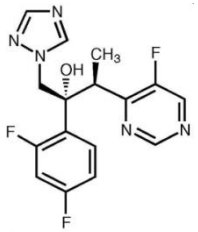
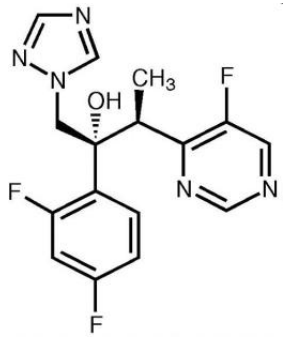
Voriconazoledosage: voor wie nuttig?

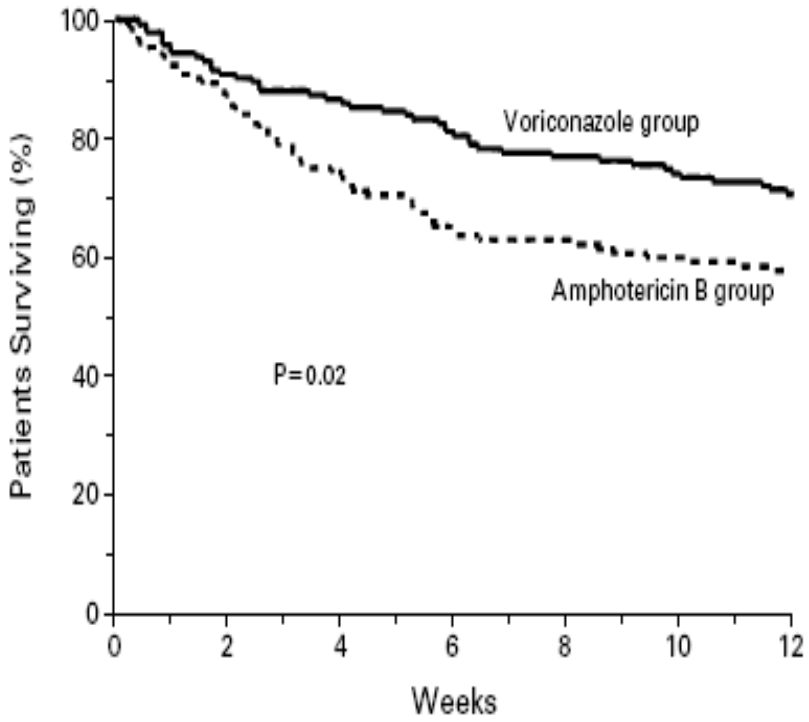


Apr. Steven Pauwels

15 maart 2011

Voriconazole





Herbrecht R et al. NEJM **2002**;347: 408–15.

Gebruik

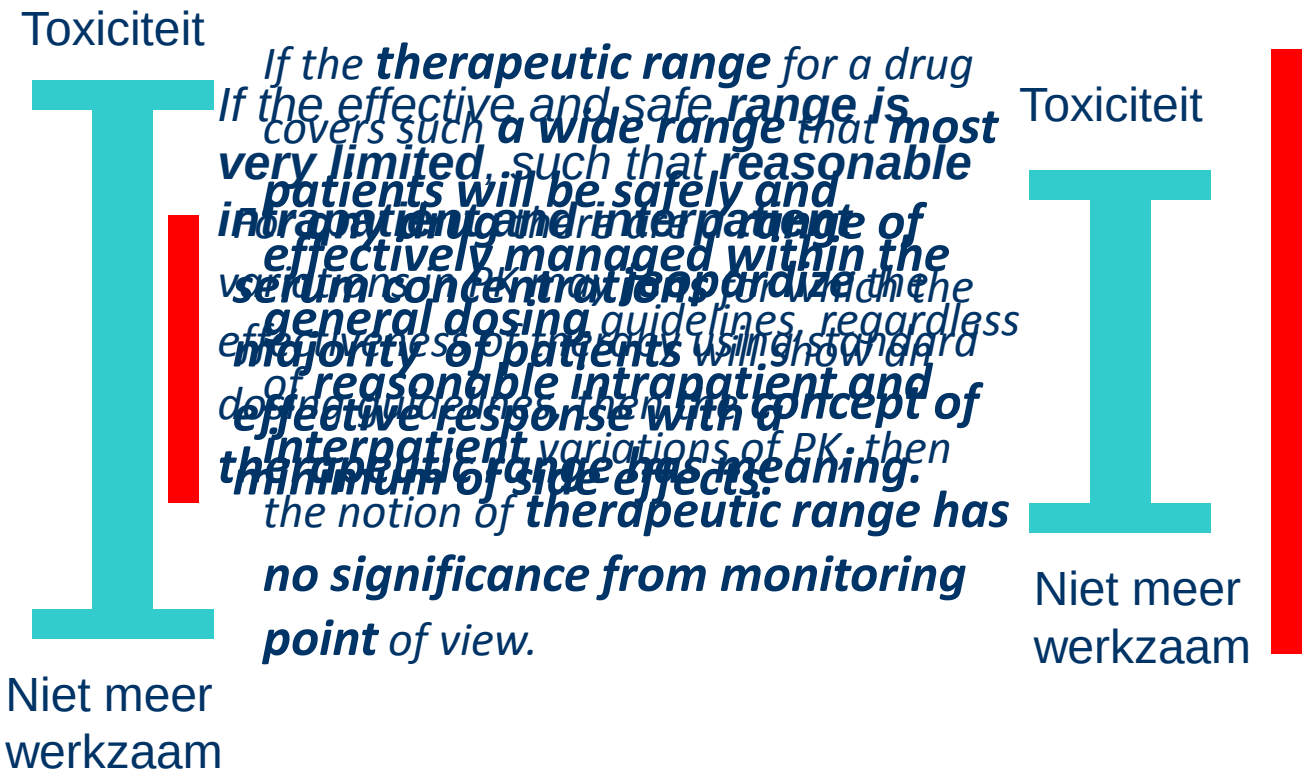
1ste lijn probable/proven IA bij ernstig immuungecompromiteerde patiënten

1ste lijn proven IA bij niet immuungecompromiteerde patiënten

behandeling van invasieve candidiase/candidemie met fluconazol-resistente *Candida spp*.

behandeling van invasieve infecties veroorzaakt door *Scedosporium* of *Fusarium* spp.

Therapeutic Drug Monitoring



*If the **therapeutic range** for a drug covers such **a wide range** that **most patients will be safely and effectively managed within the general dosing** guidelines, regardless of reasonable intrapatient and interpatient variations of PK, then the notion of **therdpeutic range has no significance from monitoring point** of view.*

*If the effective and safe **range is very limited**, such that **reasonable intrapatient and interpatient variations can jeopardize the effectiveness of therapy using standard dosing guidelines, then the therapeutic range has meaning.***

Therapeutic range** is the range of **serum concentrations** at which the **majority of patients** will show an **effective response with a minimum of side effects.

Lewis RE. CID 2008;46:212-214

Voriconazole TDM?

