

Appendices

Appendix 1- Search strategy

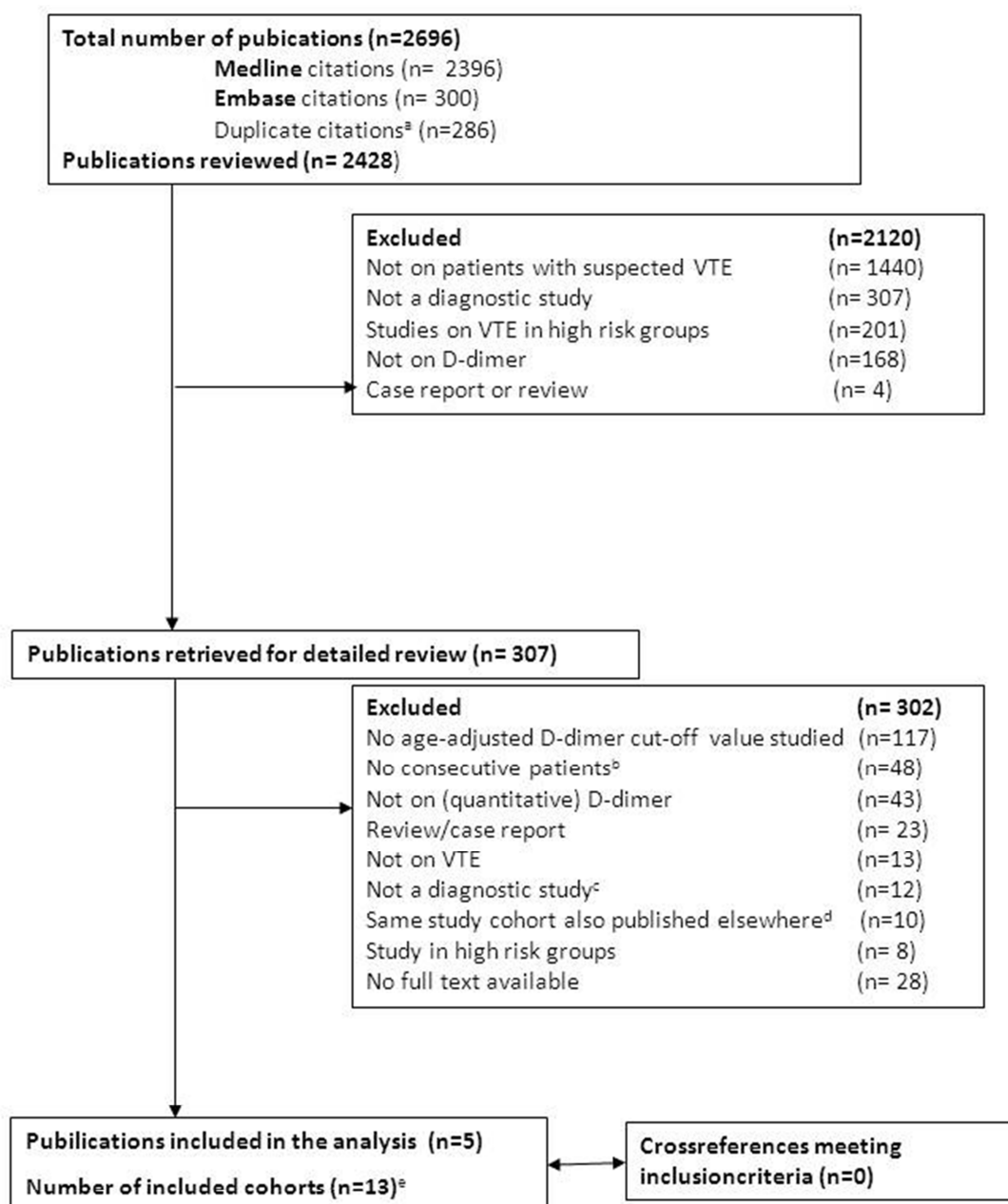
Pubmed query 21-06-2012

("embolism"[MeSH Terms] OR "embolism"[Title/Abstract] OR "emboli"[Title/Abstract] OR "embolic"[Title/Abstract] OR "embolus"[Title/Abstract] OR "pe"[Title/Abstract] OR "dvt"[Title/Abstract] OR "thrombosis"[Title/Abstract] OR "thrombose"[Title/Abstract] OR "thrombosed"[Title/Abstract] OR "thromboemboli"[Title/Abstract] OR "thromboembolic"[Title/Abstract] OR "vte"[Title/Abstract] OR "Venous Thrombosis"[Mesh] OR "Pulmonary Embolism"[Mesh]) AND (d dimer[Substance Name] OR "dimer"[Title/Abstract] OR "fibrinogen"[Title/Abstract] OR "fibrin"[Title/Abstract] OR "fibrin fragment D"[Substance Name]) AND ("aged"[Title/Abstract] OR "elderly"[Title/Abstract] OR "geriatric"[Title/Abstract] OR "nursing home"[Title/Abstract] OR "nursing homes"[Title/Abstract] OR "nursing care"[Title/Abstract] OR "old persons"[Title/Abstract]) OR age group[Title/Abstract] OR "age groups"[Title/Abstract] OR "older adult"[Title/Abstract] OR "older adults"[Title/Abstract] OR "older patient"[Title/Abstract] OR "older patients"[Title/Abstract] OR "senior"[Title/Abstract] OR "seniors"[Title/Abstract] OR "psychogeriatric"[Title/Abstract] OR "psychogeriatrics"[Title/Abstract] OR "elder population"[Title/Abstract] OR "Aged"[Mesh] OR "Health Services for the Aged"[Mesh] OR "Homes for the Aged"[Mesh] OR "Aged, 80 and over"[Mesh] OR "Frail Elderly"[Mesh] OR "Housing for the Elderly"[Mesh] OR "Nursing Homes"[Mesh] OR "Nursing Care"[Mesh] OR "age groups"[Title/Abstract] OR "elderly care"[Title/Abstract])

