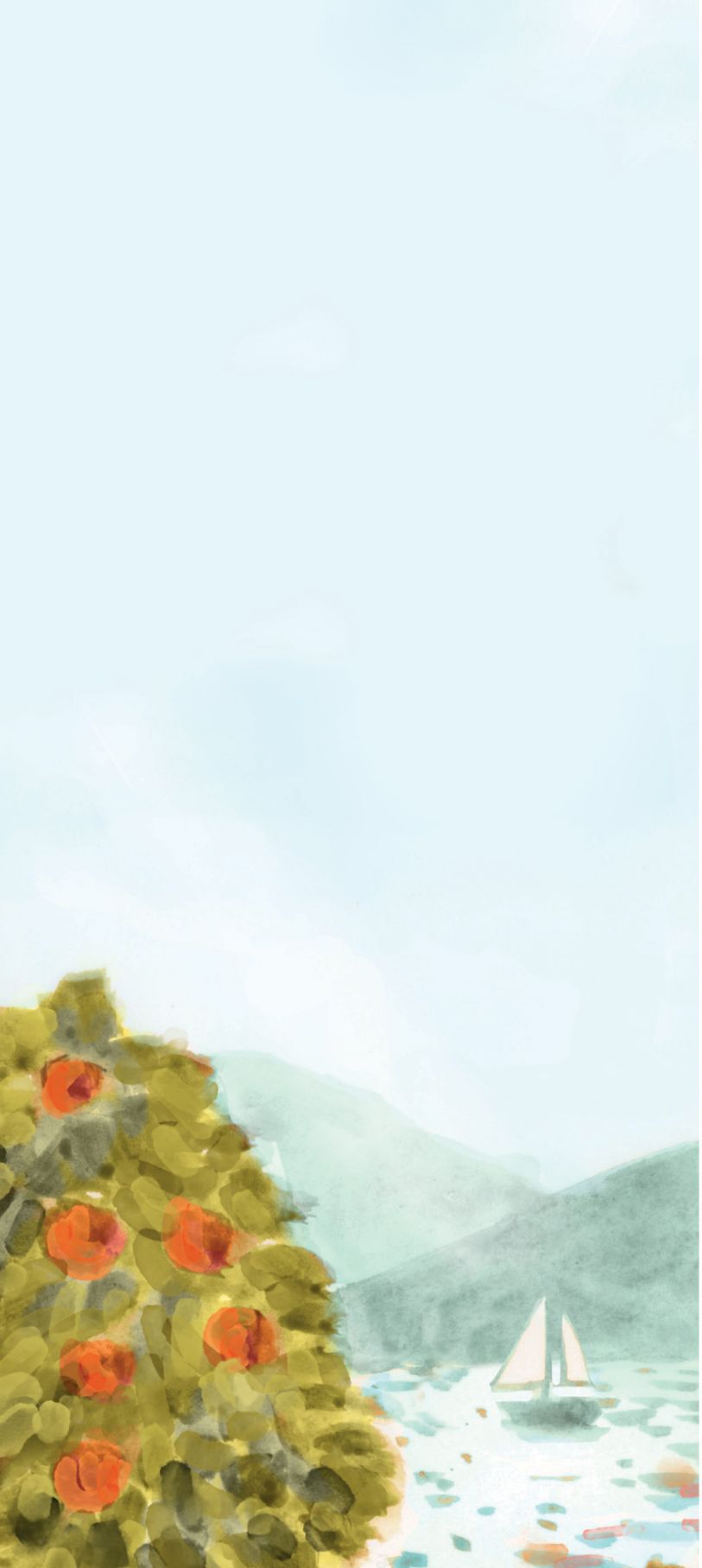
Capturing venous thromboembolism: imaging and outcomes of venous thromboembolism

Jong, C.M.M. de



CHAPTER 4

Cost-effectiveness of performing reference ultrasonography in patients with deep vein thrombosis

Cindy M.M. de Jong, Wilbert B. van den Hout, Christel E. van Dijk, Noor Heim, Lisette F. van Dam, Charlotte E.A. Dronkers, Gargi Gautam, Waleed Ghanima, Jostein Gleditsch, Anders von Heijne, Herman M.A. Hofstee, Marcel M.C. Hovens, Menno V. Huisman, Stan Kolman, Albert T.A. Mairuhu, Thijs E. van Mens, Mathilde Nijkeuter, Marcel A. van de Ree, Cornelis J. van Rooden, Robin E. Westerbeek, Jan Westerink, Eli Westerlund, Lucia J.M. Kroft, Frederikus A. Klok

Thromb Haemost. 2024 Jun; 124(6):557-567

Abstract

Background The diagnosis of recurrent ipsilateral deep vein thrombosis (DVT) with compression ultrasonography (CUS) may be hindered by residual intravascular obstruction after previous DVT. A reference CUS, an additional ultrasound performed at anticoagulant discontinuation, may improve the diagnostic work-up of suspected recurrent ipsilateral DVT by providing baseline images for future comparison.

Objectives To evaluate the cost-effectiveness of routinely performing reference CUS in DVT patients.

Methods Patient-level data (n=96) from a prospective management study (Theia study; NCT02262052) and claims data were used in a decision analytic model to compare 12 scenarios for diagnostic management of suspected recurrent ipsilateral DVT. Estimated health care costs and mortality due to misdiagnosis, recurrent venous thromboembolism, and bleeding during the first year of follow-up after presentation with suspected recurrence were compared.

