by MRDTI (scenario 7), CUS (normal/abnormal) alone (scenario 2) and the treat all scenario. All other strategies were dominated, with either higher health care costs or higher mortality.

Of the four scenarios on the efficient frontier, diagnostic scenario 10 has the lowest estimated costs of on average €1219 per patient with a predicted mortality of about 1 per 573 patients. Compared to this scenario 10, diagnostic scenario 7 increases average costs by €45 per patient and reduces mortality to 1 per 609 patients. The associated ICER for scenario 7 versus 10 is 0.4 million euros per prevented death. Scenario 2 further increases average costs by €266 per patient and decreases the predicted mortality to 1 per 737 patients. Here, the associated ICER of scenario 2 versus 7 is 0.9 million euros per prevented death. In the treat all scenario the average cost per patient further increases with €475 compared to scenario 2, while the estimated mortality decreases to 1 per 1029 patients. The associated ICER of the treat all scenario versus scenario 2 is 1.2 million euros per prevented death. For an acceptability threshold of 0.5 to 2 million euros per prevented death, scenario 10 is discarded, because scenario 7 provides lower mortality at acceptable costs (as $0.4 < 0.5$ million). Thus, scenarios 7 and 2 and the treat all scenario remain as potentially optimal strategies (as $0.5 < 0.9 < 1.2 <$ 2 million).

Figure 4. Cost-effectiveness plane and efficient frontier (dashed lines) indicating the possibly cost-effective options among the 10 diagnostic scenarios and a scenario to treat all, treat none and treat those with a likely clinical probability and/or abnormal D-dimer without diagnostic imaging (depending on willingness to pay to prevent mortality)**.**



DISCUSSION

Our aim of this analysis was to compare the estimated total 1-year health care costs in the Dutch clinical setting between different diagnostic scenarios in case of suspected recurrent ipsilateral DVT, in relation to the associated predicted mortality. We found that diagnostic strategies applying MRDTI have comparable or higher diagnostic accuracy at generally lower 1-year health care costs. Moreover, the diagnostic strategy including CUS followed by MRDTI in case of an inconclusive CUS was a potential optimal cost-effective strategy. The diagnostic strategies including CUS alone and treat all were also potential optimal strategies, but the treat all scenario is not realistic or ethically defendable for clinical practice.

Recently, MRDTI was proven to be an accurate, simple, feasible and reproducible diagnostic test in suspected recurrent ipsilateral DVT.[13] Even so, as a MRDTI scan is more expensive and less available than a CUS examination, hospitals may choose diagnostic strategies with CUS over strategies including MRDTI. Our model shows

that the total health care costs of strategies including MRDTI were comparable or even lower compared to strategies without MRDTI. Savings on treatment costs resulted from the higher specificity of MRDTI and thus less false-positive diagnoses compared to CUS. This was also found in previous publications in which CUS could not exclude recurrent DVT in 30% of patients with suspected recurrent ipsilateral DVT[7,13], resulting in overtreatment and subsequent risk for major bleeding.

Strengths and limitations

This study presents a cost-effectiveness model in which detailed estimation of patient-level costs for different diagnostic strategies are calculated. The strength of this analysis is the use of a large patient cohort to estimate the diagnostic accuracy of each test and estimate the true-positive, false-negative, true-negative, and false-positive rate of each of the 10 diagnostic scenarios. Moreover, the original study included an accurate follow-up of the included patients and adjudication of endpoints by an independent committee. Therefore, we believe that this analysis provides an accurate overview of the total health care costs in different diagnostic strategies for a Dutch health care setting.

Our model has also limitations especially since the validity and robustness of the model is depending on the impact of uncertainties in key input parameters. First, the results must be interpreted within the framework and limitation of findings of the Theia study. One of these limitations is that Theia study included a relatively limited number of patients resulting in broad confidence interval of the primary outcome. Moreover, this was a management study in which a cohort of patients followed a study algorithm in which they were subjected and treated according the MRDTI result and not according CDR, D-dimer and CUS results. Also, D-dimer levels and CUS results were not available for all patients. Even so, since few limiting exclusion criteria were applied in the Theia study, the presented results of the current study are more generalizable to a broad patient population than those from a randomized controlled trial.

Second, accurate mortality estimates could not be obtained from our Theia cohort, as none of the patients died from a missed diagnosis, recurrent fatal-PE or anticoagulant-related bleeding. We therefore estimated these risks from available literature, but this resulted in some counter-intuitive estimates: anticoagulation treatment was optimal even for true negative patients, as the 0.18% decrease in recurrent PE mortality outweighed the 0.07% bleeding mortality from

anticoagulation treatment. It is possible that the mortality risk as a result of anticoagulant-related bleeding is underestimated, as this was extrapolated from randomized controlled trials that included low-risk patients. As a result, the treat all strategy provided the lowest possible mortality in our analysis. Nevertheless, we do not consider this strategy a good advice.