Embase query 21-06-2012

(embolism:ab,ti OR emboli:ab,ti OR embolic:ab,ti OR embolus:ab,ti OR pe:ab,ti OR dvt:ab,ti OR thrombosis:ab,ti OR thrombose:ab,ti OR thrombosed:ab,ti OR thromboemboli:ab,ti OR thromboembolic:ab,ti OR vte:ab,ti) AND (dimmer:ab,ti OR fibrinogen:ab,ti OR fibrin:ab,ti) AND [embase]/lim AND (aged:ab,ti OR elderly:ab,ti OR geriatric:ab,ti OR 'nursing home':ab,ti OR 'nursing homes':ab,ti OR 'nursing care':ab,ti OR 'old persons':ab,ti OR 'age group':ab,ti OR 'older adult':ab,ti OR 'older adults':ab,ti OR 'older patient':ab,ti OR 'older patients':ab,ti OR senior:ab,ti OR seniors:ab,ti OR psychogeriatric:ab,ti OR psychogeriatrics:ab,ti OR 'elder population':ab,ti OR 'age groups':ab,ti OR 'elderly care':ab,ti)

Appendix 2- Flowchart of search strategy and included studies



Search June 21st 2012.

^a Duplicates between Medline and Embase or within Medline

^b These publications concern selected patients; for example, only patients with confirmed pulmonary embolism.

^c Not a diagnostic, but rather a therapeutic, etiologic or prognostic study

^d Two citations based on same study population

^e Three studies separately presented data derived from >1 study population (3, 3 and 5 study populations).

Appendix 3- Critical appraisal according to the QUADAS-2 tool²⁷

Studycohort ^a	Risk of Bias				Concerns regarding Applicability		
	Patient selection ^b	Index test ^c	Reference standard ^d	Flow and timing ^e	Patient selection ^b	Index test ^c	Reference standard ^d
Douma 2010, Derivation set 6;34	Low	Low	High	Low	Low	Low	Low
Douma 2010 Validation set 2 6;36	Low	Low	High	Low	Low	Low	Low
Penaloza 2012, French cohort 16;38	Low	Unclear	High	High	Low	Unclear	Low
Penaloza 2012, European cohort 16;37	Low	Unclear	High	High	Low	Unclear	Low
Penaloza 2012, USA cohort 16;42	High	Unclear	High	Low	High	Unclear	Low
Douma 2010 Validation set 1 6;35	Low	Low	High	Low	Low	Low	Low
Es, van 2012 17;55	Low	Low	High	Low	Low	Unclear	Low
Schouten 2012 18;56	Low	Low	Low	Unclear	Low	Unclear	Low
Douma 2012, cohort 1 7;19	Low	Low	High	Low	Low	Low	Low
Douma 2012, cohort 2 19;31	Low	Low	High	Low	Low	Low	Low
Douma 2012, cohort 3 19;32	Low	Low	High	Low	Low	Low	Low
Douma 2012, cohort 4 19;33	High*	Low	High	Low	Low	Low	Low
Douma 2012, cohort 5 19, 1an et al, unpublished	Low	Low	High	Low	Low	Unclear	Low

- Second given reference refers to primary studies describing the cohort
- If a consecutive sample of patients suspected of having venous thromboembolism was enrolled, the risk of bias was considered low. Studies including only patients in whom D-dimer testing and/or imaging investigations were performed or wherein >10% of patients were excluded using inappropriate exclusion criteria (e.g. unable to follow up)* were considered as having a high risk of bias. If there were concerns that the patients included in the study would differ from patients that are targeted by the review question, applicability concerns were considered high.
- If there was no room for subjective interpretation of the index-test (D-dimer result), the risk of bias was considered low. If there was no clear description of the type of D-dimer assay used, the risk of bias was considered unclear. For cohorts wherein two or more D-dimer assays were used from which results were presented unstratified, the applicability was considered unclear.
- If all patients in the sample underwent imaging investigation (reference standard), the risk of bias was considered low. However, if only patients with a high D-dimer test and/or a non-high clinical probability underwent imaging investigation, the risk of (differential verification) bias was considered high.
- If all patients who were enrolled in the studies were presented in the 2x2 tables, the risk of bias was considered low. If D-dimer results were missing for 10% or more of the enrolled patients, the risk of bias was 'unclear'. The risk of bias was considered high if not all patients underwent the same algorithm of reference testing.

Appendix 4- Sensitivity and specificity of individual included cohorts, with prevalence, pre-test probability and applied D-dimer assay.

