Implementation of 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay.

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Uw ziekenhuis.

CAT

Inleiding

+/- 10% van de patiënten op de Spoedgevallen

Acute pijn op de borst

10-20%: myocard infarct (STEMI of NSTEMI)

80-90%: andere oorzaak

<u>Diagnosepijlers:</u>
Kliniek
ECG
Troponine

1hour protocol?

CAT-vragen

VRAAG 1

Wat is de diagnostische impact van het 1h protocol?

VRAAG 2

Welke analytische problemen brengt het 1h protocol met zich mee?

VRAAG 3

Wat is de meerwaarde van het 1h protocol?

TnT: analytische performantie

Troponine = belangrijkste biochemische marker voor AMI *(in deze CAT: troponine T)*

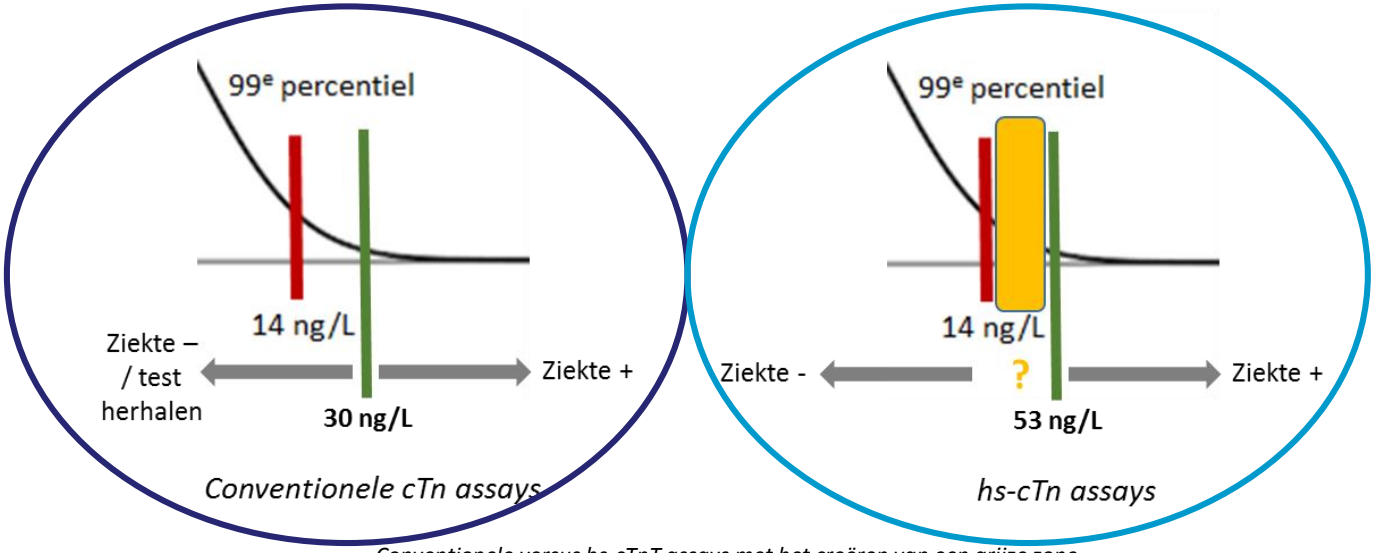
1991: eerste assay

1^e – 2^e – 3^e – 4^e generatie assays ⇨ Onvoldoende precisie in lage meetbereik

5^e generatie assays: hs-cTn ⇨ Hoge precisie in lage meetbereik

- CV < 10% t.h.v. 99^e percentiel
- Meetbaar in ≥50% van de gezonde populatie

POCT assays? ⇨ Onvoldoende sensitiviteit



Conventionele versus hs-cTnT assays met het creëren van een grijze zone

TnT: diagnostische performantie

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Sens: hs-TnT > cTnT / Spec: hs-TnT < cTnT

Table 2. Results of Troponin Testing for Diagnosis of ACS

Analyte, Cut Point	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
Diagnostic accuracy for ACS in all patients (AUC_{hsTnT}: 0.79)				
hsTnT, 13 pg/mL	62 (47–78)*	89 (85–92)	38 (26–50)	96 (93–98)
cTnT, 0.01 ng/mL	49 (33–65)	97 (96–99)†	67 (49–84)	95 (92–97)
cTnT, 0.03 ng/mL	35 (20–50)	99 (96–99)†	72 (52–93)	93 (90–95)

Hs-TnT

cTnT

Diagnostische performantie cTNT versus hs-cTnT (Januzzi Jr. et. al. 2010)

LR ?

LH	Ziekte aanwezig	Ziekte afwezig
Test +	TP / Z+ = Sn	FP / Z– = 1-Sp
Test –	FN / Z+ = 1-Sn	TN / Z– = Sp

Sn/1-Sp → **LR + = 35**, **LR + = 5,64**

1-Sn/Sp → **LR - = 0,66**, **LR - = 0,44**

LR interpretatie
1: geen klinisch nut
2-5 of 0.2-0.5: klein verschil, kan in specifieke situatie nuttig zijn
5-10 of 0.1-0.2: matig maar substantieel verschil in pretest-posttest probabiliteit
>10 of <0.1: klinisch belangrijk verschil in pretest-posttestprobabiliteit

