White Paper

INNOVANCE D-Dimer Assay for exclusion of VTE and use of an age-dependent cutoff: a critical consideration

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Since 2010, several studies on D-dimer for exclusion of venous thromboembolism (VTE) have been re-evaluated using an age-specific cutoff. The aim was to improve the effectiveness of D-dimer testing in ruling out VTE.

D-dimer levels are known to increase with age; e.g., median D-dimer levels in apparently healthy men aged 75–79 are about twice as high as in men aged 60–64.[1] This increase in the basal D-dimer concentration is responsible for the decrease in the specificity of D-dimer measurements for exclusion of VTE in the elderly, as well as during pregnancy and in cancer patients, both of which are also associated with an increase in basal D-dimer levels.

The currently most-favored approach for adjustment of the D-dimer cutoff for VTE exclusion (for assays using a cutoff of 500 µg/L) is to multiply the age of the patient by 10 for those older than 50 years, which results in a cutoff of 600 for a 60-year-old patient and 750 for a 75-year-old patient, respectively.

Retrospective meta-analyses were published for DVT as well as PE.[2–7] As expected, the age-adjusted increase of the D-dimer cutoff value improved the diagnostic specificity, with the most positive effect in those with the most advanced age. However, these studies primarily focused on specificity rather than sensitivity, and sensitivity is the most relevant criterion in validation of any D-dimer assay for VTE exclusion.

CSLI guidelines specify a minimum sensitivity of 97% or higher, with a lower limit for the 95% confidence range (one-sided) of at least 95%. In parallel, the negative predictive value (NPV) must be 98% or higher, again with a lower limit for the 95% confidence range (one-sided) of at least 95%.[8]

Meta-analysis of 13 studies using an age-adjusted D-dimer cutoff

The recent meta-analysis by Schouten[7] addressed the sensitivity aspect in more detail (but not the NPV). This meta-analysis included 13 studies in which different D-dimer assays were applied, all of which used the conventional cutoff of 500 µg/L. In total, 12,497 patients were included. Results are summarized in Table 1.

As expected, the study proves that with age-adjusted cutoffs, the specificity increases significantly, and with increasing age, the gain in specificity is more pronounced. On the other hand (again as expected), sensitivity decreases, but only very modestly, and for the >50 years subgroup in total, the sensitivity target is fulfilled, with 97.8% sensitivity and a lower 95% CI of 95.9%.

Retrospective recalculation of the INNOVANCE D-Dimer Assay validation study

Because the INNOVANCE® D-Dimer Assay was not included in any of the studies comprising this meta-analysis, we retrospectively reanalyzed our clinical validation data, applying a cutoff of age x 10 for those aged older than 50 years. Please refer to Table 2 for data of this retrospective analysis.

Applying the age-adjusted cutoff to the INNOVANCE D-Dimer Assay in our validation data set from the clinical studies before launch (the same approach as in the paper by Schouten), a significant gain in specificity (about 9%) at the cost of a moderate loss of sensitivity (about 1%) is observed. For the complete study cohort, the CSLI requirements are just fulfilled and, when compared for the Vidas D-Dimer Exclusion Assay, results are equivalent.

Study of age-adjusted cutoff for INNOVANCE D-Dimer Assay from University Münster

Recently, study results investigating the same approach of cutoff-age adjustment with the INNOVANCE D-Dimer Assay were published online in a German journal for intensive-care and emergency medicine. The University Hospital of Münster retrospectively recalculated D-dimer results from tests ordered by the emergency department for new patients admitted between December 2007 and November 2010. The study included 1033 patients who collectively had an extremely low VTE rate of 8.8%.

Due to the low number of 91 VTE-positive patients in this cohort, the study can provide only a relatively crude sensitivity estimate. No additional false-negative result was observed in addition to the one false-negative result obtained with the standard cutoff of 500. Please refer to Table 3 for results of the Münster study.

The specificity in this study was exceptionally high, with 74% for the cutoff of 500 mg/L (which seems to be a result of the patient selection for this retrospective analysis); consequently, there was only a relatively small gain in specificity when applying an age-adjusted cutoff in this study.