D-dimer tests in patients aged <= 50, cut-off 500 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 4	6	32	1	79	DVT	outpatients	Quantitative latex agglutination assay	10.0	0.86 [0.42, 1.00]	0.71 [0.62, 0.79]		
Douma 2012, cohort 2	17	56	2	66	DVT	outpatients	Quantitative latex agglutination assay	23.0	0.89 [0.67, 0.99]	0.54 [0.45, 0.63]		
Douma 2012, cohort 1	53	53	1	82	DVT	outpatients	Quantitative latex agglutination assay	39.0	0.98 [0.90, 1.00]	0.61 [0.52, 0.69]		
Douma 2012, cohort 3	10	9	0	35	DVT	outpatients	Quantitative latex agglutination assay	23.0	1.00 [0.69, 1.00]	0.80 [0.65, 0.90]		
Schouten, 2012	30	80	1	130	DVT	primary care	Quantitative latex or ELFA	19.7	0.97 [0.83, 1.00]	0.62 [0.55, 0.69]		
Es, van 2012	33	120	0	124	PE	in- and outpatients	Quantitative latex agglutination assay	27.0	1.00 [0.89, 1.00]	0.51 [0.44, 0.57]		
Douma 2010, valid.set 1	91	339	2	687	PE	in- and outpatients	Quantitative latex or ELFA	20.4	0.98 [0.92, 1.00]	0.67 [0.64, 0.70]		
Penaloza 2012, Eur cohort	30	66	0	116	PE	outpatients	Quantitative latex or ELFA	18.0	1.00 [0.88, 1.00]	0.64 [0.56, 0.71]		
Penaloza 2012, French coh	8	74	0	177	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.63, 1.00]	0.71 [0.64, 0.76]		
Douma 2010, derivationsset	49	153	0	266	PE	outpatients	ELFA	24.2	1.00 [0.93, 1.00]	0.63 [0.59, 0.68]		
Douma 2010, valid.set 2	69	169	0	307	PE	outpatients	ELFA	20.7	1.00 [0.95, 1.00]	0.64 [0.60, 0.69]		
Penaloza 2012, USA cohort	61	575	7	1262	PE	outpatients	Mixed assays	5.1	0.90 [0.80, 0.96]	0.69 [0.67, 0.71]		

D-dimer tests in patients aged 51-60, cut-off 500 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 1	31	25	0	37	DVT	outpatients	Quantitative latex agglutination assay	39.0	1.00 [0.89, 1.00]	0.60 [0.46, 0.72]		
Douma 2012, cohort 2	11	27	0	26	DVT	outpatients	Quantitative latex agglutination assay	23.0	1.00 [0.72, 1.00]	0.49 [0.35, 0.63]		
Douma 2012, cohort 3	4	8	0	22	DVT	outpatients	Quantitative latex agglutination assay	23.0	1.00 [0.40, 1.00]	0.73 [0.54, 0.88]		
Douma 2012, cohort 4	4	22	0	54	DVT	outpatients	Quantitative latex agglutination assay	10.0	1.00 [0.40, 1.00]	0.71 [0.60, 0.81]		
Schouten, 2012	15	52	0	59	DVT	primary care	Quantitative latex or ELFA	19.7	1.00 [0.78, 1.00]	0.53 [0.43, 0.63]		
Douma 2010, valid.set 1	52	146	0	160	PE	in- and outpatients	Quantitative latex or ELFA	20.4	1.00 [0.93, 1.00]	0.52 [0.47, 0.58]		
Es, van 2012	14	50	0	33	PE	in- and outpatients	Quantitative latex agglutination assay	27.0	1.00 [0.77, 1.00]	0.40 [0.29, 0.51]		
Penaloza 2012, USA cohort	30	193	0	311	PE	outpatients	Mixed assays	5.1	1.00 [0.88, 1.00]	0.62 [0.57, 0.66]		
Penaloza 2012, French coh	14	34	0	65	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.77, 1.00]	0.66 [0.55, 0.75]		
Douma 2010, derivationsset	21	71	0	97	PE	outpatients	ELFA	24.2	1.00 [0.84, 1.00]	0.58 [0.50, 0.65]		
Penaloza 2012, Eur cohort	17	45	0	41	PE	outpatients	Quantitative latex or ELFA	18.0	1.00 [0.80, 1.00]	0.48 [0.37, 0.59]		
Douma 2010, valid.set 2	45	97	0	110	PE	outpatients	ELFA	20.7	1.00 [0.92, 1.00]	0.53 [0.46, 0.60]		

D-dimer tests in patients aged 51-60, cut-off age*10 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 4	4	18	0	58	DVT	outpatients	Quantitative latex agglutination assay	10.0	1.00 [0.40, 1.00]	0.76 [0.65, 0.85]		
Douma 2012, cohort 1	31	23	0	39	DVT	outpatients	Quantitative latex agglutination assay	39.0	1.00 [0.89, 1.00]	0.63 [0.50, 0.75]		
Douma 2012, cohort 2	11	23	0	30	DVT	outpatients	Quantitative latex agglutination assay	23.0	1.00 [0.72, 1.00]	0.57 [0.42, 0.70]		
Douma 2012, cohort 3	4	7	0	23	DVT	outpatients	Quantitative latex agglutination assay	23.0	1.00 [0.40, 1.00]	0.77 [0.58, 0.90]		
Schouten, 2012	14	48	1	63	DVT	primary care	Quantitative latex or ELFA	19.7	0.93 [0.68, 1.00]	0.57 [0.47, 0.66]		
Es, van 2012	14	49	0	34	PE	in- and outpatients	Quantitative latex agglutination assay	27.0	1.00 [0.77, 1.00]	0.41 [0.30, 0.52]		
Douma 2010, valid.set 1	51	128	1	178	PE	in- and outpatients	Quantitative latex or ELFA	20.4	0.98 [0.90, 1.00]	0.58 [0.52, 0.64]		
Douma 2010, valid.set 2	45	92	0	115	PE	outpatients	ELFA	20.7	1.00 [0.92, 1.00]	0.56 [0.49, 0.62]		
Douma 2010, derivationsset	21	66	0	102	PE	outpatients	ELFA	24.2	1.00 [0.84, 1.00]	0.61 [0.53, 0.68]		
Penaloza 2012, USA cohort	30	166	0	338	PE	outpatients	Mixed assays	5.1	1.00 [0.88, 1.00]	0.67 [0.63, 0.71]		
Penaloza 2012, Eur cohort	6	23	0	14	PE	outpatients	Quantitative latex or ELFA	18.0	1.00 [0.54, 1.00]	0.38 [0.22, 0.55]		
Penaloza 2012, French coh	14	30	0	69	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.77, 1.00]	0.70 [0.60, 0.79]		