Efficacy and Safety of Voriconazole in the Treatment of Acute Invasive Aspergillosis

David W. Denning,[1] Patricia Ribaud,[2] Noel Milpied,[3] Denis Caillot,[4] Raoul Herbrecht,[5] Eckhard Thiel,[7] Andrea Haas,[6] Markus Ruhnke,[8] and Hartmut Lode[9]

Gebaseerd op de data van de registratiestudie (*Herbrecht et al. 2002*)
116 patiënten met proven/probable aspergillose

Werkzaamheid:

5 ptn met concentratie Voriconazole < 0.25 mg/L: 4 ptn falen
6 ptn met concentratie Voriconazole 0.25-0.50 mg/l: 1 pt falen
(consistent met hele populatie)

Veiligheid:

22 ptn met concentratie Voriconazole > 6 mg/L: 6 hepatotoxiciteit
7 ptn met concentratie Voriconazole > 10 mg/L: 6 ptn adverse events

Denning DW et al. CID **2002**;34:563–71. slide format aangepast naar apr. I Spriet,

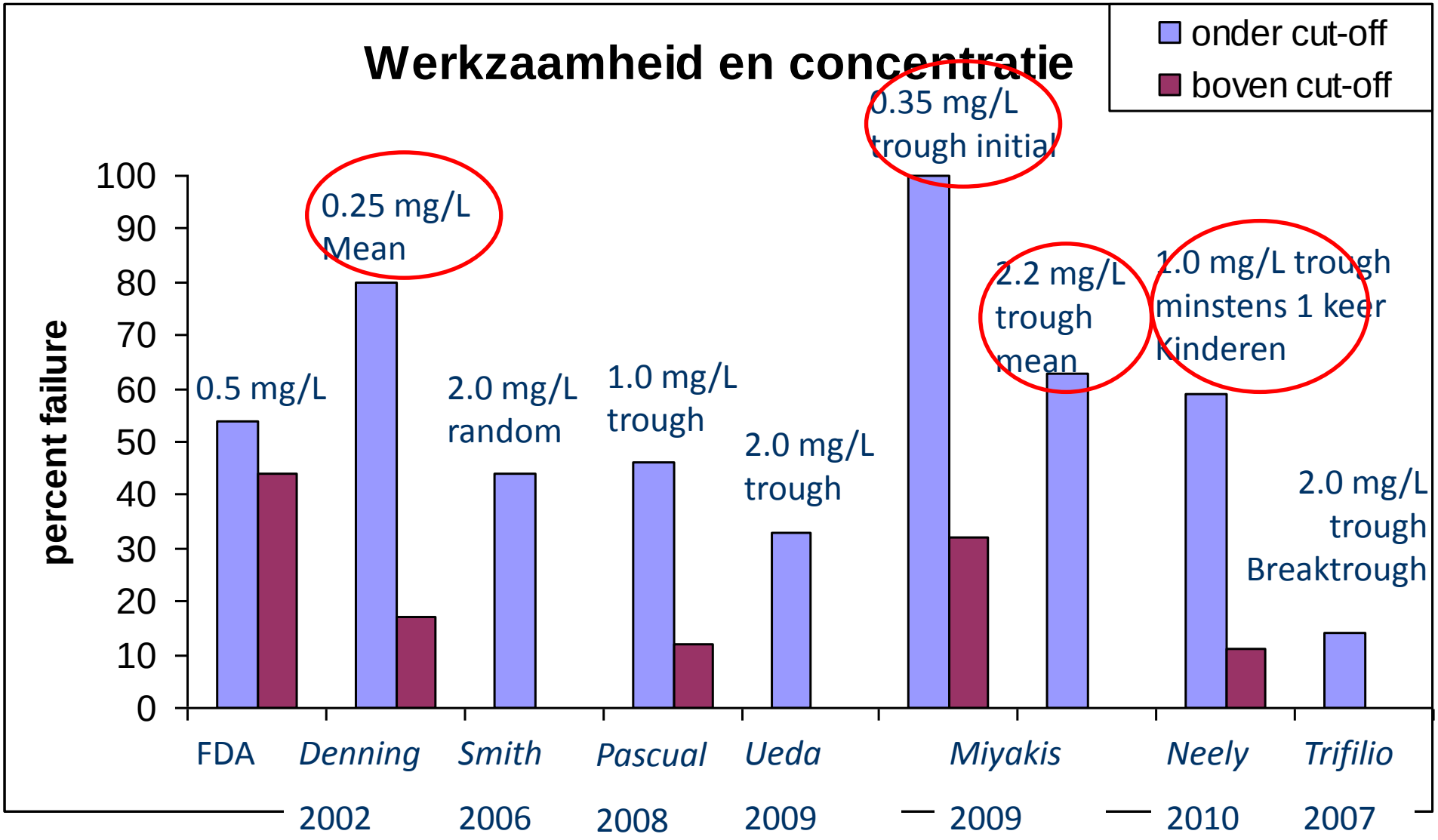
Study Design	Patient Population	Voriconazole Dosage	Comments	Clinical Findings: Efficacy
Prospective, observational	52 patients with proven, probable, or possible invasive fungal infections; 60% with hematologic malignancy; voriconazole was used as primary or secondary therapy	Loading dose: 12 mg/kg/day Maintenance dose: 5–8 mg/kg/day 77% received i.v. formulation	Trough levels: 12 hrs after dosing; first trough level measured 5 days (median) after start of therapy and repeated every 7 days (range 1–62 days)	Therapy failure more frequent with trough level of ≤ 1 mg/L vs > 1 mg/L (46% vs 12%) Nonresponders with trough levels < 1 mg/L responded with dose escalation
Open-label, noncomparative	116 patients with proven or probable invasive aspergillosis; 78% with leukemia and BMT; voriconazole was primary or salvage therapy	6 mg/kg i.v. q12h 2 doses, then 3 mg/kg i.v. q12h 2 doses followed by 200 mg p.o. q12h	Random levels measured	Almost one third of patients failed treatment Treatment success in 70% of patients with random levels > 0.5 mg/L vs 20% in patients with random levels < 0.25 mg/L
Retrospective, observational	71 allo-HSCT recipients with hematologic malignancy; voriconazole used for fungal prophylaxis	200 mg p.o. q12h	Steady-state trough level measured at least 5 days after start of therapy	6 of 43 patients with trough level ≤ 2 mg/L had breakthrough fungal infection vs no patients with trough level > 2 mg/L (p=0.061)

Study Design	Patient Population	Voriconazole Dosage	Comments	Clinical Findings: Efficacy	Clinical Findings: Toxicity
Retrospective, observational	34 Japanese patients receiving chemotherapy for hematologic malignancies; voriconazole given for proven, probable, or possible fungal infection or febrile neutropenia	Began orally (according to manufacturer's recommendation) unless patient unable to tolerate oral intake	First trough level measured 9 days (median) after start of therapy	No correlation between trough levels and response to therapy in patients with refractory disease In patients without refractory disease, trough level > 2 mg/L was associated with treatment success	Trend of elevated LFT results observed with trough level > 6 mg/L
Retrospective, observational[11]	25 immunocompromised patients receiving voriconazole for treatment of proven or probable fungal infections	Average dose: 6.7 mg/kg/day 76% received oral formulation	Steady-state trough level measured 7 days (median) after start of therapy	Initial steady-state trough level was best predictor of survival, with 100% mortality if level ≤ 0.35 mg/L Median voriconazole level > 2.2 mg/L was best predictor of response	No linear relationship between trough level and elevated LFT results