Results All six scenarios including reference CUS had higher estimated 1-year costs (€1763-€1913), than the six without reference CUS (€1192-€1474). Costs were higher because reference CUS results often remained unused, as 20% of patients (according to claims data) would return with suspected recurrent DVT. Estimated mortality was comparable in scenarios with (14.8-17.9 per 10,000 patients) and without reference CUS (14.0-18.5 per 10,000). None of the four potentially most desirable scenarios included reference CUS.

Conclusion One-year health care costs of diagnostic strategies for suspected recurrent ipsilateral DVT including reference CUS are higher compared to strategies without reference CUS, without mortality benefit. These results can inform policymakers regarding use of health-care resources during follow-up after DVT. From a cost-effectiveness perspective, the findings do not support the routine application of reference CUS.

Introduction

The diagnosis of recurrent ipsilateral deep vein thrombosis (DVT) with compression ultrasonography (CUS) may be hampered by residual venous obstruction after a previous DVT. Residual venous obstruction has been reported in 70 to 80% of patients with DVT after 3 months of anticoagulant treatment, and in 40 to 50% of patients at 12 months following the initial event.[1-4] When a patient presents with ipsilateral recurrent symptoms, a diagnostic dilemma can occur where it is impossible to determine whether a visualized obstruction is new or represents residual clot. As a result, non-diagnostic inconclusive CUS has been reported in up to 32% of patients with suspected recurrent ipsilateral DVT, which likely leads to overdiagnosis and overtreatment.[5,6] The application of reference compression ultrasound in daily clinical practice has the potential to improve the diagnostic work-up in patients with suspected recurrent ipsilateral DVT.[5] A reference compression ultrasound is an additional CUS performed directly prior or after discontinuation of anticoagulants in patients diagnosed with and treated for DVT, providing a baseline evaluation at the time of anticoagulant cessation.[5] Obtaining reference imaging after completion of anticoagulant treatment has been shown to help improve the interpretation of diagnostic imaging findings at the time of suspected recurrence, and to lower the proportion of patients with an inconclusive diagnosis of recurrence.[3, 7, 8] Another non-invasive technique that could contribute to achieving an ultimate diagnosis is magnetic resonance direct thrombus imaging (MRDTI), which can be used to visualize the metabolism of a fresh thrombus and differentiate acute recurrent ipsilateral DVT from residual thrombosis.[9]

Current international guidelines do not consistently include recommendations on the use of baseline or reference imaging.[10-15] This may be partly explained by the absence of reliable cost-effectiveness analyses. For the purpose of the delivery of patient-centered care, with the focus "no more and no less than necessary", the Dutch National Health Care Institute assessed the care pathway for patients with DVT or pulmonary embolism (PE) within the framework of the "Appropriate Care" program and described potential improvements.[16] One of the knowledge gaps reported during the program is that the value of using reference imaging is not yet sufficiently understood. There is no consensus on the use and type of imaging to provide a baseline situation and current Dutch guidelines thus do not include specific recommendations.[16] In addition, claims data analysis showed that there is considerable variation between Dutch hospitals in providing such reference ultrasound examinations, ranging from 0% up to 35%.[17]

With the current study, we set out to perform a cost-effectiveness analysis of different diagnostic scenarios for suspected recurrent ipsilateral DVT, with and without reference CUS as part of the scenarios, in order to compare health care costs

and mortality in the Dutch health care setting between the diagnostic scenarios for suspected recurrent ipsilateral DVT during the first year of treatment and follow-up after presentation with suspected recurrence.

Methods

Data sources

For this cost-effectiveness analysis, patient-level data of the Theia study (NCT02262052), analyses on claims data from all Dutch health insurers, and data from the literature were used in a decision analytic model.

The Theia study was a prospective international multicentre diagnostic management study evaluating the safety of excluding recurrent ipsilateral DVT with MRDTI.[6] Adult patients with suspected recurrent ipsilateral DVT of the leg were managed according to the MRDTI result. Patients were followed during a period of 3 months to assess the occurrence of recurrent venous thromboembolism (VTE), major bleeding and all-cause mortality. The design, study population and results of the Theia study have been described thoroughly in previous publications.[6,18] Patients who received therapeutic anticoagulant treatment ≥48 hours prior to inclusion in the Theia study were excluded from the current analysis, since the estimation of mortality risks and costs in the model is not applicable to this patient group.

To estimate how often reference CUS is performed in Dutch hospitals in patients who were diagnosed with DVT, analyses on claims data were used from all Dutch health insurers, provided by the centre for information of Dutch health insurers, Vektis.[17] Data on lower extremity ultrasound examinations after diagnosis of DVT in combination with the Diagnosis-Treatment Combinations (DTCs) that these ultrasounds were linked to were collected from the year 2016. Lower extremity ultrasound examinations (Dutch health care product code 89070 and 39775) that were linked to a DTC for which (duplex) ultrasonography is expected, such as peripheral artery disease or osteoarthritis, and thus, were likely performed for a different reason than suspected recurrent DVT or as reference imaging after DVT, were excluded from the claims data analysis. Lower extremity ultrasound examinations performed after 3 to 7 months after start of the initial DTC were assumed to be reference ultrasound examinations. Lower extremity ultrasound examinations in the period of 7 months to 3 years after start of the initial DTC were assumed to be performed because of suspected recurrent DVT. These data were used to estimate the proportion of DVT patients presenting with suspected recurrent DVT and the proportion of patients with suspected recurrent DVT returning to the same hospital as during the previous DVT episode, i.e. the hospital where reference CUS could have been performed after discontinuation of anticoagulant therapy. Given the proportion of patients

with suspected recurrent DVT visiting the same hospital, we estimated the availability and actual use of reference CUS in case a reference CUS was performed.