D-dimer tests in patients aged 61-70, cut-off 500 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 3	5	21	0	31	DVT	outpatients	Quantitative latex agglutination assay	23.0	1.00 [0.48, 1.00]	0.60 [0.45, 0.73]		
Douma 2012, cohort 4	13	29	0	67	DVT	outpatients	Quantitative latex agglutination assay	10.0	1.00 [0.75, 1.00]	0.64 [0.54, 0.74]		
Douma 2012, cohort 1	17	28	0	20	DVT	outpatients	Quantitative latex agglutination assay	39.0	1.00 [0.80, 1.00]	0.42 [0.28, 0.57]		
Douma 2012, cohort 2	12	44	0	21	DVT	outpatients	Quantitative latex agglutination assay	23.0	1.00 [0.74, 1.00]	0.32 [0.21, 0.45]		
Douma 2012, cohort 5	6	26	0	11	DVT	outpatients	Quantitative latex agglutination assay	37.0	1.00 [0.54, 1.00]	0.30 [0.16, 0.47]		
Schouten, 2012	13	59	1	34	DVT	primary care	Quantitative latex or ELFA	19.7	0.93 [0.66, 1.00]	0.37 [0.27, 0.47]		
Es, van 2012	18	63	1	18	PE	in- and outpatients	Quantitative latex agglutination assay	27.0	0.95 [0.74, 1.00]	0.22 [0.14, 0.33]		
Douma 2010, valid.set 1	50	151	0	69	PE	in- and outpatients	Quantitative latex or ELFA	20.4	1.00 [0.93, 1.00]	0.31 [0.25, 0.38]		
Penaloza 2012, Eur cohort	26	48	1	28	PE	outpatients	Quantitative latex or ELFA	18.0	0.96 [0.81, 1.00]	0.37 [0.26, 0.49]		
Penaloza 2012, French coh	7	34	0	32	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.59, 1.00]	0.48 [0.36, 0.61]		
Douma 2010, derivationsset	33	115	0	63	PE	outpatients	ELFA	24.2	1.00 [0.89, 1.00]	0.35 [0.28, 0.43]		
Douma 2010, valid.set 2	48	133	0	79	PE	outpatients	ELFA	20.7	1.00 [0.93, 1.00]	0.37 [0.31, 0.44]		
Penaloza 2012, USA cohort	21	171	0	127	PE	outpatients	Mixed assays	5.1	1.00 [0.84, 1.00]	0.43 [0.37, 0.48]		

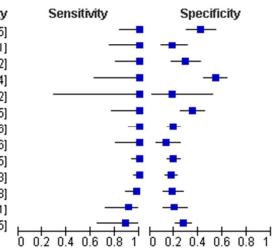
D-dimer tests in patients aged 61-70, cut-off age*10 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Douma 2012, cohort 4	13	29	0	75	DVT	outpatients	Quantitative latex agglutination assay	10.0	1.00 [0.75, 1.00]	0.72 [0.62, 0.80]		
Douma 2012, cohort 3	4	15	1	37	DVT	outpatients	Quantitative latex agglutination assay	23.0	0.80 [0.28, 0.99]	0.71 [0.57, 0.83]		
Douma 2012, cohort 5	6	23	0	14	DVT	outpatients	Quantitative latex agglutination assay	37.0	1.00 [0.54, 1.00]	0.38 [0.22, 0.55]		
Douma 2012, cohort 2	12	35	0	30	DVT	outpatients	Quantitative latex agglutination assay	23.0	1.00 [0.74, 1.00]	0.46 [0.34, 0.59]		
Douma 2012, cohort 1	17	23	0	25	DVT	outpatients	Quantitative latex agglutination assay	39.0	1.00 [0.80, 1.00]	0.52 [0.37, 0.67]		
Schouten, 2012	13	52	1	41	DVT	primary care	Quantitative latex or ELFA	19.7	0.93 [0.66, 1.00]	0.44 [0.34, 0.55]		
Es, van 2012	18	53	1	28	PE	in- and outpatients	Quantitative latex agglutination assay	27.0	0.95 [0.74, 1.00]	0.35 [0.24, 0.46]		
Douma 2010, valid.set 1	48	126	2	94	PE	in- and outpatients	Quantitative latex or ELFA	20.4	0.96 [0.86, 1.00]	0.43 [0.36, 0.50]		
Penaloza 2012, French coh	5	31	2	35	PE	outpatients	Quantitative latex or ELFA	28.0	0.71 [0.29, 0.96]	0.53 [0.40, 0.65]		
Penaloza 2012, Eur cohort	26	42	1	34	PE	outpatients	Quantitative latex or ELFA	18.0	0.96 [0.81, 1.00]	0.45 [0.33, 0.57]		
Penaloza 2012, USA cohort	21	135	0	163	PE	outpatients	Mixed assays	5.1	1.00 [0.84, 1.00]	0.55 [0.49, 0.60]		