Study Design	Patient Population	Voriconazole Dosage	Comments	Clinical Findings: Efficacy	Clinical Findings: Toxicity
Retrospective, observational	25 allo-HSCT recipients with hematologic disease; voriconazole used either prophylactically or empirically for febrile neutropenia	200 mg p.o. q12h, increased to 300 mg p.o. q12h in four patients with low serum levels	Steady-state trough levels measured 15 days (median) after start of therapy	Not reported	Elevated aspartate aminotransferase and alkaline phosphatase levels correlated with increased voriconazole trough levels
Retrospective, observational	25 patients with Hematologic malignancy who received voriconazole for proven or probable invasive fungal infection	200–400 mg p.o. q12h	Trough levels Measured	Not reported	Elevated trough levels significantly associated with neurologic adverse events No correlation between voriconazole levels and elevated LFT results
Prospective cohort	72 patients with cancer	Standard doses	Trough levels measured	Not reported	6 patients developed auditory and visual hallucinations; voriconazole trough levels in 5 of the 6 were > 5 mg/L

Study Design	Patient Population	Voriconazole Dosage	Comments	Clinical Findings: Efficacy	Clinical Findings: Toxicity
Retrospective, observational	25 allo-HSCT recipients with hematologic disease; voriconazole used either prophylactically or empirically for febrile neutropenia	200 mg p.o. q12h, increased to 300 mg p.o. q12h in four patients with low serum levels	Steady-state trough levels measured 15 days (median) after start of therapy	Not reported	Elevated aspartate aminotransferase and alkaline phosphatase levels correlated with increased voriconazole trough levels
Retrospective analysis of safety and pharmacokinetic data from 10 phases II and III clinical trials	1053 heterogeneous patients but all were immunocompromised and 50% were neutropenic; voriconazole used as both empiric and targeted antifungal therapy	Not reported	Weekly mean plasma concentration measured	Not reported	Positive association between mean voriconazole level and visual adverse events (p=0.011) and a weaker but still significant association with increased LFT results

Hussaini et al.Pharmacotherapy 2011;31:214-225


Werkzaamheid en concentratie
onder cut-off
boven cut-off
percent failure
100
90
80
70
60
50
40
30
20
10
0
0.5 mg/L
0.25 mg/L Mean
2.0 mg/L random
1.0 mg/L trough
2.0 mg/L trough
0.35 mg/L trough initial
2.2 mg/L trough mean
1.0 mg/L trough minstens 1 keer Kinderen
2.0 mg/L trough Breaktrough
FDA
Denning 2002
Smith 2006
Pascual 2008
Ueda 2009
Miyakis 2009
Neely 2010
Trifilio 2007

Concentratie en toxiciteit

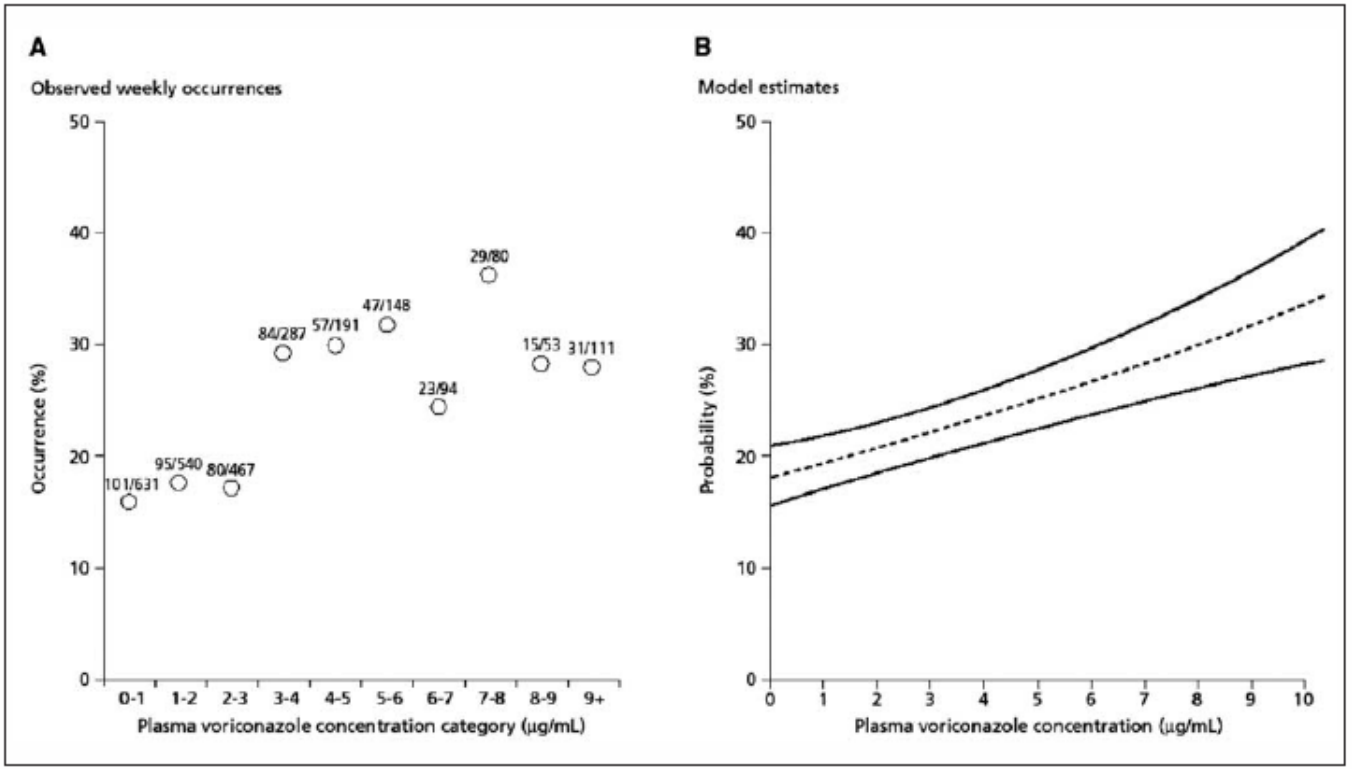


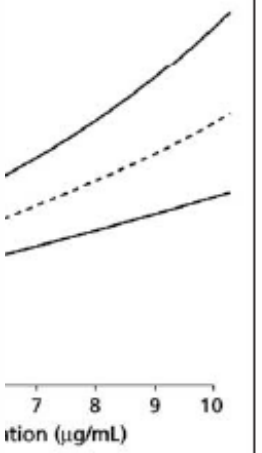
Figure 1. Plasma voriconazole concentrations and visual adverse events. The percentage weekly occurrence shown is the number of events observed in weekly time periods over the total number of weekly time periods (numbers shown above each symbol) for each plasma voriconazole concentration category.

Tan K, et al. J Clin Pharmacol 2006;46:235–43.