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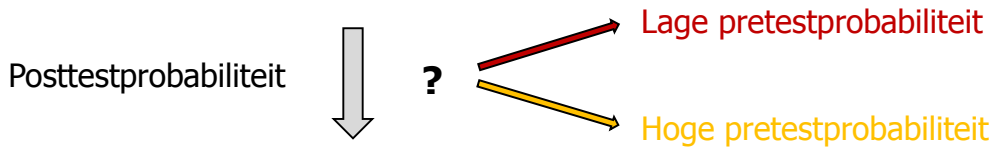
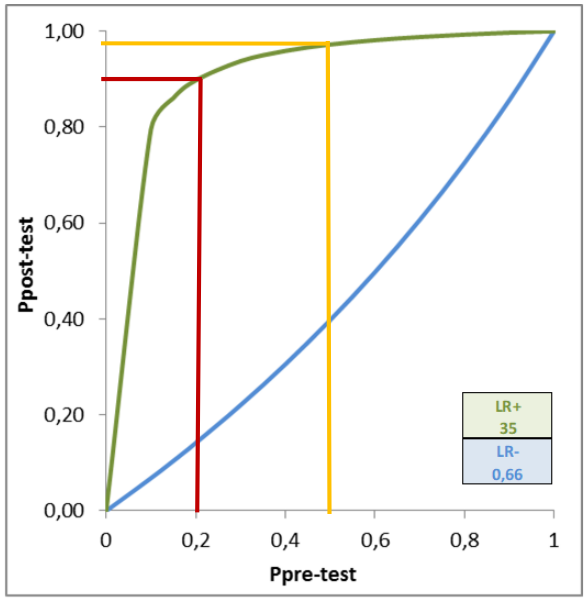
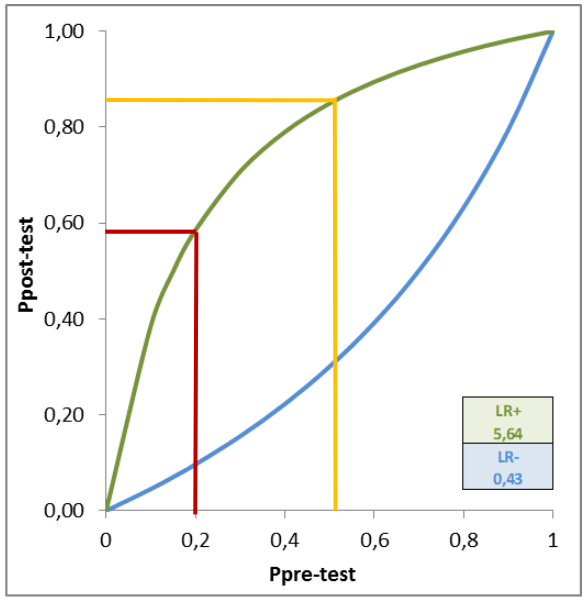
Sens: hs-TnT > cTnT / Spec: hs-TnT < cTnT

LR+ ('rule-in'): cTnT >> hs-TnT





cTnT: cut-off op 30 ng/L



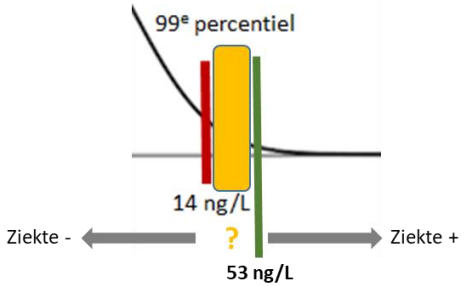
Hs-cTnT: cut-off op 13 ng/L

Bayes Theorema toegepast op de data van Januzzi Jr. et.al. 2010.

Hs-TnT: 'betere' test MAAR → interpretatieprobleem ⇨ Nood aan algoritmes!

3h protocol

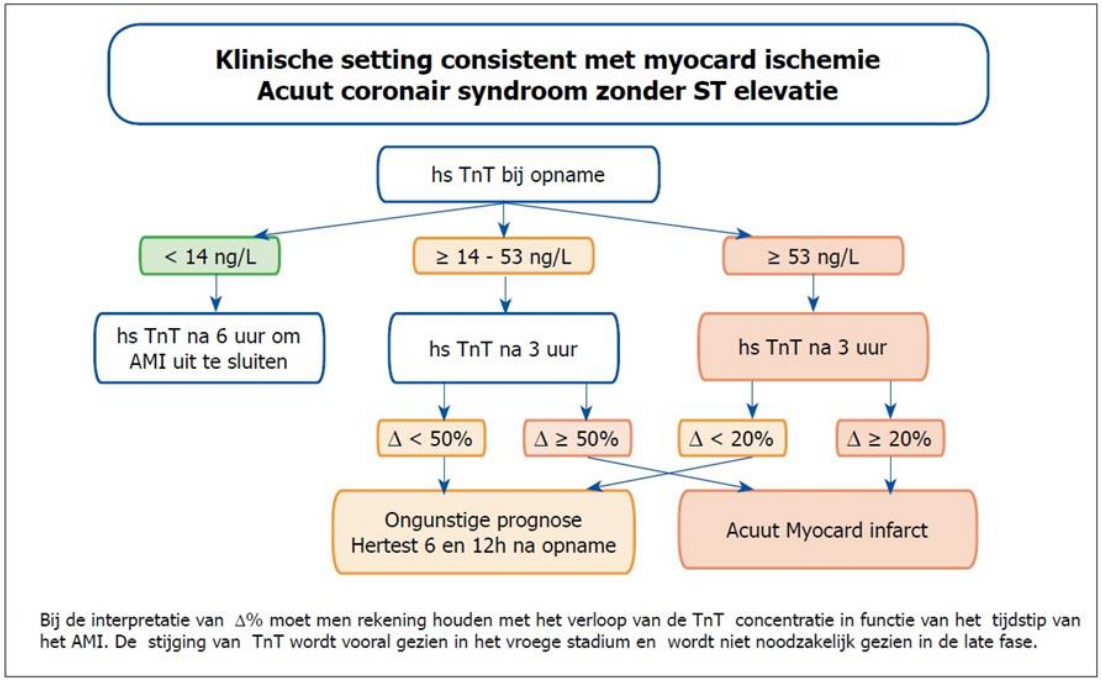
Combinatie
- Concentratie op tijdstip 0h
- Relatieve verandering na 3h