Appendix 4- Sensitivity and specificity of individual included cohorts, with prevalence, pre-test probability and applied D-dimer assay- continued

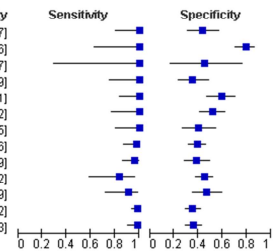
D-dimer test in patients aged 71-80, cut-off 500 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity	Specificity
Douma 2012, cohort 3	21	41	0	30	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.84, 1.00]	0.42 [0.31, 0.55]
Douma 2012, cohort 2	13	48	0	11	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.75, 1.00]	0.19 [0.10, 0.31]
Douma 2012, cohort 1	17	44	0	18	DVT	outpatients	Quantitative latex aglutination assay	39.0	1.00 [0.80, 1.00]	0.29 [0.18, 0.42]
Douma 2012, cohort 4	8	50	0	60	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.63, 1.00]	0.55 [0.45, 0.64]
Douma 2012, cohort 5	3	9	0	2	DVT	outpatients	Quantitative latex aglutination assay	37.0	1.00 [0.29, 1.00]	0.18 [0.02, 0.52]
Schouten, 2012	14	63	0	34	DVT	primary care	Quantitative latex or ELFA	19.7	1.00 [0.77, 1.00]	0.35 [0.26, 0.45]
Douma 2010, valid.set 1	41	164	0	40	PE	in- and outpatients	Quantitative latex or ELFA	20.4	1.00 [0.91, 1.00]	0.20 [0.14, 0.26]
Es, van 2012	17	45	0	7	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	1.00 [0.80, 1.00]	0.13 [0.06, 0.26]
Douma 2010, derivationset	58	167	0	40	PE	outpatients	ELFA	24.2	1.00 [0.94, 1.00]	0.19 [0.14, 0.25]
Douma 2010, valid.set 2	85	205	0	43	PE	outpatients	ELFA	20.7	1.00 [0.96, 1.00]	0.17 [0.13, 0.23]
Penaloza 2012, Eur cohort	48	76	1	17	PE	outpatients	Quantitative latex or ELFA	18.0	0.98 [0.89, 1.00]	0.18 [0.11, 0.28]
Penaloza 2012, French coh	21	56	2	14	PE	outpatients	Quantitative latex or ELFA	20.0	0.91 [0.72, 0.99]	0.20 [0.11, 0.31]
Penaloza 2012, USA cohort	16	138	2	53	PE	outpatients	Mixed assays	5.1	0.89 [0.65, 0.99]	0.28 [0.22, 0.35]



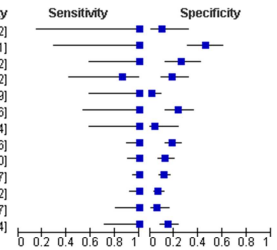
D-dimer test in patients aged 71-80, cut-off age*10ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity	Specificity
Douma 2012, cohort 1	17	35	0	27	DVT	outpatients	Quantitative latex aglutination assay	39.0	1.00 [0.80, 1.00]	0.44 [0.31, 0.57]
Douma 2012, cohort 4	8	23	0	87	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.63, 1.00]	0.79 [0.70, 0.86]
Douma 2012, cohort 5	3	6	0	5	DVT	outpatients	Quantitative latex aglutination assay	37.0	1.00 [0.29, 1.00]	0.45 [0.17, 0.77]
Douma 2012, cohort 2	13	38	0	21	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.75, 1.00]	0.36 [0.24, 0.49]
Douma 2012, cohort 3	21	29	0	42	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.84, 1.00]	0.59 [0.47, 0.71]
Schouten, 2012	14	47	0	20	DVT	primary care	Quantitative latex or ELFA	19.7	1.00 [0.77, 1.00]	0.52 [0.41, 0.62]
Es, van 2012	17	31	0	51	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	1.00 [0.80, 1.00]	0.40 [0.27, 0.55]
Douma 2010, valid.set 1	40	124	1	80	PE	in- and outpatients	Quantitative latex or ELFA	20.4	0.98 [0.87, 1.00]	0.39 [0.32, 0.46]
Penaloza 2012, Eur cohort	47	57	2	36	PE	outpatients	Quantitative latex or ELFA	18.0	0.96 [0.86, 1.00]	0.39 [0.29, 0.49]
Penaloza 2012, USA cohort	15	105	3	86	PE	outpatients	Mixed assays	5.1	0.83 [0.59, 0.96]	0.45 [0.38, 0.52]
Penaloza 2012, French coh	21	37	2	33	PE	outpatients	Quantitative latex or ELFA	28.0	0.91 [0.72, 0.99]	0.47 [0.35, 0.59]
Douma 2010, valid.set 2	84	160	1	88	PE	outpatients	ELFA	20.7	0.99 [0.94, 1.00]	0.35 [0.30, 0.42]
Douma 2010, derivationset	57	133	1	74	PE	outpatients	ELFA	24.2	0.98 [0.91, 1.00]	0.36 [0.29, 0.43]