Concentratie en toxiciteit

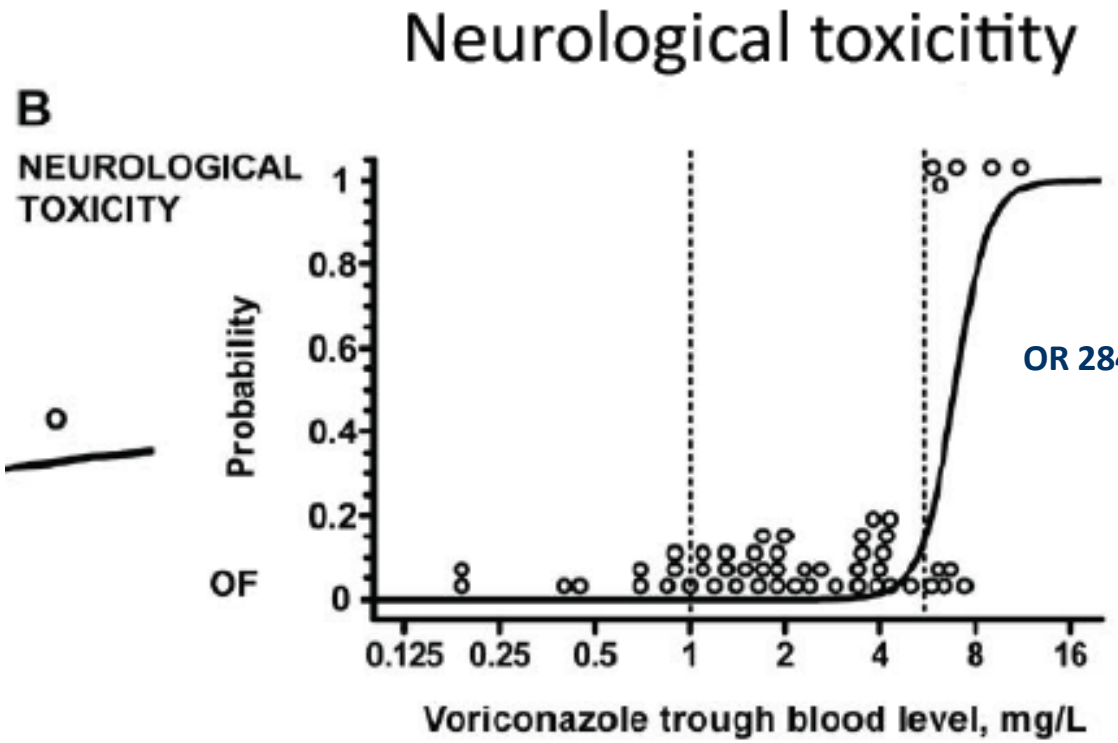
Table II Key Statistics From Longitudinal Logistic Regression (Odds Ratios per 1 µg/mL After Adjusting for Covariates)

Abnormality/Event	Odds Ratio	Lower 95% Bound	Upper 95% Bound
ALT	1.07	0.97	1.19
AST	1.13	1.06	1.20
ALP	1.16	1.08	1.25
Bilirubin	1.17	1.08	1.27



Tan K, et al. J Clin Pharmacol 2006;46:235–43.

Concentratie en toxiciteit

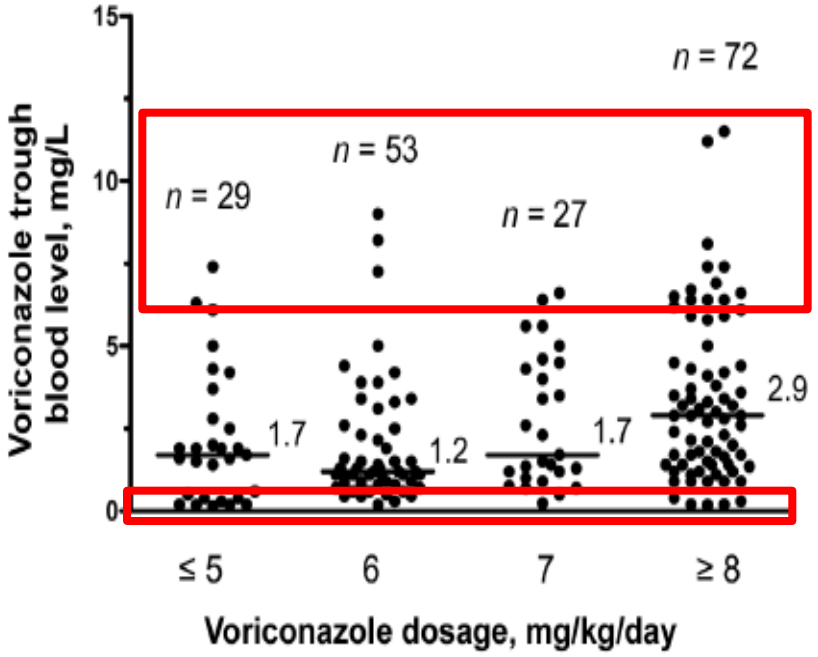


OR 284, 0.96-84 407 95%CI

Einde na stop Voriconazole

Pascual A, et al. CID 2008;46:201–11.