\+ Goede sensitiviteit, goede 'rule-in'

\- Beperkte 'rule-out', uitval door lange wachttijden

Algoritme voor het gebruik van hs Troponine bepaling in de diagnose van Acuut Myocard infarct (H.D. White. Am Heart J. 2010;159: 933)



Bij de interpretatie van Δ% moet men rekening houden met het verloop van de TnT concentratie in functie van het tijdstip van het AMI. De stijging van TnT wordt vooral gezien in het vroege stadium en wordt niet noodzakelijk gezien in de late fase.

1h protocol

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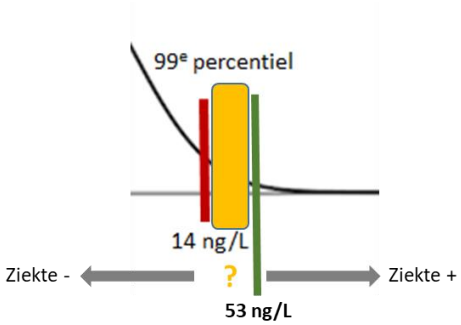
Combinatie
- Concentratie op tijdstip 0h
- Absolute verandering na 1h



\+ / − Diagnostische performantie?

Patiënten onderverdelen in 3 groepen

0-Hour/1-Hour hs-TnT Decision Rule from TRAPID-AMI

Baseline hsTnT <12 ng/L AND Delta hsTnT < 3 ng/L at 1 hr	OTHERS: Not meeting "Rule in" or "Rule out" criteria	Baseline hsTnT ≥ 52ng/L or Delta hsTnT ≥ 5 ng/L at 1hr
Rule Out	**Observe**	**Rule In**
Early discharge from ED	Further testing in 4 hours	Admit and Treat as MI
63% of population	23% of population	14% of population

Sensitivity: 96.7% (93.4-98.7%) Total N=1282 Specificity: 96.1% (94.7-97.2%)
Negative Predictive Value: 99.1% (98.2-99.6%) Positive Predictive Value: 77.2% (70.4-83.0%)

Diagnostische impact van het 1h protocol?

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Algoritme classificatie	Ziekte aanwezig	Ziekte afwezig	Totaal
Test+ ('rule-in')	142 (TP)	42 (TP)	184
Observatie zone (tijdelijke 'rule-in')	*64*	*221*	*285*
Test- ('rule-out')	7 FN)	806 (TN)	813
Totaal	213	1069	1282

Sensitiviteit: 96,7% ('rule-out') - Specificiteit: 96,1% ('rule-in')

	Ziekte aanwezig	Ziekte afwezig
Test +	TP	FP
Test –	FN	TN

$$Sn = \frac{TP}{TP + FN} \qquad Sp = \frac{TN}{TN + FP}$$

NPV: 99,1% ('rule-out') - PPV: 77,1% ('rule-in')

	Ziekte aanwezig	Ziekte afwezig
Test +	TP	FP
Test –	FN	TN

$$PV(+) = \frac{TP}{TP + FP} \qquad PV(-) = \frac{TN}{TN + FN}$$

Table 2. Two×two tables and calculation of negative and positive predictive value, as well as sensitivity and specificity for the rule-out and rule-in of myocardial infarction.

A, Algorithm classification versus adjudicated diagnosis.

Algorithm Classification	AMI	Non-AMI	Total
Rule-out status	7	806	813
Observational zone	64	221	285
Rule-in status	142	42	184
Total	213	1,069	1,282

AMI, Acute myocardial infarction.

B, Negative and positive predictive value.

Diagnostic Test Performance Measures	Estimate, %	95% CI	Counts
NPV	99.14	98.23–99.65	806/813
PPV	77.17	70.42–83.03	142/184

NPV, Negative predictive value; *PPV*, positive predictive value.

C, Sensitivity and specificity.*

Diagnostic Test Performance Measures	Estimate, %	95% CI	Counts
Sensitivity in the rule-out zone	96.71	93.35–98.67	206/213
Specificity in the rule-in zone	96.07	94.73–97.15	1,027/1,069

*Sensitivity: true positive/diseased (AMI). The rule-out zone defines patients with no AMI according to the 0-hour/1-hour hs-cTnT algorithm. Only patients in this zone are ruled out. Accordingly, for the rule-out it is irrelevant whether patients are in the observational zone or the rule-in zone, and both zones are combined. True positive=206; diseased (AMI)=213; sensitivity=96.71%. Specificity: true negative/non-diseased (non-AMI). The rule-in zone defines patients with AMI according to the 0-hour/1-hour hs-cTnT algorithm. Only patients in this zone are ruled in. Accordingly, for the rule-in it is irrelevant whether patients are in the observational zone or the rule-out zone, and both zones are combined. True negative=1,027; non-diseased (non-AMI) 1,069; specificity=96.07%.