Third, long-term complications of a missed DVT, including post-thrombotic syndrome (PTS), chronic thrombo-embolic pulmonary hypertension (CTEPH) and post-PE syndrome due to delayed or total lack of anticoagulant treatment, were not included in the analyses.[37-39] The reason is difficulty in estimating the impact of these long-term complications on health care costs.

Fourth, we estimated costs per prevented death, whereas in the Netherlands only threshold for costs per QALY are used. These QALY thresholds roughly translate to 0.5 to 2 million euros per prevented death in our population. Based on this range of acceptability thresholds the diagnostic scenarios including CUS alone, CUS followed by MRDTI in case of an inconclusive CUS and treat all were potential optimal strategies.

Finally, this analysis was based on a Dutch health care setting and health care costs for DVT may vary by country. Also, the hospital length of stay (LOS) may differ in other settings. For the current analysis, LOS was based on available literature which included no studies specifically in patients with suspected recurrent DVT. It is therefore possible, that the true LOS is higher due to higher comorbidity rate in suspected recurrent DVT patients compared to patients with suspected first DVT episode. On the other hand, most studies were performed before the DOAC era and thus LOS in these studies may be longer due to routine laboratory monitoring and injectable bridging therapy in anticoagulant management with LMWHs and VKA's. We performed a sensitivity analysis to compare the total health care costs in the setting with 3 hospitalization days instead of 7.2 days and did not find relevant differences.

Clinical implications

What is the relevance of our findings for clinical practice? First, our model shows that there is a very small difference in the total 1-year health care costs between the different diagnostic scenarios. In contrast to what many clinicians may believe, strategies including MRDTI were not more expensive than strategies without

MRDTI but had comparable or higher diagnostic certainty. Importantly, due to uncertainty of the risk for recurrent VTE, bleeding and mortality at long-term, we did not calculate the total health care costs >1 year. Even so, the results would then be even more favorable for strategies including MRDTI, with a lower false-positive rate, since patients diagnosed with recurrent DVT are often treated with lifelong anticoagulants with subsequent risk for bleeding. This result, in the view of this detailed cost-effectiveness analysis, is an argument to incorporate the MRDTI scan in local protocols and international guidelines for the diagnostic work-up of suspected recurrent ipsilateral DVT in daily clinical practice. Since we did not directly compare the different strategies prospectively and had to base the model on several assumptions, we cannot determine which one would be the best strategy. Our analysis does however suggest to omit costs as a reason to dismiss the use of MRDTI in the diagnostic management of suspected recurrent ipsilateral DVT.

In conclusion, our analysis shows that the diagnostic strategies involving MRDTI for suspected recurrent ipsilateral DVT have comparable or lower total 1-year health care costs, compared to strategies without MRDTI. Therefore, compared to CUS alone, applying MRDTI in clinical practice will not increase health care costs.

REFERENCES

1. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. *Arterioscler Thromb Vasc Biol*. 2014;34(11):2363-2371.
2. Zorginstituut Nederland. Screeningsrapport Systematische analyse Bloed- en immuunziekten Zinnige Zorg. [Available from: https://www.zorginstituutnederland.nl/publicaties/rapport/2019/04/23/zinnige-zorg---rapport-screeningsfase-bloed--en-immuunziekten]. (January, 22, 2021)
3. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. *Am J Prev Med*. 2010;38(4 Suppl):S495-501.
4. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*. 2018;2(22):3226-3256.
5. Ageno W, Squizzato A, Wells PS, Buller HR, Johnson G. The diagnosis of symptomatic recurrent pulmonary embolism and deep vein thrombosis: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2013;11(8):1597-1602.
6. Barco S, Konstantinides S, Huisman MV, Klok FA. Diagnosis of recurrent venous thromboembolism. *Thromb Res*. 2018;163:229-235.
7. Tan M, Velthuis SI, Westerbeek RE, V. A. N. Rooden C, Van Der Meer F, Huisman MV. High percentage of non-diagnostic compression ultrasonography results and the diagnosis of ipsilateral recurrent proximal deep vein thrombosis. *J Thromb Haemost*. 2010;8(4):848-850.
8. Piovella F, Crippa L, Barone M, et al. Normalization rates of compression ultrasonography in patients with a first episode of deep vein thrombosis of the lower limbs: association with recurrence and new thrombosis. *Haematologica*. 2002;87(5):515-522.
9. Moody AR. Magnetic resonance direct thrombus imaging. *J Thromb Haemost*. 2003;1(7):1403-1409.
10. Tan M, Mol GC, Rooden van CJ, et al. Ability of magnetic resonance direct thrombus imaging (MRDTI) to differentiate acute recurrent ipsilateral deep vein thrombosis from residual thrombosis. *Blood*. 2014(124(4)):623-627.
11. Klok FA, Pruefer D, Rolf A, Konstantinides SV. Magnetic resonance direct thrombus imaging for pre-operative assessment of acute thrombosis in chronic thromboembolic pulmonary hypertension. *Eur Heart J*. 2019;40(11):944.
12. Klok FA, Tan M, Huisman MV. Letter by Klok et al Regarding Article, "18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Enables the Detection of Recurrent Same-Site Deep Vein Thrombosis by Illuminating Recently Formed, Neutrophil-Rich Thrombus". *Circulation*. 2015;131(24):e530.
13. van Dam LF, Dronkers CEA, Gautam G, et al. Magnetic resonance imaging for diagnosis of recurrent ipsilateral deep vein thrombosis. *Blood*. 2020;135(16):1377-1385.