Objective

The aim of this study was to compare the health care costs and mortality between diagnostic scenarios for management of suspected recurrent ipsilateral DVT during the first year of treatment and follow-up after presentation with suspected recurrence. By directly comparing hypothetical scenarios with and without reference CUS, we aimed to confirm whether the application of reference CUS is cost-effective or whether diagnostic strategies without the use of reference CUS would be more desirable. The scenarios were assessed using the decision analytic model that was set up for a previous cost-effectiveness analysis, which was a predefined secondary analysis of the Theia study evaluating the cost-effectiveness of MRDTI for diagnosis of recurrent ipsilateral DVT.[19]

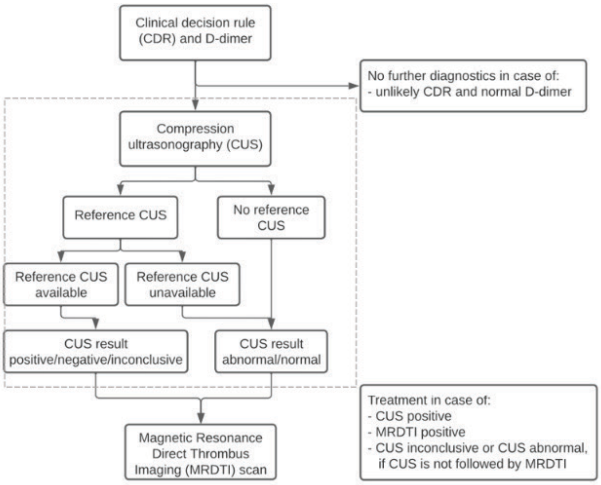
Diagnostic scenarios

The scenarios included clinical decision rule (CDR) assessment combined with D-dimer test, and imaging with CUS performed by the radiologist at the moment of suspected recurrent ipsilateral DVT and/or MRDTI, with or without a performed reference CUS which was available or unavailable (**Figure 1**). In the scenarios in which reference CUS was performed and available, the results of CUS at the moment of suspected recurrent ipsilateral DVT were defined as positive, negative, or inconclusive. The results of CUS were defined as either abnormal or normal in the scenarios in which there was no reference CUS performed or in case reference CUS was unavailable.[19] Twelve scenarios were included in the decision analytic model: three scenarios consisted of a diagnostic imaging test only, three included a combination of diagnostic imaging tests, and six combined CDR assessment and D-dimer testing with diagnostic imaging tests.

In two scenarios, CUS would have been performed in all patients (positive/negative/inconclusive result in case of available reference CUS; abnormal/normal result in case of unavailable or no reference CUS). Anticoagulant treatment would have been started in case of a positive or inconclusive CUS, or abnormal CUS. These scenarios were further extended by the use of MRDTI, which would be performed in case of an inconclusive or abnormal CUS. Anticoagulant treatment would subsequently have been started in patients with positive MRDTI. In an additional scenario (scenario 5; **Figure 1**), MRDTI would be performed directly if reference CUS was unavailable. Furthermore, a scenario where all patients would undergo an MRDTI scan was included. These six scenarios were expanded by adding CDR assessment combined with D-dimer testing as an initial step of

the strategy, resulting in scenarios 7 to 12. In these scenarios, only patients with a likely clinical probability and/or abnormal D-dimer test result would undergo the imaging tests according to the strategies, and anticoagulant treatment would be started based on the CUS or MRDTI result. Patients with unlikely clinical probability and normal D-dimer test result would not receive treatment. The diagnostic scenarios apply to patients who do not receive therapeutic anticoagulant treatment at the time of presentation with suspected recurrent ipsilateral DVT, because a decision to change anticoagulant treatment requires a different analysis than a decision to start anticoagulant treatment.

Figure 1: Twelve scenarios for the diagnostic management of suspected recurrent ipsilateral deep vein thrombosis with and without a performed or available reference CUS, consisting of the components CDR assessment combined with D-dimer test, CUS and/or MRDTI scan.[19]



12 diagnostic scenarios:

1. MRDTI only
2. CUS only: positive/negative/inconclusive *(rCUS available)* or abnormal/normal *(rCUS unavailable)*
3. CUS only: abnormal/normal *(no rCUS)*
4. MRDTI in case of inconclusive CUS *(rCUS available)* or abnormal CUS *(rCUS unavailable)*
5. MRDTI in case of inconclusive CUS *(rCUS available)* **or** MRDTI in all patients *(rCUS unavailable)*
6. MRDTI in case of abnormal CUS *(no rCUS)*
7. MRDTI in case of likely CDR and/or abnormal D-dimer
8. CUS positive/negative/inconclusive *(rCUS available)* or abnormal/normal *(rCUS unavailable)* in case of likely CDR and/or abnormal D-dimer
9. CUS abnormal/normal *(no rCUS)* in case of likely CDR and/or abnormal D-dimer
10. MRDTI in case of likely CDR and/or abnormal D-dimer, and inconclusive CUS *(rCUS available)* or abnormal CUS *(rCUS unavailable)*
11. MRDTI in case of likely CDR and/or abnormal D-dimer, and inconclusive CUS *(rCUS available)* **or** MRDTI in case of likely CDR and/or abnormal D-dimer *(rCUS unavailable)*
12. MRDTI in case of likely CDR and/or abnormal D-dimer, and abnormal CUS *(no rCUS)*

Abbreviations CUS: compression ultrasound, CDR: clinical decision rule, MRDTI: magnetic resonance direct thrombus imaging, rCUS: reference compression ultrasound.

Furthermore, two hypothetical reference scenarios that treat all patients and treat no patients were added to the model, although performing these strategies would not be considered justifiable in clinical practice.

Definitions

Clinical probability scoring was performed according to the Wells criteria for DVT. A Wells score of ≥2 points indicated a likely clinical probability.[20] Since different D-dimer assays were used in the Theia study, an abnormal D-dimer was defined as abnormal test result according to the assay-dependent threshold.[18] In accordance with the previous cost-effectiveness analysis of the Theia study, 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.[19] 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/or a <2 mm increase in the vein diameter of a previously non-compressible vein.[19] An inconclusive CUS was defined as one or more non-compressible venous segment(s), when recurrent DVT could not be diagnosed or excluded despite a performed and available reference CUS for comparison. A normal CUS was defined as full compressibility along the venous system; an abnormal CUS was defined as one or more non-compressible venous segments.[19] A positive MRDTI, indicating acute DVT, was defined as a high signal in the location of a deep vein segment against the suppressed background greater than that observed in the contiguous segments of the ipsilateral vein.[6, 9, 21] Major bleeding and clinically relevant non-major (CRNM) bleeding were defined according to the criteria of the *International Society on Thrombosis and Haemostasis* (*ISTH*).[22, 23]

Model parameters

The prevalence of recurrent ipsilateral DVT and the diagnostic accuracy of each test depending on the outcome of the consecutive steps of the diagnostic management scenarios were calculated from the Theia study, where diagnosis was based on MRDTI results. In view of internal validity, the same selection of patients was used for each of the diagnostic strategies. As described in the previous cost-effectiveness analysis, the true-positive, false-negative, true-negative, and false-positive fractions were calculated.[19] We assumed that all patients with an initial false-negative diagnosis would return to the emergency department (ED) and have a true-positive diagnosis after repeated diagnostic tests.[19] Moreover, we assumed that availability of reference CUS was independent of the accuracy of the CUS examination at the moment of suspected recurrent ipsilateral

DVT. Lastly, the availability of reference CUS was assumed to be independent of having recurrent DVT.

Estimated costs include DVT-related health care costs over a 1-year time horizon, reported in euros at Dutch price level of 2021.[24] Full details have been published previously.[19] Diagnostic costs were defined as costs for initial admission at the ED, basic laboratory measurements, and diagnostic tests according to the diagnostic scenario. Both for reference CUS and CUS at the moment of suspected recurrence, costs for ultrasound examinations performed by the radiologist were taken into account. Treatment costs were defined as costs for anticoagulant medication, management costs (i.e. costs for hospital admission, outpatient visits, and compression stockings) and costs caused by bleeding complications. To estimate the hospital admission costs, a hospital admission rate of 14% and a mean length of stay of 7.2 days were used in the base-case analysis, similar to the previous cost-effectiveness analysis, as 7.3 to 14% of patients diagnosed with DVT would be admitted to the hospital according to the literature.[25-27] A mean length of stay of 7.2 days as used in the previous cost-effectiveness analysis was reported by studies that were performed before the era of the direct oral anticoagulants (DOACs) and may therefore not be applicable to current practice.[25,26] A shorter duration of hospitalization, ranging from 3.5 to 5 days, was found in patients receiving rivaroxaban compared to patients on vitamin K antagonist or enoxaparin.[28,29] A sensitivity analysis was performed to assess variations in the rate and duration of hospitalization. Costs for the diagnostic tests, i.e. D-dimer, CUS, and MRDTI, were obtained from available data from the Dutch health care setting.[30,31]

The mortality risks applied in this analysis were the same as the risks used in the previously published model.[19] Mortality risk included mortality from 1) misdiagnosis (2.05%),[32-36] 2) recurrent fatal PE during 1-year follow-up period (set as 0.0% in patients with a false-positive diagnosis as the risk for fatal PE in patients with no recurrent DVT at baseline who falsely received anticoagulant treatment was estimated to be negligible; 0.07% in patients with true-positive and initial false-negative diagnosis[37]; 0.18% in patients with true-negative diagnosis who were not treated with anticoagulants[38,39]), and 3) anticoagulant-associated bleeding (estimated as 0.07% if receiving anticoagulant treatment; applicable to true-positive, false-negative, and false-positive patients).[37]

Analysis

The estimated 1-year health care costs were plotted against the estimated mortality for each scenario. The scenarios that were not dominated by other scenarios in terms of

costs and mortality had the potential to be most cost-effective and formed the "efficient frontier".[40,41] To assess the cost-effectiveness of the potentially most desirable scenarios, the incremental cost-effectiveness ratio was calculated by dividing the difference in costs by the difference in mortality between the scenarios in order to select the optimal scenario. In the Netherlands, no reference values exist for what costs are acceptable to prevent mortality. Given a range of 20,000 to 80,000 euros used as a reference value per quality-adjusted life year (QALY) in the Netherlands, and assuming a quality-adjusted life expectancy of about 25 years for our study population, acceptable costs per prevented death would be 0.5 to 2 million euros.[42,43] All analyses were performed using Microsoft Excel (for Microsoft 365, version 2208).