2016 Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. C. Mueller et al. Annals of Emergency Medicine.

Diagnostische impact van het 1h protocol?

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Likelihoods (LH)

LH	Ziekte aanwezig	Ziekte afwezig
Test +	TP / Z+ = *Sn*	FP / Z– = *1-Sp*
Test –	FN / Z+ = *1-Sn*	TN / Z– = *Sp*

LH	Ziekte aanwezig	Ziekte afwezig
Test +	0.667 (142/213)	0.039 (42/1069)
Test –	0,033 (7/213)	0.754 (806/1069)

LR interpretatie
1: geen klinisch nut
2-5 of 0.2-0.5: klein verschil, kan in specifieke situatie nuttig zijn
5-10 of 0.1-0.2: matig maar substantieel verschil in pretest-posttest probabiliteit
>10 of <0.1: klinisch belangrijk verschil in pretest-posttestprobabiliteit

Likelihoodratio's (LR)

	Ziekte aanwezig	Ziekte afwezig
Test +	TP / Z+	FP / Z–
Test –	FN / Z+	TN / Z–

"Positieve likelihood ratio "

$$LR(+) = \frac{TP / Z+}{FP / Z-} = \frac{142 / 213}{42 / 1069} = 17$$

$$LR(-) = \frac{FN / Z+}{TN / Z-} = \frac{7 / 213}{806 / 1069} = 0.04$$

"Negatieve likelihood ratio"

Diagnostische impact van het 1h protocol?

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Posttestprobabiliteit

$$P_{POST} = \frac{LR \cdot P_{PRE}}{1 + (LR - 1) \cdot P_{PRE}}$$

→ Pretestprobabiliteit

→ Likelihoodratio's

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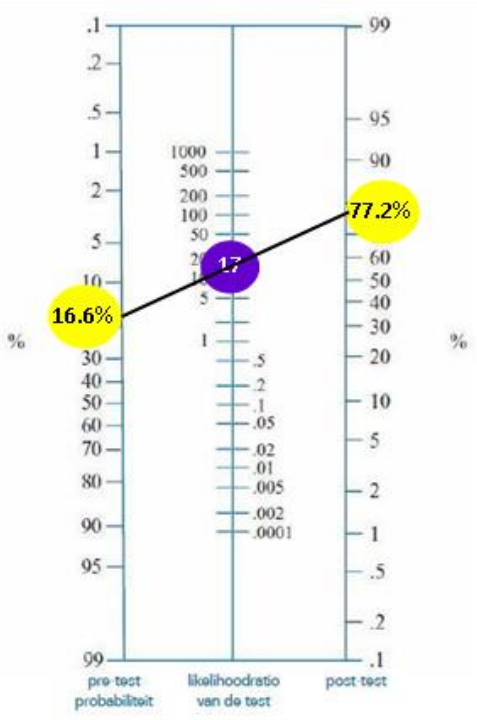
	AMI	Geen AMI	LR	95%CI
Rule-out	7	806	0,0436	[0,0210 - 0,0904]
Observatie	64	221	1,453	[1,148 - 1841]
Rule-in	142	42	16,968	[12,429 - 23,164]



Posttestprobabiliteit voor de LR+.
Fagan TJ. ***Nomogram for Bayes Theorem.***
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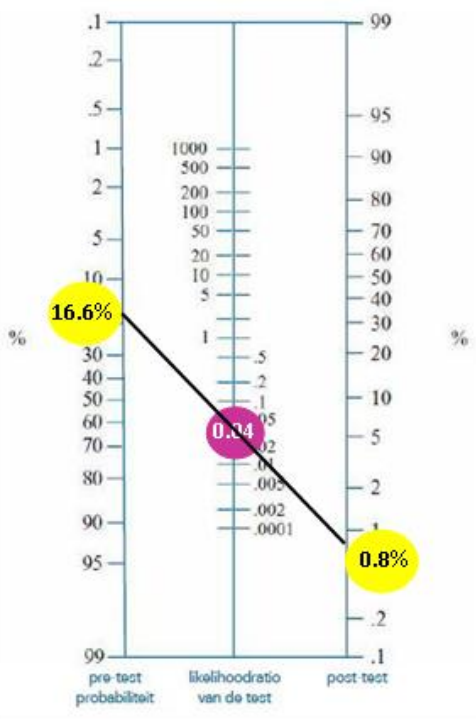