14. Linkins LA, Stretton R, Probyn L, Kearon C. Interobserver agreement on ultrasound measurements of residual vein diameter, thrombus echogenicity and Doppler venous flow in patients with previous venous thrombosis. *Thromb Res*. 2006;117(3):241-247.
15. Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. *J Thromb Haemost*. 2013;11(3):412-422.
16. Wells PS, Hirsh J, Anderson DR, et al. Accuracy of clinical assessment of deep-vein thrombosis. *Lancet*. 1995;345(8961):1326-1330.
17. van Dam LF, Gautam G, Dronkers CEA, et al. Safety of using the combination of the Wells rule and D-dimer test for excluding acute recurrent ipsilateral deep vein thrombosis. *J Thromb Haemost*. 2020.
18. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.
19. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.
20. Zorginstituut Nederland. Medicijnkosten. [Available from: https://www.medicijnkosten.nl/]. (January, 22, 2021)
21. Federatie van Nederlandse Trombosediensten. Samenvatting Medische jaarverslagen. [Available from: https://www.fnt.nl/algemeen/jaarverslagen]. (January, 22, 2021)
22. van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet*. 2017;390(10091):289-297.
23. Mansour S, Alotaibi G, Wu C, McMurtry MS. Trends in admission rates and in-hospital stay for venous thromboembolism. *Thromb Res*. 2017;156:149-154.
24. Dentali F, Di Micco G, Giorgi Pierfranceschi M, et al. Rate and duration of hospitalization for deep vein thrombosis and pulmonary embolism in real-world clinical practice. *Ann Med*. 2015;47(7):546-554.
25. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost*. 2014;12(3):320-328.
26. Huisman MV, Büller HR, ten Cate JW, et al. Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. *Chest*. 1989;95(3):498-502.
27. Bikdeli B, Wang Y, Jimenez D, et al. Pulmonary Embolism Hospitalization, Readmission, and Mortality Rates in US Older Adults, 1999-2015. *Jama*. 2019;322(6):574-576.
28. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. *Nat Rev Dis Primers*. 2018;4:18028.

29. Barco S, Mahmoudpour SH, Valerio L, et al. Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO Mortality Database. *Lancet Respir Med*. 2020;8(3):277-287.
30. Barco S, Valerio L, Ageno W, et al. Age-sex specific pulmonary embolism-related mortality in the USA and Canada, 2000-18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database. *Lancet Respir Med*. 2020.
31. van der Wall SJ, van der Pol LM, Ende-Verhaar YM, et al. Fatal recurrent VTE after anticoagulant treatment for unprovoked VTE: a systematic review. *Eur Respir Rev*. 2018;27(150).
32. Douketis JD, Gu CS, Schulman S, Ghirarduzzi A, Pengo V, Prandoni P. The risk for fatal pulmonary embolism after discontinuing anticoagulant therapy for venous thromboembolism. *Ann Intern Med*. 2007;147(11):766-774.
33. Mühlbacher AC, Sadler A. The Probabilistic Efficiency Frontier: A Framework for Cost-Effectiveness Analysis in Germany Put into Practice for Hepatitis C Treatment Options. *Value Health*. 2017;20(2):266-272.
34. Zorginstituut Nederland. Cost-effectiveness in practice. [Available from: https://english.zorginstituutnederland.nl/publications/reports/2015/06/16/cost-effectiveness-in-practice]. (January, 22, 2021)
35. Opendata. Central Bureau voor Statistiek (CBS), StatLine. Gezonde levensverwaching; vanaf 1981. [Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/71950ned/table?ts=1600339908339]. (January, 22, 2021)
36. M MV, K MV, S MAAE, de Wit GA, Prenger R, E AS. Dutch Tariff for the Five-Level Version of EQ-5D. *Value Health*. 2016;19(4):343-352.
37. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. *Blood Rev*. 2014;28(6):221-226.
38. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J*. 2017;49(2).
39. Rabinovich A, Kahn SR. How I treat the postthrombotic syndrome. *Blood*. 2018;131(20):2215-2222.
40. Kanters TA, Bouwmans CAM, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. *PLoS One*. 2017;12(11):e0187477.
41. Simonneau G, D'Armini AM, Ghofrani HA, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). *Eur Respir J*. 2015;45(5):1293-1302.
42. Fukui S, Ogo T, Goto Y, et al. Exercise intolerance and ventilatory inefficiency improve early after balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. *Int J Cardiol*. 2015;180:66-68.

43. de Jong LA, Dvortsin E, Janssen KJ, Postma MJ. Cost-effectiveness Analysis for Apixaban in the Acute Treatment and Prevention of Venous Thromboembolism in the Netherlands. *Clin Ther*. 2017;39(2):288-302.e284.