Sensitivity analyses

To assess the impact of certain parameter values in the decision analytic model, we performed sensitivity analyses. In the current literature, the incidence of recurrent ipsilateral DVT among patients presenting with suspected recurrent ipsilateral DVT varies and therefore a range from 25% up to 45% was applied in the model.[7, 8, 19, 44] Second, a sensitivity analysis was performed using a sensitivity and specificity of MRDTI set at 95%.[9, 21] Third, the percentage of inconclusive or non-diagnostic CUS, in cases where previous CUS information was available, could be up to 30%, and CUS could be false-negative in approximately 1% of patients: both variations were analysed in the model.[5,6,45] Lastly, a sensitivity analysis including hospital admission in 7.3% of patients and a range of duration of hospitalization (1-7.2 days) was performed.

In addition, a sensitivity analysis in a different decision context was performed to analyse the clinical situation in which reference CUS was both performed and available. The objective of this sensitivity analysis was to specifically assess whether to use or not to use the results of the reference CUS if already performed and available. In this analysis, reference CUS was assumed to have been performed in all patients and to always be available. Therefore, four strategies (scenario 2, 4, 8 and 10) were adjusted: reference CUS was "used" (instead of "performed and available") and the arm of reference CUS "unavailable" was removed. The two scenarios containing a different decision solely based on unavailability of reference CUS (scenario 5 and 11) were not assessed. The costs for reference CUS were excluded in this analysis since reference CUS was already performed and available, and were therefore considered "sunk costs": an economic term for costs that have been incurred in the past – and are therefore no longer relevant to decisions about the future.[46]

Results

Study patients and data

Among the Theia study population (n=305), reference CUS was performed after treatment of the first/previous DVT in 139 patients of which 43 patients were excluded due to the following: treatment with therapeutic anticoagulant ≥48 hours prior to presentation (n=41), inconclusive MRDTI because of artifacts secondary to a knee prosthesis (n=1), and MRDTI not performed because of claustrophobia (n=1). Thus, 96 patients were included in the current analysis (**Table 1**). Compared to the complete Theia study population, a smaller proportion of the patients included in the current analysis had an active malignancy or known genetic thrombophilia. The prevalence of recurrent ipsilateral DVT (composite prevalence at baseline and 3-month follow-up) was 39% (37/96 patients). The diagnostic accuracy of the tests in each of the strategies is reported in **Table 2**.

According to claims data, the proportion of DVT patients presenting with a suspicion of recurrent DVT was 20%.[17] The proportion of patients with suspected recurrent DVT returning to the same hospital as the initial presentation, i.e. where the reference CUS would have been performed, was 81%.[17]

Table 1: Baseline characteristics of 96 patients with suspected recurrent ipsilateral deep vein thrombosis included in the current analysis.

Characteristics	Data (n=96)
Mean age (+/- SD), years	55 (15)
Male, n (%)	43 (45)
Median duration of complaints (IQR), days	4 (2-7)
More than 1 prior VTE episode, n (%)	25 (26)
Mean time since the last DVT episode (+/- SD), years	5 (6)
Active malignancy, n (%)	1 (1.0)
Immobility for >3 days or recent long travel >6 hours in the past 4 weeks, n (%)	8 (8.3)
Trauma/surgery during the past 4 weeks, n (%)	3 (3.1)
Hormone (replacement) therapy, n (%)	2 (2.1)
Known genetic thrombophilia, n (%)	9 (9.4)

Abbreviations SD: standard deviation, n: number, IQR: interquartile range, VTE: venous thromboembolism, DVT: deep vein thrombosis.

Costs

The estimated health care costs per patient during first year of treatment and follow-up after suspected recurrent ipsilateral DVT are shown in **Figure 2** and **Table 2** for each of the 12 diagnostic scenarios and the scenarios to treat all patients and treat no patients. The six diagnostic scenarios with reference CUS (scenario 2, 4, 5, 8, 10, and 11: in the

figure referred to as "CUSr") showed higher costs (range €1763-€1913) than the six diagnostic scenarios without reference CUS (range €1192-€1474). The scenarios with reference CUS had higher initial diagnostic costs for performing the reference CUS examination. More importantly, the results of reference CUS often remained unused: reference CUS examinations needed to be performed in five patients to use the results of reference CUS in one patient, as the probability to return with a suspicion of recurrent DVT was found to be 20%. Moreover, in case reference CUS was used, its availability became relevant.

Table 2: The estimated diagnostic accuracy, one-year health care costs and mortality for the scenarios for the diagnostic work-up of suspected recurrent ipsilateral deep vein thrombosis.