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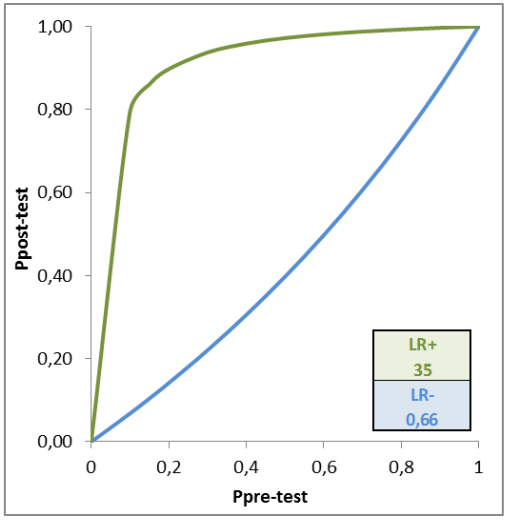
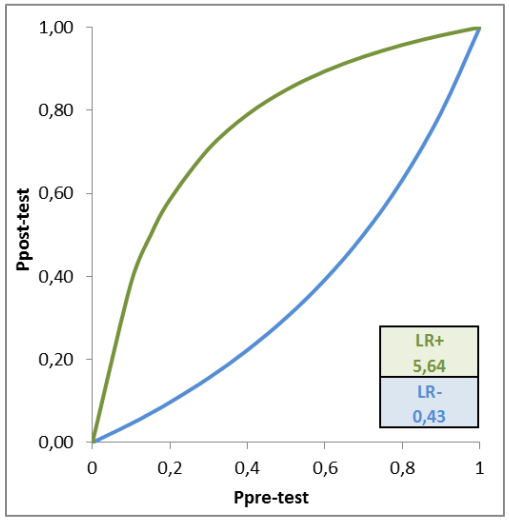


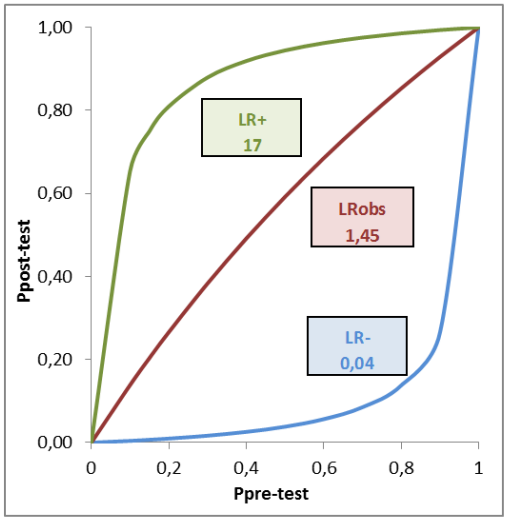
cTnT: cut-off op 30 ng/L

Als Ppre = 16.6%:
Ppost voor LR+ = 87%
Ppost voor LR- = 12%



Hs-cTnT: cut-off op 13 ng/L

Als Ppre = 16.6%:
Ppost voor LR+ = 53%
Ppost voor LR- = 8%



1h protocol

Als Ppre = 16.6%:
Ppost voor LR+ = 77%
Ppost voor LR- = 0.8%
Ppost voor LRobs = 22%

Diagnostische impact van het 1h protocol?

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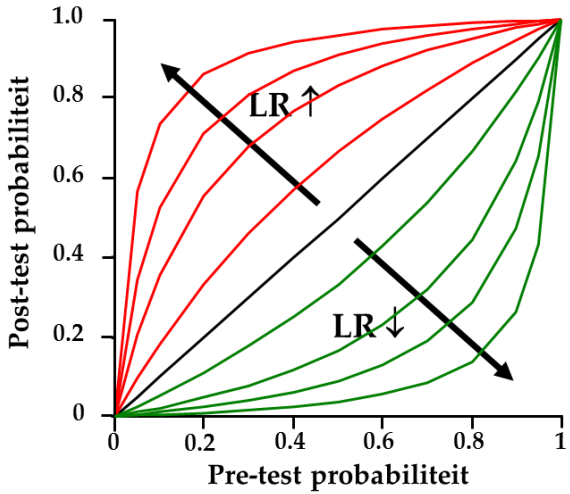
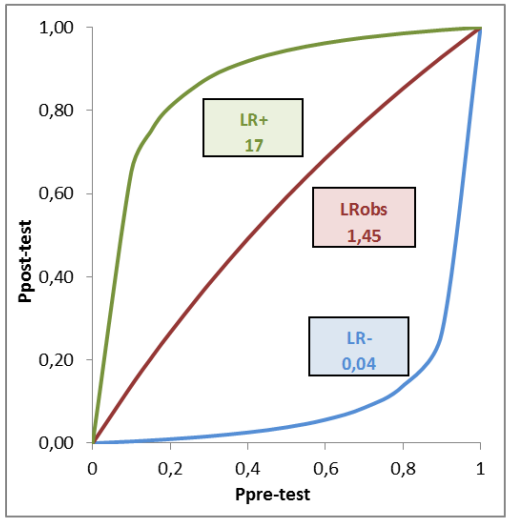


		Ziekte +	Ziekte –	
↑ troponine	Rule-in	142	42	LR = **17**
	Observatie: 'tijdelijke rule-in'	64	221	LR = **1,45**

Multipele resultaat-intervallen



1h protocol

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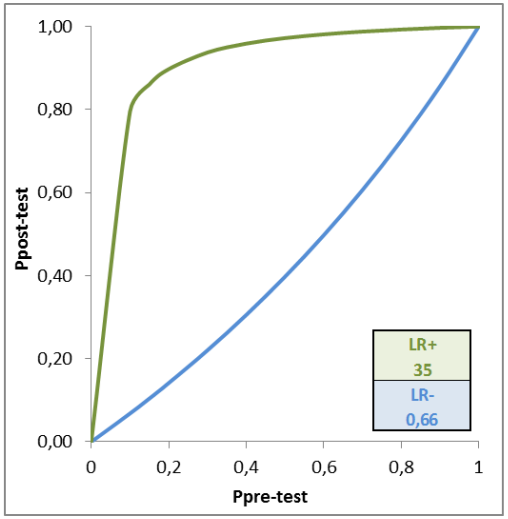
Diagnostische impact van het 1h protocol?