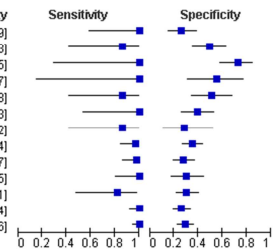
D-dimer test in patients aged >80, cut-off 500 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity	Specificity
Douma 2012, cohort 5	2	18	0	2	DVT	outpatients	Quantitative latex aglutination assay	37.0	1.00 [0.16, 1.00]	0.10 [0.01, 0.32]
Douma 2012, cohort 4	3	26	0	22	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.29, 1.00]	0.46 [0.31, 0.61]
Douma 2012, cohort 1	7	29	0	10	DVT	outpatients	Quantitative latex aglutination assay	39.0	1.00 [0.59, 1.00]	0.26 [0.13, 0.42]
Douma 2012, cohort 3	6	43	1	10	DVT	outpatients	Quantitative latex aglutination assay	23.0	0.86 [0.42, 1.00]	0.19 [0.09, 0.32]
Douma 2012, cohort 2	7	57	0	1	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.59, 1.00]	0.02 [0.00, 0.09]
Schouten, 2012	6	43	0	13	DVT	primary care	Quantitative latex or ELFA	19.7	1.00 [0.54, 1.00]	0.23 [0.13, 0.36]
Es, van 2012	7	20	0	1	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	1.00 [0.59, 1.00]	0.05 [0.00, 0.24]
Douma 2010, valid.set 1	33	108	0	25	PE	in- and outpatients	Quantitative latex or ELFA	20.4	1.00 [0.89, 1.00]	0.19 [0.13, 0.26]
Penaloza 2012, Eur cohort	37	92	0	13	PE	outpatients	Quantitative latex or ELFA	18.0	1.00 [0.91, 1.00]	0.12 [0.07, 0.20]
Douma 2010, valid.set 2	68	163	0	22	PE	outpatients	ELFA	20.7	1.00 [0.95, 1.00]	0.12 [0.08, 0.17]
Douma 2010, derivationset	43	144	0	11	PE	outpatients	ELFA	24.2	1.00 [0.92, 1.00]	0.07 [0.04, 0.12]
Penaloza 2012, French coh	17	47	0	3	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.80, 1.00]	0.06 [0.01, 0.17]
Penaloza 2012, USA cohort	11	83	0	15	PE	outpatients	Mixed assays	5.1	1.00 [0.72, 1.00]	0.15 [0.09, 0.24]



D-dimer test in patients aged >80, cut-off age*10 ug/L

Study	TP	FP	FN	TN	PE or DVT	setting	assay	Prevalence	Sensitivity	Specificity
Douma 2012, cohort 2	7	43	0	15	DVT	outpatients	Quantitative latex aglutination assay	23.0	1.00 [0.59, 1.00]	0.26 [0.15, 0.39]
Douma 2012, cohort 3	6	27	1	26	DVT	outpatients	Quantitative latex aglutination assay	23.0	0.86 [0.42, 1.00]	0.49 [0.35, 0.63]
Douma 2012, cohort 4	3	13	0	35	DVT	outpatients	Quantitative latex aglutination assay	10.0	1.00 [0.29, 1.00]	0.73 [0.58, 0.85]
Douma 2012, cohort 5	2	9	0	11	DVT	outpatients	Quantitative latex aglutination assay	37.0	1.00 [0.16, 1.00]	0.55 [0.32, 0.77]
Douma 2012, cohort 1	6	19	1	20	DVT	outpatients	Quantitative latex aglutination assay	39.0	0.86 [0.42, 1.00]	0.51 [0.35, 0.68]
Schouten, 2012	6	34	0	22	DVT	primary care	Quantitative latex or ELFA	19.7	1.00 [0.54, 1.00]	0.39 [0.26, 0.53]
Es, van 2012	6	15	1	6	PE	in- and outpatients	Quantitative latex aglutination assay	27.0	0.86 [0.42, 1.00]	0.29 [0.11, 0.52]
Douma 2010, valid.set 1	32	86	1	47	PE	in- and outpatients	Quantitative latex or ELFA	20.4	0.97 [0.84, 1.00]	0.35 [0.27, 0.44]
Penaloza 2012, Eur cohort	36	76	1	29	PE	outpatients	Quantitative latex or ELFA	18.0	0.97 [0.86, 1.00]	0.28 [0.19, 0.37]
Penaloza 2012, French coh	17	35	0	15	PE	outpatients	Quantitative latex or ELFA	28.0	1.00 [0.80, 1.00]	0.30 [0.18, 0.45]
Penaloza 2012, USA cohort	9	88	2	30	PE	outpatients	Mixed assays	5.1	0.82 [0.48, 0.98]	0.31 [0.22, 0.41]
Douma 2010, derivationset	43	114	0	41	PE	outpatients	ELFA	24.2	1.00 [0.92, 1.00]	0.26 [0.20, 0.34]
Douma 2010, valid.set 2	68	131	0	54	PE	outpatients	ELFA	20.7	1.00 [0.95, 1.00]	0.29 [0.23, 0.36]



Appendix 5- Hypothetical 2x2 tables for patients with suspected venous thromboembolism (VTE) within hypothetical cohorts with a median, low and high prevalence of VTE