Diagnostic scenario	Sensitivity	Specificity	Initial diagnostic costs (all)	Return diagnostic costs (FN)	Treatment costs (TP, FN)	Over-treatment costs (FP)	Total health care costs	Mortality
1.MRDTI	1,000	1,000	560	0	681	0	1241	16,4
2.CUSr	1,000	0,771	983	0	681	249	1913	14,8
3.CUS	1,000	0,661	425	0	681	368	1474	14,0
4.CUSr-MRDTI	1,000	0,918	1026	0	681	90	1796	15,8
5.CUSr-MRDTI*	1,000	0,918	1024	0	681	90	1794	15,8
6.CUS-MRDTI	1,000	1,000	571	0	681	0	1252	16,4
7.CDR/DD-MRDTI	0,973	1,000	506	6	681	0	1192	18,5
8.CDR/DD-CUSr	0,973	0,868	964	6	681	143	1794	17,6
9.CDR/DD-CUS	0,973	0,814	406	6	681	203	1295	17,2
10.CDR/DD-CUSr-MRDTI	0,973	0,918	992	6	681	90	1767	17,9
11.CDR/DD-CUSr-MRDTI*	0,973	0,918	988	6	681	90	1763	17,9
12.CDR/DD-CUS-MRDTI	0,973	1,000	527	6	681	0	1213	18,5
Treat all	1,000	0,000	313	0	681	1087	2081	9,4
Treat none	0,000	1,000	313	211	667	0	1191	95,4

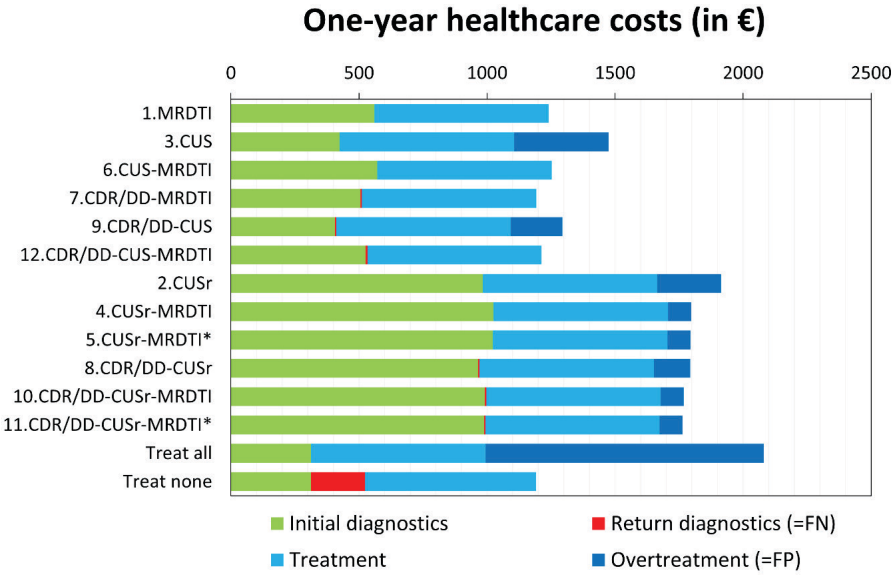
Costs in euros. Mortality per 10,000 patients.

Abbreviations MRDTI: magnetic resonance direct thrombus imaging, CUSr: diagnostic scenarios including reference compression ultrasound which could be available or unavailable (more details shown in Figure 1), CUS: diagnostic scenarios without reference compression ultrasound, CDR: clinical decision rule, DD: D-dimer, FN: false-negative, TP: true-positive, FP: false-positive.

Compared to the scenario of CUSr (scenario 2), scenario 3 consisting of CUS abnormal/normal in all patients without reference CUS (in the figure referred to as "CUS") had lower estimated costs (€1474) despite a higher false-positive rate. This higher number of false positives could be explained by the absence of reference CUS in scenario 3 and therefore the inability to compare results of CUS at the time of suspected

recurrent DVT with a reference examination. Consequently, CUS would be classified as abnormal in all patients with one or more non-compressible venous segments, and no differentiation between acute recurrent ipsilateral DVT and chronic residual thrombotic abnormalities could be made. Total estimated costs for scenario 2 (CUSr) were higher due to higher costs for initial diagnostics, despite lower costs for overtreatment. Of all 10 strategies that include ultrasonography, which were scenarios with and without reference CUS ("CUSr" or "CUS"), the scenario consisting of CDR assessment with D-dimer testing followed by CUS (abnormal/normal) and MRDTI in case of abnormal CUS (scenario 12) would have the lowest costs (€1213). Notably, this was a scenario without reference CUS.

Figure 2: Estimated one-year health care costs per patient for the 12 diagnostic scenarios and the scenarios to treat all patients and treat no patients.