Antwoord vraag 1

Wat is de diagnostische impact van het 1h protocol?

Sensitiviteit: 96,7% ('rule-out') - Specificiteit: 96,1% ('rule-in')

NPV: 99,1% ('rule-out') - PPV: 77,1% ('rule-in')



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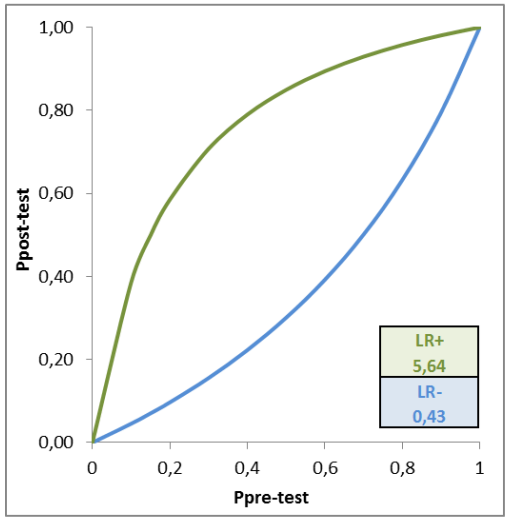

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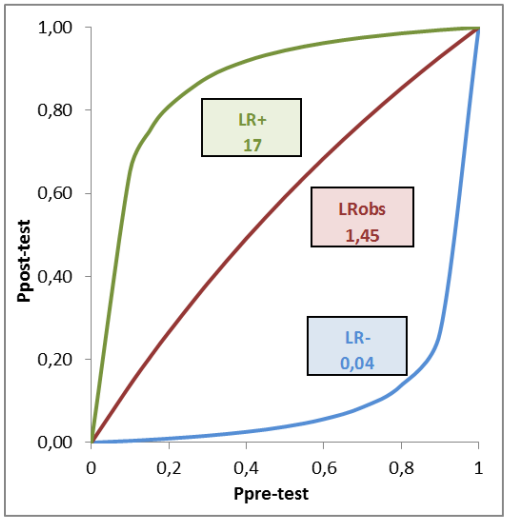

1h protocol

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Analytische problemen?

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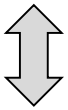
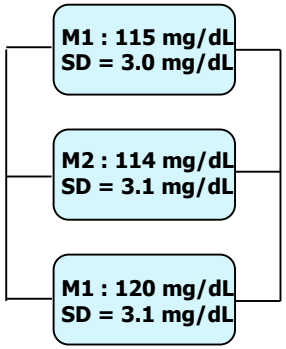
1 toestel

CVw





Geautomatiseerd systeem met meerdere identieke modules

CVas < 0.5 * CVw

Vb.glucose

CVricos = 5.7%
CV1 = 2.6% < 2.85%
CV2 = 2.7% < 2.85%
CV3 = 2.6% < 2.85%

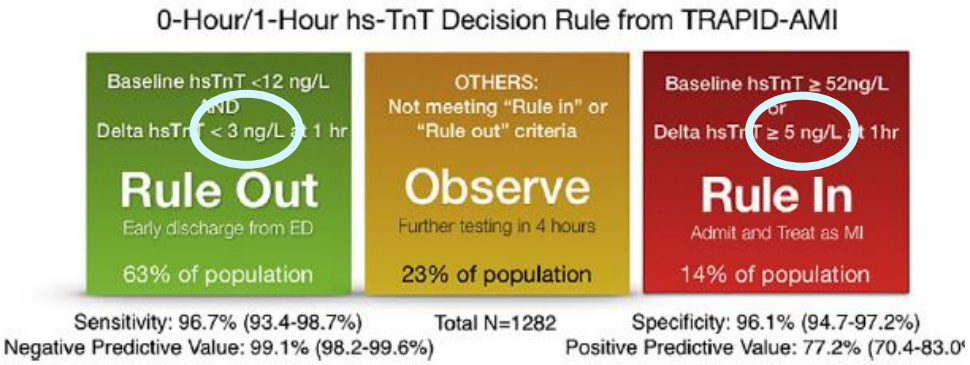
$$M_{as} = \sum_i f_i m_i$$

$$SD_{as} = \sqrt{\sum_i f_i SD_i^2 + \sum_i f_i (M_i - M_{as})^2}$$

$$CV_{as}(\%) = 100\left(\frac{SD_{as}}{M_{as}}\right)$$

f1 = f2 = f3 = 1/3

Mas = 116.3 mg/dL
SDas = 4.0 mg/dL
CVas = 3.5% > 2.85%



Kleine verschillen moeten meetbaar zijn: mag niet te wijten zijn aan analytische fouten!

Analytische problemen?