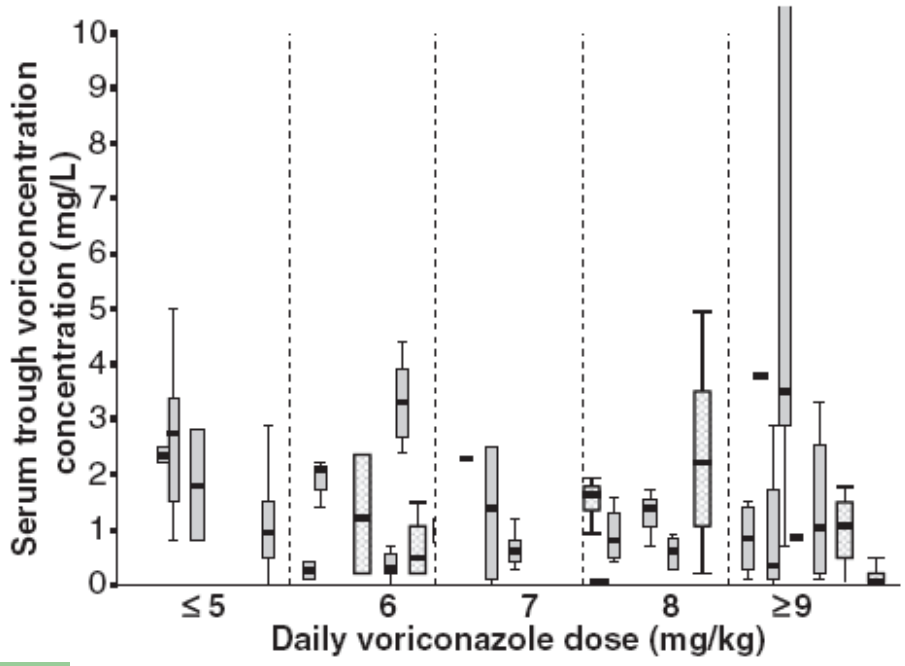
Variabiliteit



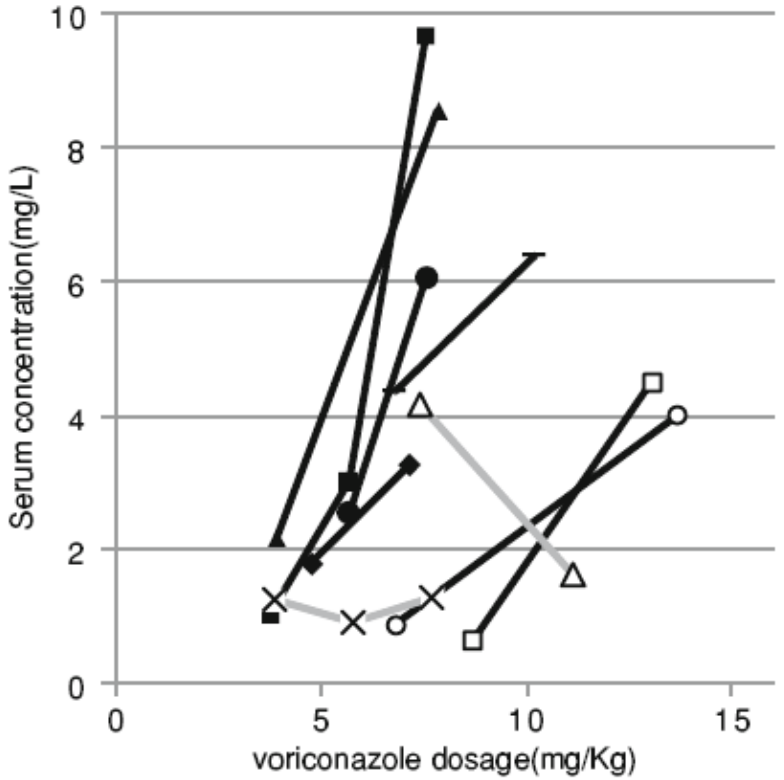
1. Niet-lineaire kinetiek bij volwassenen
2. Uitgebreid CYP450 metabolisme: Geneesmiddeleninteracties
3. Genetisch polymorfisme CYP2C19
4. Bij perorale behandeling: invloed van voeding
5. Subgroepen (vb. kinderen: lineair)

Pascual A et al. CID 2008;46:201–1.

Variabiliteit

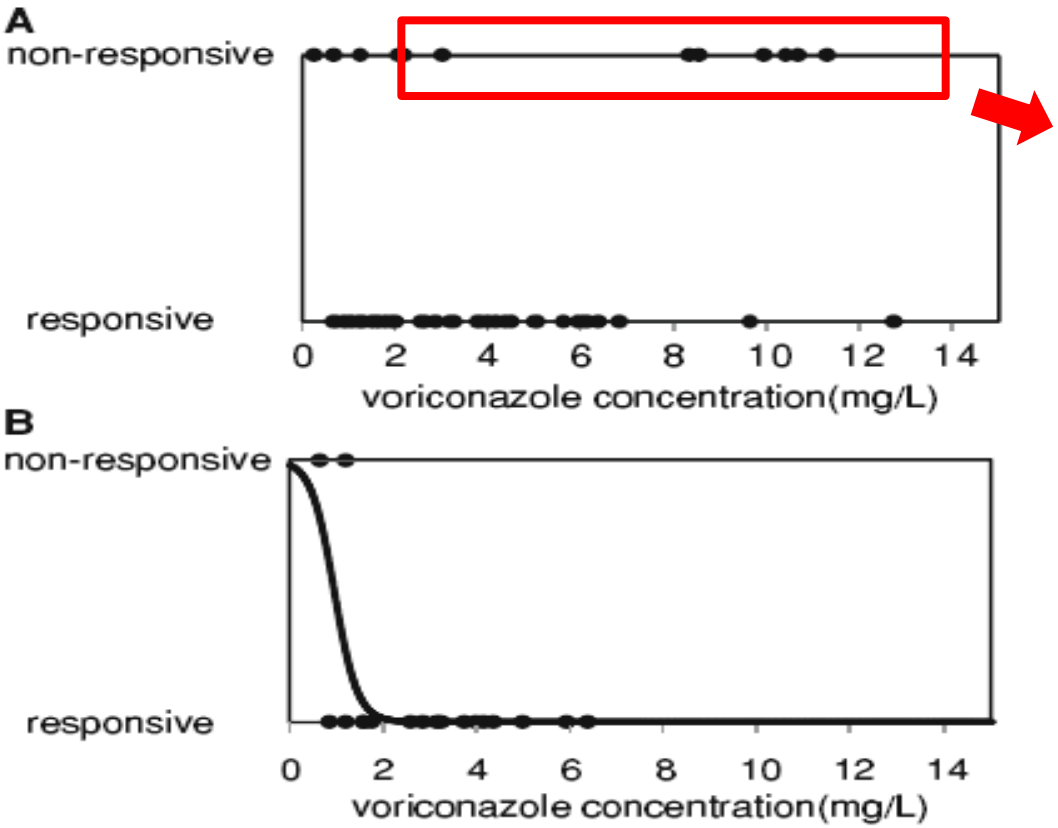


Miyakis S, van Hal SJ, Ray J, Marriott D.
Clin Microbiol Infect 2010;16:927–33.