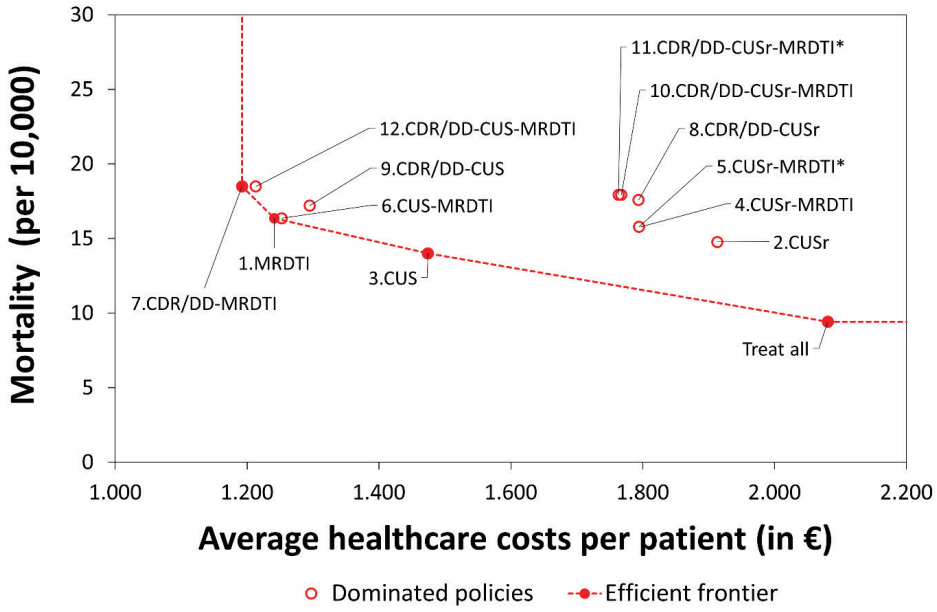
Abbreviations MRDTI: magnetic resonance direct thrombus imaging, CUS: diagnostic scenarios without reference compression ultrasound, CDR: clinical decision rule, DD: D-dimer, CUSr: diagnostic scenarios including reference compression ultrasound which could be available or unavailable (more details shown in Figure 1), FN: false-negative, FP: false-positive.

Cost-effectiveness

The 1-year health care costs were plotted against the estimated mortality per 10,000 patients for each strategy (**Table 2**), as shown in **Figure 3**. The four diagnostic scenarios at the bottom-left side of the plot were not dominated by other strategies and therefore

formed the efficient frontier. The other scenarios had higher estimated costs and/or higher estimated mortality. The six diagnostic scenarios with reference CUS had estimated mortality ranging from 1 per 676 patients (14.8 per 10,000) to 1 per 559 patients (17.9 per 10,000). For the six diagnostic scenarios without reference CUS, mortality showed a very similar range from 1 per 714 patients (14.0 per 10,000) to 1 per 541 patients (18.5 per 10,000).

Figure 3: One-year health care costs plotted against the estimated mortality per 10,000 patients for the 12 diagnostic scenarios and the scenario to treat all patients.



The dashed line indicates the efficient frontier. The scenario to treat no patients is not included in this figure, as this scenario was not considered to be desirable due to high estimated mortality.

Abbreviations CDR: clinical decision rule, DD: D-dimer, CUS: diagnostic scenarios without reference compression ultrasound, CUSr: diagnostic scenarios including reference compression ultrasound which could be available or unavailable (more details shown in Figure 1), MRDTI: magnetic resonance direct thrombus imaging.

Economically, the strategies including CUSr are not preferred, as the initial reference CUS makes them more expensive without improved outcome. From an economic perspective, scenario 7 (CDR/DD followed by MRDTI), scenario 1 (MRDTI only), and scenario 3 (CUS only, without reference CUS) would be more favourable. Compared to scenario 7, scenario 1 increases costs by 49 euro per patient and reduces mortality by 2.1 per 10,000, with an estimated ratio of 230,000 euro per prevented death. Compared

to scenario 1, scenario 3 further increases costs by 233 euro per patient and reduces mortality by 2.4 per 10,000, with an estimated ratio of 990,000 euro per prevented death. Based on an acceptability threshold of 0.5 to 2 million euros per prevented death, scenario 7 would be discarded, and the choice could be for either scenario 1 (MRDTI only) or scenario 3 (CUS only).

Sensitivity analyses

The sensitivity analyses with ranging prevalence of recurrent ipsilateral DVT of 25 to 45% and a sensitivity and specificity of MRDTI set at 95% did not show relevant differences regarding the cost-effectiveness of scenarios including reference CUS (online **supplementary Tables A1-A2** and **Figures A1-A2**). Sensitivity analysis with up to 30% inconclusive ultrasounds, in case earlier CUS information was available, revealed no relevant differences (online **supplementary Table A3** and **Figure A3**), and applying 1% false-negative ultrasounds resulted in scenario 2, 4 and 5 becoming less cost-effective due to higher mortality risk from misdiagnosis (online **supplementary Table A4** and **Figure A4**). We did not find relevant differences between scenarios with and without reference CUS in the sensitivity analysis with variations in hospital admission rate (7.3% instead of 14%) and length of stay ranging from 1 to 7.2 days (online **supplementary Table A5** and **Figure A5**).