With a median prevalence in patients with a non-high clinical probability of VTE

Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years						
Conventional cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	PPV/NPV	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV			
D-dimer high	120	291	411	29.2	134	367	501	26.7	154	512	666	23.2	212	593	805	26.4	151	724	876	17.3			
D-dimer low	3	586	589	99.5	0	499	499	100.0	2	332	334	99.5	3	192	195	98.5	1	124	124	99.5			
Total	123	877	1,000		134	866	1,000		156	844	1,000		215	785	1,000		152	848	1,000				
Sensitivity/specificity	97.6	66.8			100.0	57.6			99.0	39.4			98.7	24.5			99.6	14.6					
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV			
D-dimer high					133	327	460	28.9	152	427	578	26.2	209	438	648	32.3	147	550	697	21.2			
D-dimer low					1	539	540	99.8	4	417	422	99.0	6	347	352	98.4	5	298	303	98.5			
Total					134	866	1,000		156	844	1,000		215	785	1,000		152	848	1,000				
Sensitivity/specificity					99.4	62.3			97.3	49.5			97.3	44.2			97.0	35.2					
Number of reclassified patients					1	40			2	85			3	155			4	175					
SCENARIO HYPOTHETICAL 2X2; LOWER LIMIT CONFIDENCE INTERVALS SENS/SPEC																							
Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years						
Conventional cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV			
D-dimer high	117	340	456	25.6	134	421	555	24.1	151	561	712	21.2	207	628	835	24.8	147	752	899	16.4			
D-dimer low	6	537	544	98.9	0	445	445	100.0	5	283	288	98.1	8	157	165	95.4	5	96	101	95.3			
Total	123	877	1000		134	866	1,000		156	844	1,000		215	785	1,000		152	848	1,000				
Sensitivity/specificity	95.0	61.3			100.0	51.4			96.6	33.5			96.5	20.0			96.9	11.3					
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV			
D-dimer high					130	380	510	25.6	146	480	626	23.4	203	487	689	29.4	141	599	740	19.1			
D-dimer low					4	486	490	99.2	10	364	374	97.4	12	298	311	96.0	11	249	260	95.9			
Total					134	866	1,000		156	844	1,000		215	785	1,000		152	848	1,000				
Sensitivity/specificity					97.3	56.2			93.8	43.2			94.3	38.0			92.9	29.4					
Number of reclassified patients					4	41			5	81			4	141			6	153					
SCENARIO HYPOTHETICAL 2X2; UPPER LIMIT CONFIDENCE INTERVALS SENS/SPEC																							
Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years						
Conventional cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV			
D-dimer high	122	246	368	33.1	134	315	449	29.8	156	459	615	25.3	214	552	766	27.9	152	690	842	18.0			
D-dimer low	1	631	632	99.8	0	551	551	100.0	0	385	385	99.9	1	233	234	99.6	0	158	158	99.9			
Total	123	877	1000		134	866	1,000		156	844	1,000		215	785	1,000		152	848	1,000				
Sensitivity/specificity	98.9	72.0			100.0	63.6			99.7	45.6			99.5	29.7			99.9	18.6					
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV			
D-dimer high					134	277	411	32.6	154	373	527	29.2	212	388	601	35.4	150	496	647	23.2			
D-dimer low					0	589	589	100.0	2	471	473	99.6	3	397	399	99.3	2	352	353	99.5			
Total					134	866.0	1,000		156	844	1,000		215	785	1,000		152	848	1,000				
Sensitivity/specificity					99.9	68.0			98.8	55.8			98.8	50.5			98.8	41.5					
Number of reclassified patients					0	38			2	86			2	164			2	194					

Appendix 5 (continued) - Hypothetical 2x2 tables for patients with suspected venous thromboembolism (VTE) within hypothetical cohorts with a median, low and high prevalence of VTE

With the lowest (MINIMAL) prevalence in patients with a non-high clinical probability of VTE

Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years							
Conventional cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high	30	322	352	8.6	50	403	453	11.0	65	566	631	10.3	67	703	771	8.7	59	804	863	6.8				
D-dimer low	1	647	648	99.9	0	547	547	100.0	1	368	369	99.8	1	229	229	99.6	0	137	137	99.8				
Total	31	969	1000		50	950	1,000		66	934	1,000		68	932	1,000		59	941	1,000					
Sensitivity/specificity	97.6	66.8			100.0	57.6			99.0	39.4			98.7	24.5			99.6	14.6						
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high					50	359	408	12.2	64	472	536	12.0	66	520	587	11.3	57	610	667	8.6				
D-dimer low					0	591	592	99.9	2	462	464	99.6	2	412	413	99.6	2	331	333	99.5				
Total					50	950	1,000		66	934	1,000		68	932	1,000		59	941	1,000					
Sensitivity/specificity					99.4	62.3			97.3	49.5			97.3	44.2			97.0	35.2						
Number of reclassified patients					0	44				1	94				1	183				2	194			
SCENARIO HYPOTHETICAL 2X2; LOWER LIMIT CONFIDENCE INTERVALS SENS/SPEC																								
Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years							
Conventional cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high	29	375	405	7.3	50	462	512	9.8	64	621	685	9.3	66	746	811	8.1	57	835	892	6.4				
D-dimer low	2	594	595	99.7	0	488	488	100.0	2	313	315	99.3	2	186	189	98.7	2	106	108	98.3				
Total	31	969	1000		50	950	1,000		66	934	1,000		68	932	1,000		59	941	1,000					
Sensitivity/specificity	95.0	61.3			100.0	51.4			96.6	33.5			96.5	20.0			96.9	11.3						
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high					49	416	465	10.5	62	531	593	10.4	64	578	642	10.0	55	665	720	7.6				
D-dimer low					1	534	535	99.7	4	403	407	99.0	4	354	358	98.9	4	276	280	98.5				
Total					50	950	1,000		66	934	1,000		68	932	1,000		59	941	1,000					
Sensitivity/specificity					97.3	56.2			93.8	43.2			94.3	38.0			92.9	29.4						
Number of reclassified patients					1	46				2	90				2	168				2	170			
SCENARIO HYPOTHETICAL 2X2; UPPER LIMIT CONFIDENCE INTERVALS SENS/SPEC																								
Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years							
Conventional cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high	31	272	302	10.1	50	346	396	12.6	66	508	574	11.5	68	655	723	9.4	59	766	825	7.1				
D-dimer low	0	697	698	99.9	0	604	604	100.0	0	426	426	100.0	0	277	277	99.9	0	175	175	100.0				
Total	31	969	1000		50	950	1,000		66	934	1,000		68	932	1,000		59	941	1,000					
Sensitivity/specificity	98.9	72.0	1000		100.0	63.6			99.7	45.6			99.5	29.7			99.9	18.6						
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high					50	304	354	14.1	65	413	478	13.6	67	461	528	12.7	58	551	609	9.6				
D-dimer low					0	646	646	100.0	1	521	522	99.9	1	471	472	99.8	1	390	391	99.8				
Total					50	950.0	1,000		66	934	1,000		68	932	1,000		59	941	1,000					
Sensitivity/specificity					99.9	68.0			98.8	55.8			98.8	50.5			98.8	41.5						
Number of reclassified patients					0	42				1	95				1	194				1	215			