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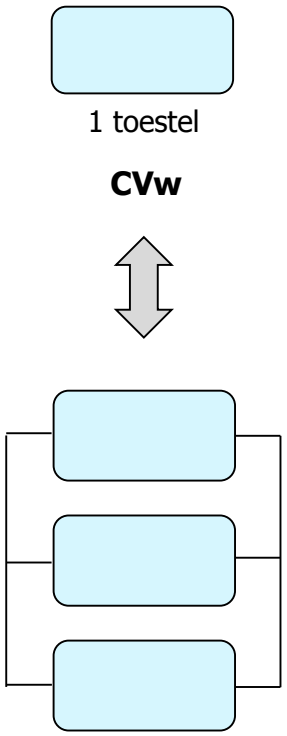
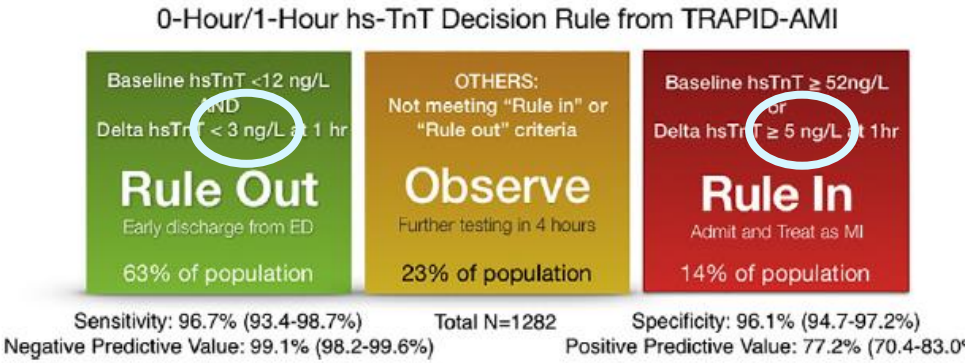


1 toestel

CVw

Geautomatiseerd systeem met meerdere identieke modules

CVas < 0.5 * CVw



Kleine verschillen moeten meetbaar zijn: mag niet te wijten zijn aan analytische fouten!

Stalen van éénzelfde patiënt altijd over zelfde module?

Wat met negatieve verandering na 1h?

Praktisch: etikettensysteem, stiptheid op spoed, tubes markeren,…?

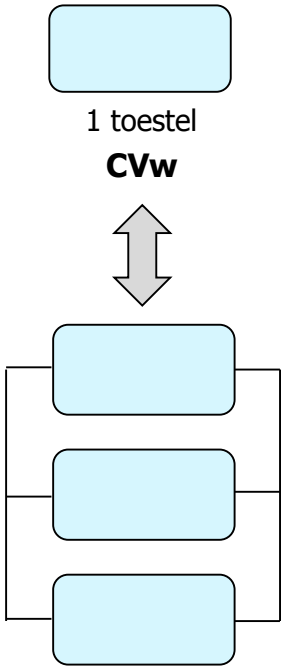
?

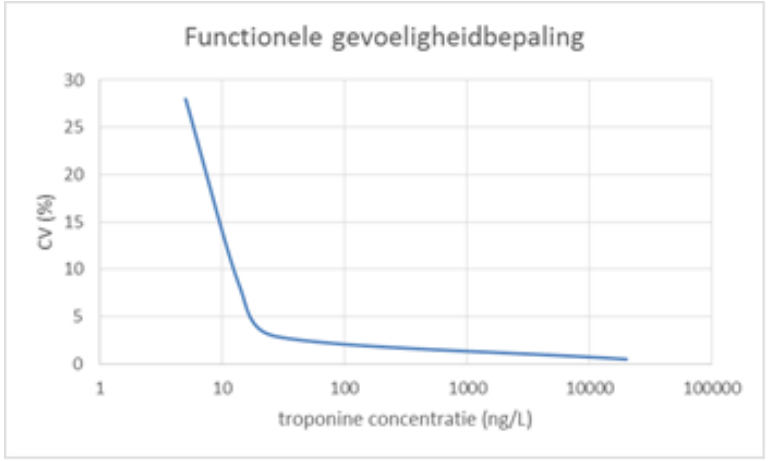
Analytische problemen?

Antwoord vraag 2

Welke analytische problemen brengt het 1h protocol met zich mee?

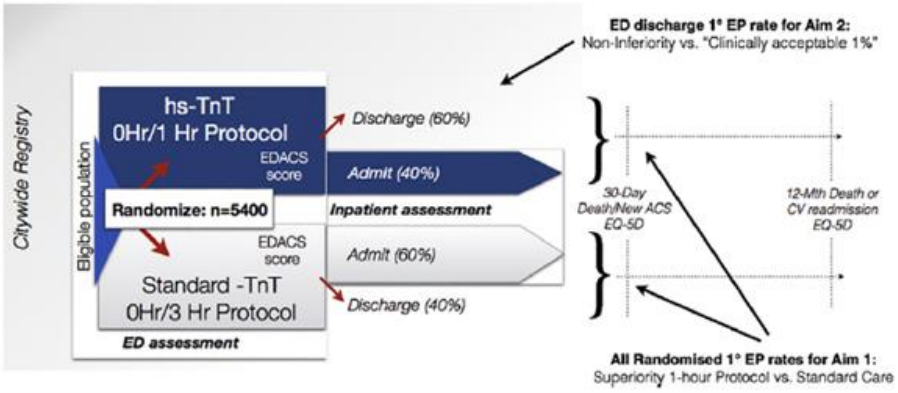
Hoe streng zullen we moeten zijn?





Meerwaarde van het 1h protocol?