The sensitivity analysis in a different decision context, when reference CUS was already performed and available, showed that the diagnostic scenarios with use of reference CUS (scenario 2, 4, 8, and 10: range €1208 to €1327) had lower costs than the similar scenarios without use of reference CUS (scenario 3, 6, 9, and 12: range €1213 to €1474), due to the excluded sunk costs of the reference ultrasonography that was performed in the past (online **supplementary Table B1** and **Figure B1**). The estimated mortality of the scenarios remained unchanged compared to the main analysis. Plotting the costs against estimated mortality (online **supplementary Figure B2**), showed that economically, the more beneficial scenarios were scenario 7 (CDR/DD followed by MRDTI), scenario 4 (CUSr with use of reference CUS, followed by MRDTI), scenario 2 (CUSr only), and scenario 3 (CUS only, without use of reference CUS). Compared to scenario 7, scenario 4 increases costs by 42 euro per patient and reduces mortality by 2.9 per 10,000, with an estimated ratio of 150,000 euro per prevented death. Compared to scenario 4, scenario 2 further increases costs by 93 euro per patient and reduces mortality by 0.7 per 10,000, with an estimated ratio of 1,310,000 euro per prevented death. Compared to scenario 2, scenario 3 further increases costs by 147 euro per patient and reduces mortality by 0.9 per 10,000, with an estimated ratio of 1,570,000 euro per prevented death. Based on an acceptability threshold of 0.5 to 2 million euros per

prevented death, scenario 7 would be discarded, and the choice could be for either scenario 4 (CUSr-MRDTI), scenario 2 (CUSr only), or scenario 3 (CUS only).

Discussion

In this cost-effectiveness analysis, we found higher 1-year health care costs of diagnostic strategies for suspected recurrent ipsilateral DVT that included reference CUS, compared to strategies without reference CUS, without mortality benefit. All scenarios with reference CUS were dominated by other diagnostic strategies and are therefore less cost-effective. The sensitivity analysis in a different decision context when the reference CUS is already performed and available, showed that the diagnostic scenarios that included use of reference CUS had lower costs than the scenarios without use of reference CUS. Economically, two scenarios that included use of reference CUS and one scenario without use of reference CUS are the preferred strategies. Thus, the findings based on this model discourage the routine application of reference CUS in terms of cost-effectiveness, at least in the Dutch health care setting. However, if reference CUS is already performed and available, the reference CUS results could be incorporated into the diagnostic strategy.

In clinical practice, uncertainty about the diagnosis of recurrent ipsilateral DVT could arise in some cases, particularly when reference CUS is not available. MRDTI scanning could provide the solution to achieve an ultimate diagnosis and guide clinical decision-making in such situations, as MRDTI was both shown to be an accurate and reproducible diagnostic test and as its application would not lead to higher costs when compared with performing CUS only.[6,19] When MRDTI is not (routinely) available, a strategy of performing reference CUS for high-risk patients who stop anticoagulant treatment may be reasonable. With the current model and data, we could not explore this scenario. The current model and analysis provide a framework for further research into cost-effectiveness of reference CUS in specific patient populations. Moreover, in clinical practice, patient preferences could be taken into account.

This study has limitations. The analysis is based on data of patients who participated in the Theia study, in whom reference CUS was performed after treatment of the first/previous DVT, whereas not all patients in the Theia study had a reference CUS. The use of a larger patient population would reduce the uncertainties of input parameters used in the model. In addition, some strategies analysed in the model are less feasible to apply in practice, for instance the scenario of performing MRDTI in all patients with suspected recurrent ipsilateral DVT given magnetic resonance imaging scan availability and planning. Furthermore, as described in the previous cost-effectiveness analysis,

the "treat all" scenario appears to be a surprisingly favourable strategy, due to the parameters used in the model which were estimated from available literature: patients with true-negative diagnosis still have a mortality risk from recurrent PE during 1-year follow-up, which is higher than the mortality risk based on anticoagulant-associated bleeding for false-positive patients. According to the assumptions and parameters in the model, false-positives are -counterintuitively- not discouraged. Regarding the analyses on claims data from all Dutch health insurers, despite deliberate selection of DTCs to estimate certain parameters according to the ultrasound investigations performed after diagnosis of DVT, the choice for DTCs may have resulted in an under- or overestimation of the probability of presenting with suspected recurrent DVT and the availability of reference CUS. The exclusion of ultrasound investigations from the claims data analysis according to the linked DTC, based on which we assumed the ultrasound examinations to be performed for a different reason than reference imaging or suspected recurrent DVT, could have resulted in underestimation of these parameter values, while the inability to determine the involved side of the leg could have led to overestimation of suspected recurrent ipsilateral DVT events and the availability of reference CUS. We assessed variations in parameters and did not find relevant differences in outcome. In addition to estimations derived from claims data, several parameters in the model were based on the Dutch health care setting. We acknowledge that the results may be different in other health care settings, and therefore, the Excel spreadsheet is published (**supplementary material**, available in the online version) to facilitate the use of parameters applicable to other health care settings. As acknowledged in the previous cost-effectiveness analysis, the length of stay used in the model was obtained from studies performed before the introduction of DOACs and therefore potentially longer than in current practice, at least compared to the Dutch health care setting, for which we performed a sensitivity analysis. Length of stay and hospitalization rate may also vary between countries. Lastly, the impact of recurrent DVT and long-term complications of a confirmed or missed diagnosis, such as post-thrombotic syndrome, are not included in this analysis since we did not have data available to estimate the impact.

To conclude, the findings based on our decision analytic model do not support the routine application of reference CUS from a cost-effectiveness perspective, at least in the Dutch health care setting. These results can inform policymakers regarding the use of health-care resources during follow-up after DVT.

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