From an age-specific ROC analysis, a further alternative cutoff strategy was developed for patients older than 50 years—providing a cutoff by multiplying age by 16. However, these higher cutoffs resulted in five additional false-negative results, suppressing sensitivity to only 93.4%, a value that most clinicians will not accept for a VTE exclusion test.

Table 1. Sensitivity and specificity in relation to age-adjusted cutoff[7]

Age (years)	N	Median prevalence (%)	Sensitivity (%, 95% CI)		Specificity (%, 95% CI)	
			Cutoff 500	Age-adjusted	Cutoff 500	Age-adjusted
≤50	5528	12.3	97.6 (95.9–98.9)	NA	66.8	NA
51–60	2043	13.4	100	99.4 (97.3–99.9)	57.6	62.3
61–70	1815	15.6	99.0 (96.6–99.7)	97.3 (93.8–98.8)	39.4	49.5
71–80	1842	21.5	98.7 (96.5–99.5)	97.3 (94.4–98.8)	24.5	44.2
>80	1269	15.2	99.6 (96.9–99.9)	97.0 (92.9–98.8)	14.7	35.2
Total cohort >50	6969	./.	99.3 (98.4–99.7)	97.8 (95.9–98.9)	36.1	48.8

Table 2. Retrospective reanalysis of the INNOVANCE D-Dimer Assay validation study

Age (years)	N	Prev. (%)	Sensitivity (%, 95% CI)		NPV (%, lower 95% CI)		Specificity (%, 95% CI)	
			Cutoff 500	Age-adjusted	Cutoff 500	Age-adjusted	Cutoff 500	Age-adjusted
INNOVANCE D-Dimer Assay								
≤50	805	12.7	99.0 (95.4)	NA	99.7 (98.8)	NA	53.3	NA
>50	2006	23.2	98.7 (97.5)	96.8 (95.1)	98.7 (97.7)	97.8 (96.8)	29.9	42.9
all	2811	20.2	98.8 (97.7)	97.2 (95.8)	99.2 (98.5)	98.5 (97.8)	37.2	46.1
VIDAS D-Dimer Exclusion Assay								
≤50	362	15.6	96.4 (89.0)	NA	99.0 (97.1)	NA	64.0	NA
>50	1269	24.0	98.8 (97.4)	97.1 (95.1)	98.7 (97.2)	97.9 (96.6)	27.0	41.5
all	1796	22.3	98.5 (97.1)	97.0 (95.2)	98.8 (97.8)	98.2 (97.2)	34.9	46.3

Table 3. Age-adjusted INNOVANCE D-Dimer Assay in Münster study[9]

Age (years)	N	Prevalence (%)	Sensitivity (%, 95% CI)		Specificity (%, 95% CI)	
			Cutoff 500	Age-adjusted	Cutoff 500	Age-adjusted
Total cohort	1033	8.8	98.9	98.9 [93.4]*	74.0	77.4 [84.1]*

Conclusion

Until now, no prospective study has investigated the performance and safety of an age-adjusted cutoff for D-dimer with respect to VTE exclusion.

When applying the strategy of multiplying age by 10 for cutoff calculation for patients above 50 years for the INNOVANCE D-Dimer Assay, the resulting sensitivity and NPV are just within the target limits (for the complete study cohort) that comply with the CSLI guidelines. On the other hand, the substantial gain in specificity is attractive, as the specificity determines how many further diagnostic work-ups are indicated; with each percent gain in specificity, the cost-effectiveness of D-dimer screening for exclusion of VTE increases.

Depending on the local patients' characteristics and prevalence of VTE in the local patient population, and taking the data shown above into consideration, each hospital should carefully evaluate whether to apply the age-adjusted cutoff—with the advantage of substantially better specificity in a large subset of the patient population—or to continue using an age-independent cutoff of 500 mg/L, which was validated in prospective studies for the INNOVANCE D-Dimer Assay, until the concept of age-adjusted cutoffs is proven in further prospective studies.

**[...] applying alternative age-adjusted cutoff for >50 years: age x 16*

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