Appendix 5 (continued) - Hypothetical 2x2 tables for patients with suspected venous thromboembolism (VTE) within hypothetical cohorts with a median, low and high prevalence of VTE

With the highest (MAXIMAL) prevalence in patients with a non-high clinical probability of VTE

Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years							
Conventional cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high	279	237	516	54.1	333	283	616	54.1	259	557	816	31.7	340	494	835	40.8	268	624	892	30.0				
D-dimer low	7	477	484	98.6	0	384	384	100.0	3	181	184	98.1	5	161	165	97.2	1	107	108	99.0				
Total	286	714	1000		333	667	1,000		262	738	1,000		345	655	1,000		269	731	1,000					
Sensitivity/specificity	97.6	66.8			100.0	57.6			98.7	24.5			98.7	24.5			99.6	14.6						
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high					331	252	583	56.8	255	412	667	38.2	336	366	702	47.9	261	474	735	35.5				
D-dimer low					2	415	417	99.5	7	326	333	97.9	9	289	298	96.9	8	257	265	97.0				
Total					333	667	1,000		262	738	1,000		345	655	1,000		269	731	1,000					
Sensitivity/specificity					99.4	62.3			97.3	44.2			97.3	44.2			97.0	35.2						
Number of reclassified patients					2	31					4	145					4	128					7	150
SCENARIO HYPOTHETICAL 2X2; LOWER LIMIT CONFIDENCE INTERVALS SENS/SPEC																								
Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years							
Conventional cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high	272	277	548	49.6	333	324	657	50.7	265	580	845	31.4	292	558	850	34.4	261	648	909	28.7				
D-dimer low	14	437	452	96.8	0	343	343	100.0	10	145	155	93.7	11	139	150	92.9	8	83	91	90.9				
Total	286	714	1000		333	667	1,000		275	725	1,000		303	697	1,000		269	731	1,000					
Sensitivity/specificity	95.0	61.3			100.0	51.4			96.5	20.0			96.5	20.0			96.9	11.3						
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high					324	292	616	52.6	259	449	709	36.6	286	432	718	39.8	250	516	766	32.6				
D-dimer low					9	375	384	97.6	16	276	291	94.6	17	265	282	93.8	19	215	234	91.9				
Total					333	667	1,000		275	725	1,000		303	697	1,000		269	731	1,000					
Sensitivity/specificity					97.3	56.2			94.3	38.0			94.3	38.0			92.9	29.4						
Number of reclassified patients					9	32					6	131					6	126					11	132
SCENARIO HYPOTHETICAL 2X2; UPPER LIMIT CONFIDENCE INTERVALS SENS/SPEC																								
Hypothetical 2x2 tabs	≤50 years				51-60 years				61-70 years				71-80 years				>80 years							
Conventional cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high	283	200	483	58.5	333	243	576	57.8	274	510	784	34.9	302	490	792	38.1	269	595	864	31.1				
D-dimer low	3	514	517	99.4	0	424	424	100.0	1	215	217	99.4	1	207	208	99.3	0	136	136	99.9				
Total	286	714	1000		333	667	1,000		275	725	1,000		303	697	1,000		269	731	1,000					
Sensitivity/specificity	98.9	72.0			100.0	63.6			99.5	29.7			99.5	29.7			99.9	18.6						
Age adjusted cut-off value	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV	VTE +	VTE-	Total	PPV/NPV				
D-dimer high					333	214	546	60.9	272	359	630	43.1	299	345	644	46.5	266	428	694	38.3				
D-dimer low					0	453	454	99.9	3	366	370	99.1	4	352	356	99.0	3	303	306	98.9				
Total					333	667.0	1,000		275	725	1,000		303	697	1,000		269	731	1,000					
Sensitivity/specificity					99.9	68.0			98.8	50.5			98.8	50.5			98.8	41.5						
Number of reclassified patients					0	29					2	151					3	145					3	167