Effectiviteit

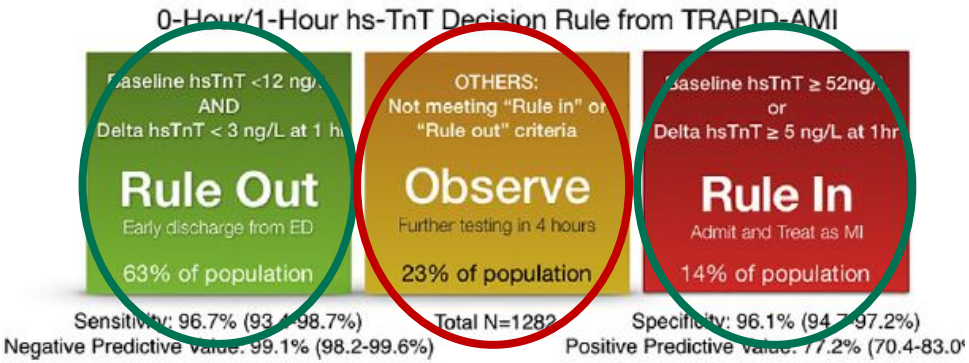


3h protocol versus 1h protocol (Pendick et.al. 2017)

- Hoger % in de 'rule-out'
- Betere definitie van de 'rule-in'
- Nood aan individuele inschatting van de pretestprobabiliteit a.d.h.v. risicoscore.
- Vanaf welke posttestprobabiliteit een behandeling starten?

Duidelijkheid

Diagnostische mist opklaren

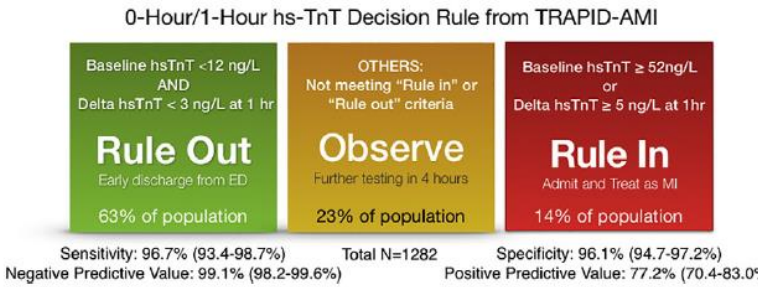


Meerwaarde van het 1h protocol?

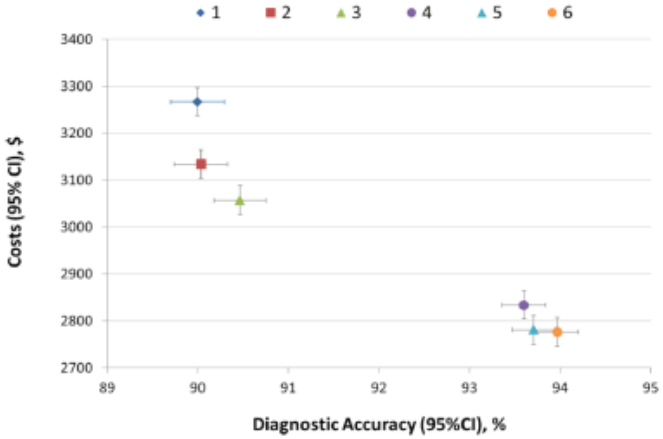
Snelheid

3h protocol ⟺ 1h protocol

Niet-invasieve aanpak



Kostenbatenanalyse



Jülicher et.al. 2017

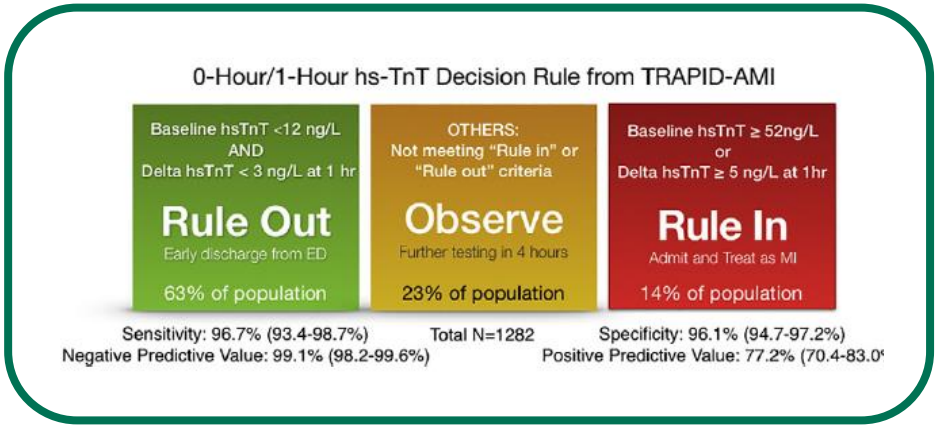
Meerwaarde van het 1h protocol?

Antwoord vraag 3

Wat is de meerwaarde van het 1h protocol?

Duidelijk

Effectief



Snel

Mogelijkheid tot niet-invasieve benadering

Kostenbesparend

To Do's

Studie zal opgestart worden:

Bevestigen meetbaarheid lage concentraties met een CV onder de 10%.

Functionele gevoeligheidsbepaling voor al onze verschillende analyzers tot n=6 om te achterhalen of het 1h protocol haalbaar is in een multimodale setting.

Bijkomende studies zijn nodig:

Om de 'outcome' te bestuderen om op die manier te kunnen inschatten welke posttestprobabiliteit voldoende hoog is om een behandeling te starten. Want belangrijker dan het verbeteren van de test zelf, is het verbeteren van de interpretatie ervan.

Referenties

INLEIDING
TNT-ASSAYS
ANALYITSCHE PERFORMANTIE
DIAGNOSTISCHE PERFORMANTIE
DIAGNOSTISCHE ALGORITMES
3H PROTOCOL
1H PROTOCOL
TO DO'S

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Bedankt voor uw aandacht!
Vragen?