Ueda K, Nannya Y, Kumano K, et al. Int J Hematol **2009**;89:592–9

Multifactorieel

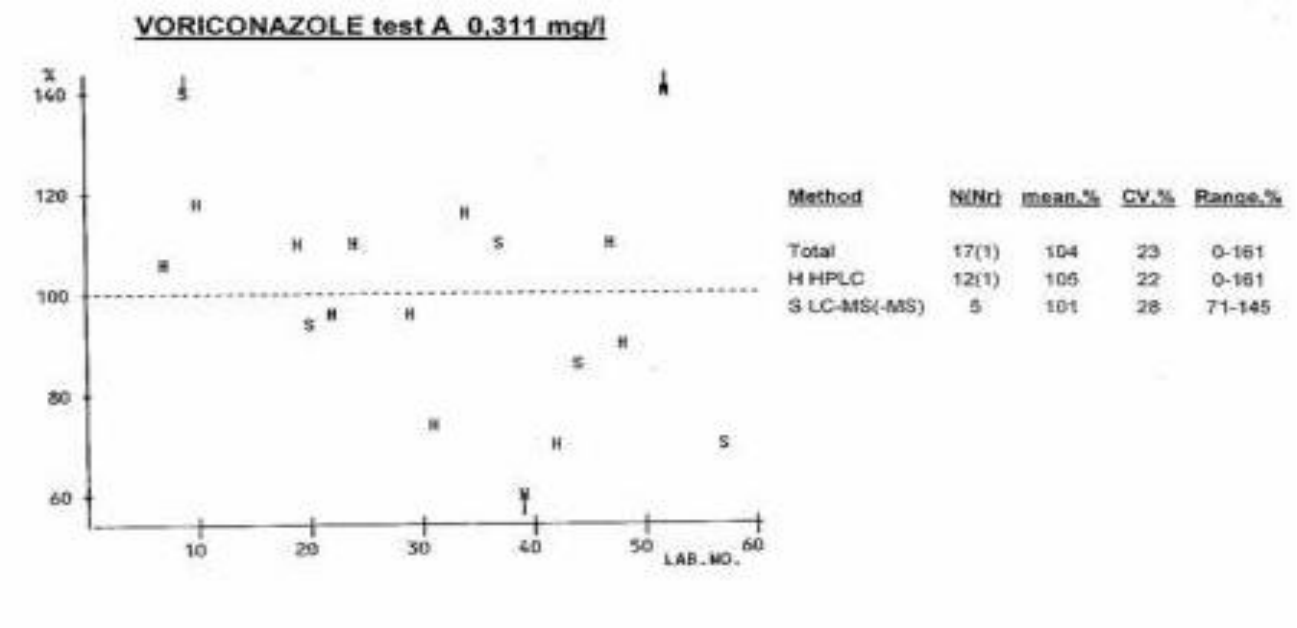


Refractaire hematologische ziekte

Andes D, Pascual A, Marchetti O. AAC **2009**;53:24-34

Ueda K, Nannya Y, Kumano K, et al. Int J Hematol **2009**;89:592–9

Analytische variatie



Method	N(Nr)	mean,%	CV,%	Range,%
Total	17(1)	104	23	0-161
H HPLC	12(1)	105	22	0-161
S LC-MS(-MS)	5	101	28	71-145

KKGT-rapport, 2010

Controlegroep

nAE bij 5/52, allen > 5.5 mg/L

LFT (ernstig) > 5.5 mg/L (3/16) (19%) vs. 3/36 (8%) lagere spiegel, totaal 6/52 (12%)

P=0.7, FE

nAE bij 2/39

LFT (ernstig) bij 5/39 (13%)

TDM (prospectief) (52 ptn)

Geen TDM (retrospectief) (39 ptn)

P= 1.00, FE

Respons 41

Geen respons 11

Respons 30

Geen respons 9

≤ 1 mg/L 6

>1 mg/L 5

6/6 via +50%

3/4 (5?) via salvage

2/3* via +50%

1/2 via salvage

4 geen verandering

9/11 respons

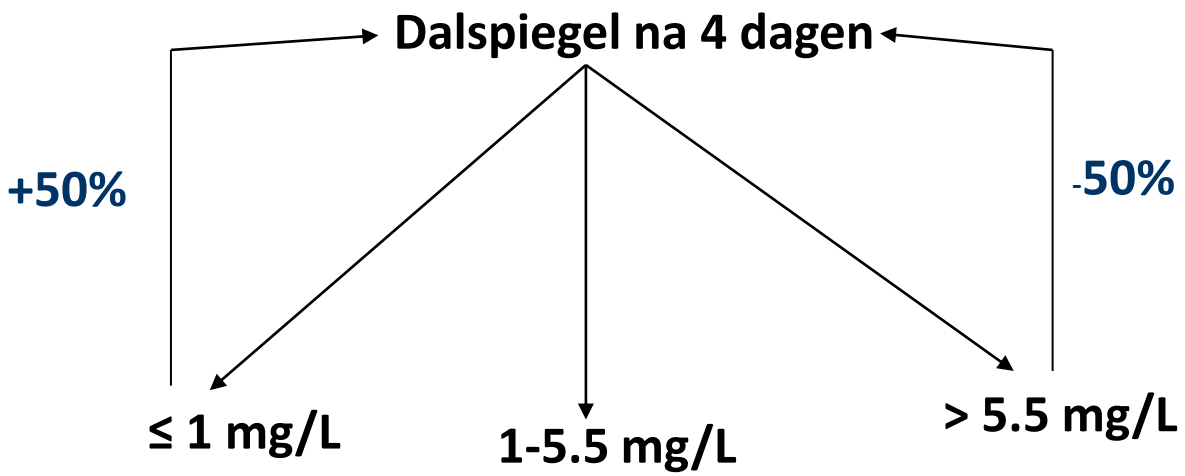
P= 0.06, FE, 1tailed

3/8 (9,P =0.04)* (1 geen FU) **respons**

Pascual A et al. CID 2008;46:201–1.

UZ Leuven

Basis: studie impact TDM voriconazole (Brüggemann)



Respons
Toxiciteit
GI-dysfunctie
IV-PO
Kinderen
Interacties
IZ

	1e meting (dagen, type)	Werkzaamheid (mg/L)	Toxiciteit (mg/L)	Indicatie	Opmerkingen
Hussaini. 2011	5 , dal	>1-2	<5-6	TDM **noodzakelijk** om therapie te optimaliseren (**geen subgroep onderscheid**)	Breekpunten niet goed gedefinieerd Onzekerheid over tijdstip 1e staalname en frequentie (waarschijnlijk 1 niet representatief) Geen systematische aanpak voor dosis aanpassingen
Pasqualotto . 2010	5-6		<5-6	Minimalisatie van toxiciteit door TDM	Toxiciteit meestal klinisch duidelijk of via andere labtesten; meestal mild-matige bijwerkingen Tijdstip 1e afname onzeker Hertesten nodig voor werkzaamheid
Andes. 2009	4-7 , dal	> 0.5 profylaxe > 1-2 therapie	< 6	**Alle patiënten** bij start; Verder: slechte respons, GI-dysfunctie, comedicatie, kinderen, iv naar po, ernstige levertoxiciteit of neurologische tekenen eci	Therapeutisch interval onzeker Concentratie in bloed is niet noodzakelijk gelijk concentratie in doelorgaan Resultaten best < 1 week beschikbaar
Smith.2008	2-3 , dal	> 0.5-2		**Alle patiënten** bij start; verder bij slechte respons, comedicatie (interactie), switch iv naar po	Slecht gedefinieerde minimum dalspiegel Geen TDM voor toxiciteit (weinig frequent leverfalen en voorbijgaande visusstoornissen)
Brüggemann . 2008	5-7 , dal (korter indien opladen)	> 1 > 2 voor hersenen, ogen	< 6	**Subgroep** patiënten: Kinderen, hoog BMI, abnormale leverfunctie, comedicatie (interferentie), uitgesproken toxiciteit, switch iv naar po, compliance, na dosisaanpassing, Aziaten	Slecht gedefinieerd therapeutisch interval Geen dosis aanpassingsschemas TAT best < 48 uur Frequent monitoren na dosisaanpassing (1 maal per week)
Hopel. 2008	Dal, SS	>1	< 5-6	**Routinematig**	Meerdere spiegelbepalingen nodig om initieel therapeutische spiegels aan te tonen
Goodwin. 2008		>2 (dal)	<6 (piek)	**Progressieve ziekte, toxiciteit , interactie** , compliance	Voor studie van *Pascual et al.*
Dodds . 2006	7, dal	>2	<6		Voor studie van P*ascual et al.*

Routinematig spiegel + aanpassen?

- **Werkzaamheid**: geen hard bewijs voor nut, wel **vele indicaties** (studie lopende)
  - Vele studies die wijzen op belang voldoende hoge begin – en aangehouden (dal)spiegel
  - Vele **te lage spiegels, zelfs niet-kwantificeerbaar** (tot 19.4%) en variabiliteit in kwasi alle subgroepen die voriconazole krijgen beschreven

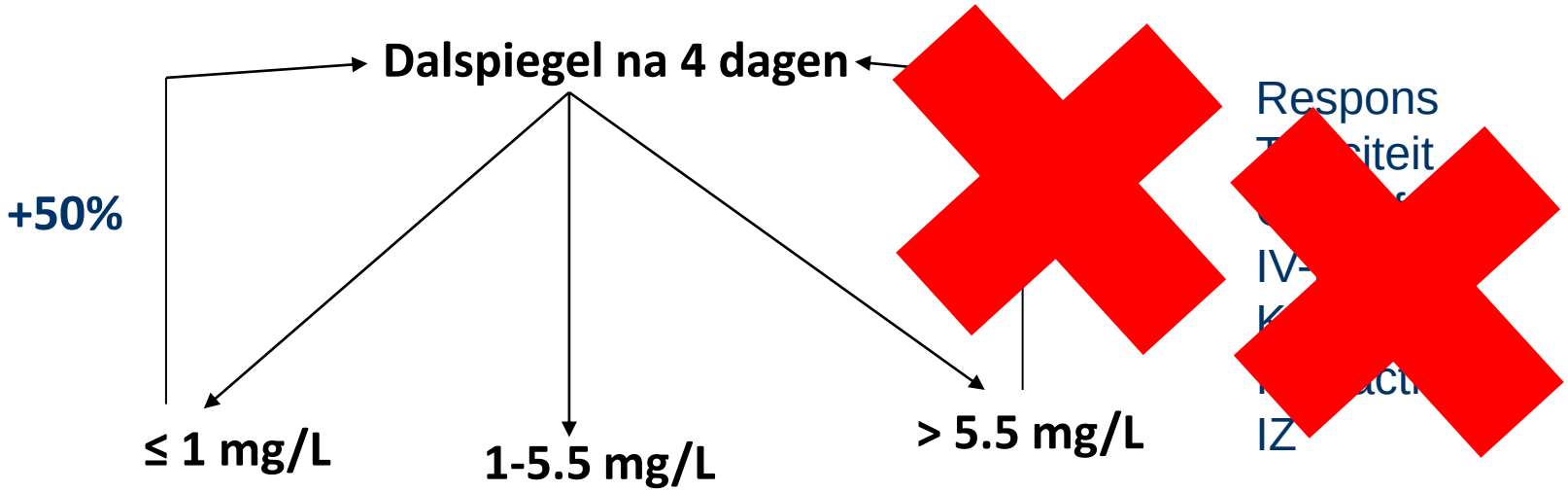
Routinematig spiegel + aanpassen?

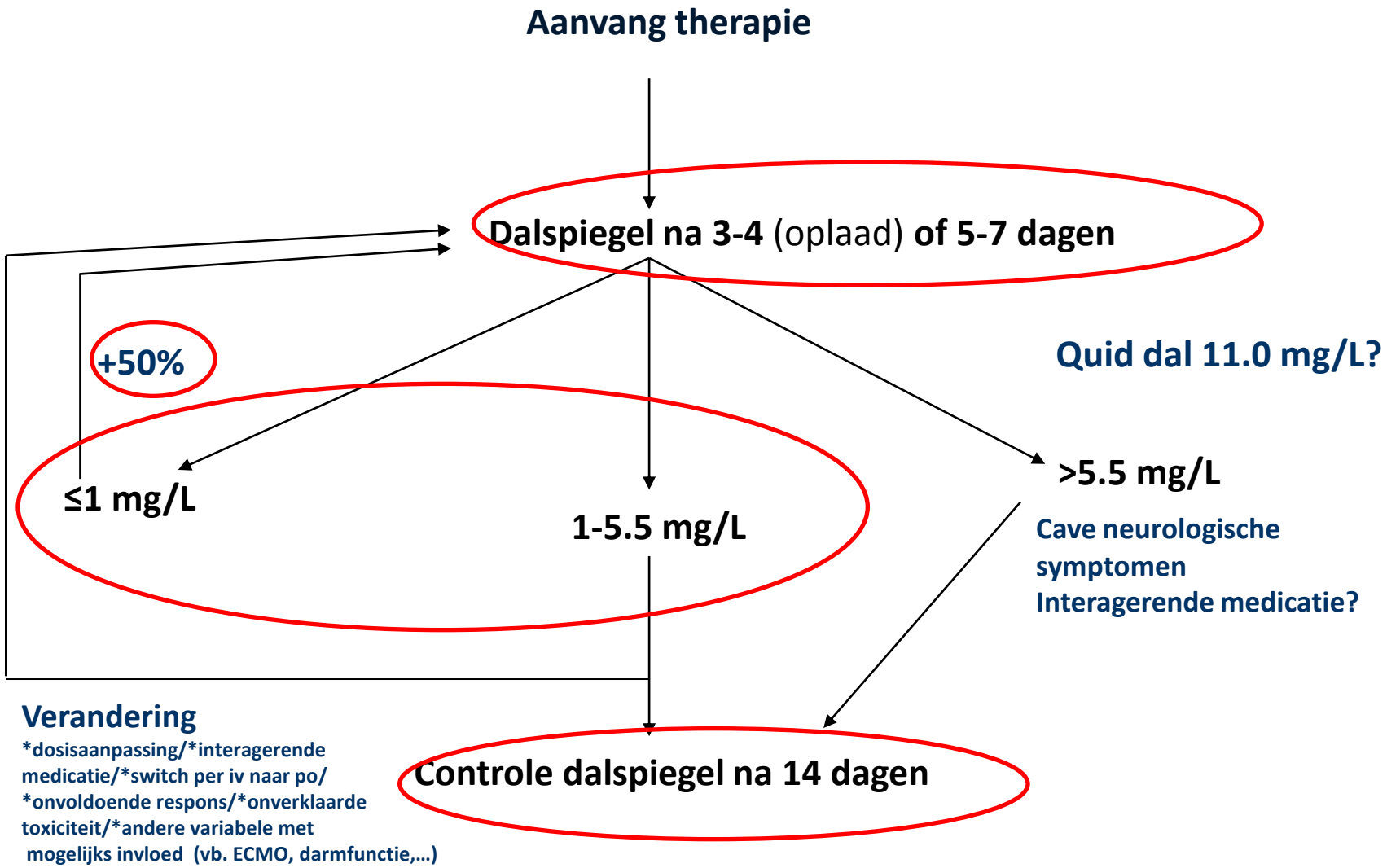
- Niet aangewezen voor **toxiciteit**
  - Visusstoornissen transient, zonder restletsels
  - Rash: wss niet gecorreleerd met spiegel
  - Leverfunctie: zeer zwakke correlatie!
  - nAE (gepoolde analyse 3 publicaties cfr. CAT)
    - Gevaar verlagen dosis (1 op 2 boven 5.5 mg/L onterecht verlaagd)
    - Beginnen vroeg (mediaan 3 dagen na start (1-30))
    - Vd=4.7 L/kg
    - Ook bij lagere spiegels (sensitiviteit=76%, bij cut-off=5.5 mg/L))

Tan K, et al. J Clin Pharmacol 2006;46:235–43.

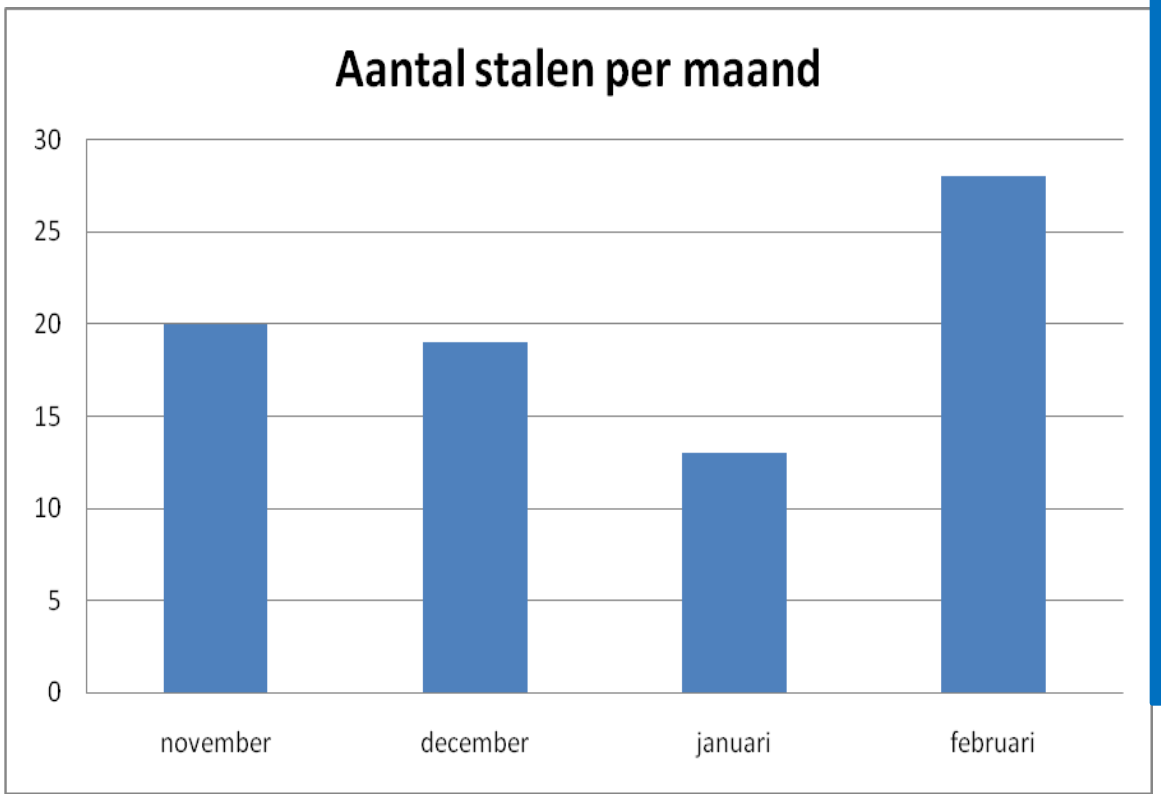
UZ Leuven

Basis: studie impact TDM voriconazole (Brüggemann)



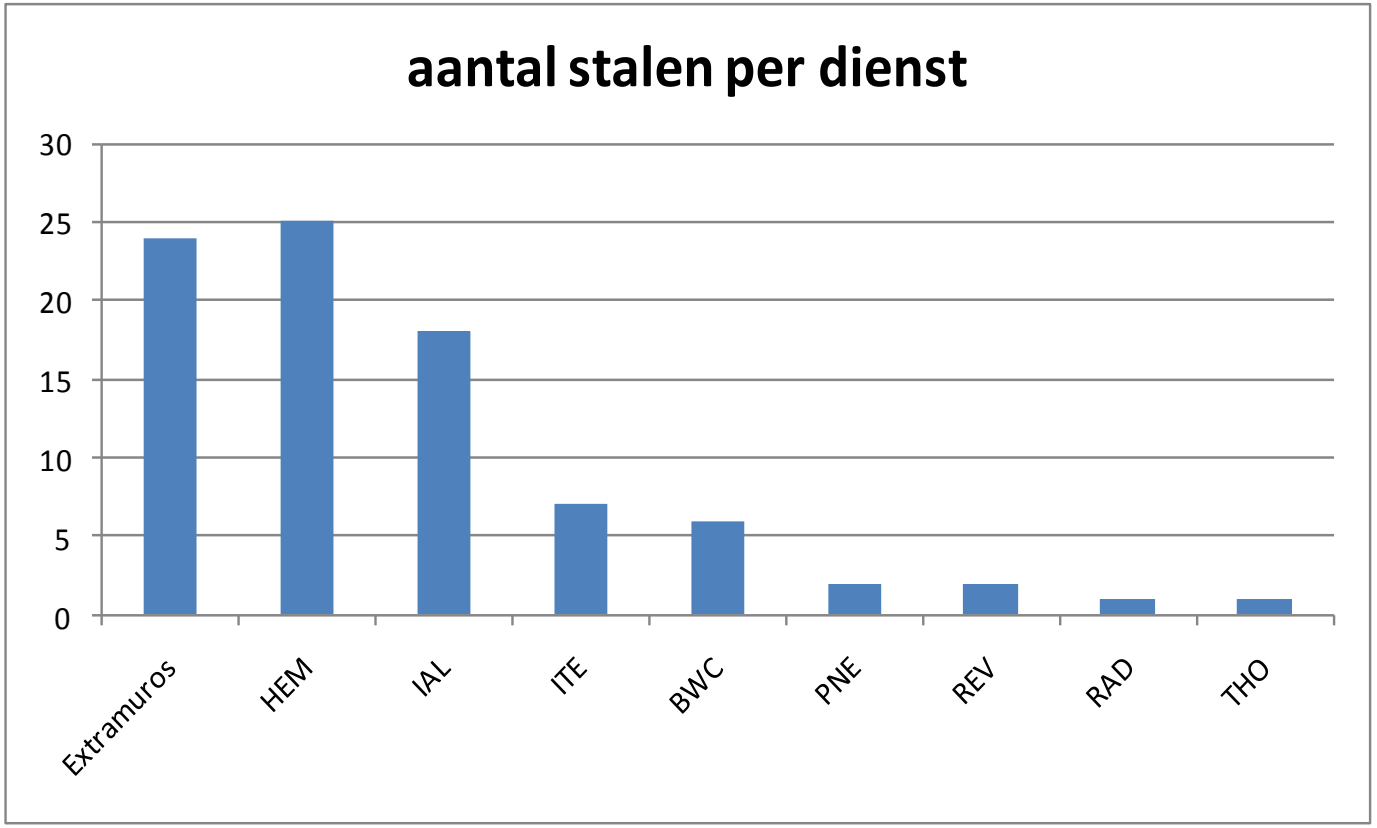

Aanvang therapie
Dalspiegel na 3-4 (oplaad) of 5-7 dagen
+50%
≤1 mg/L
1-5.5 mg/L
>5.5 mg/L
Quid dal 11.0 mg/L?
Cave neurologische symptomen
Interagerende medicatie?
Verandering
*dosisaanpassing/*interagerende medicatie/*switch per iv naar po/ *onvoldoende respons/*onverklaarde toxiciteit/*andere variabele met mogelijks invloed (vb. ECMO, darmfunctie,…)
Controle dalspiegel na 14 dagen

Praktijk



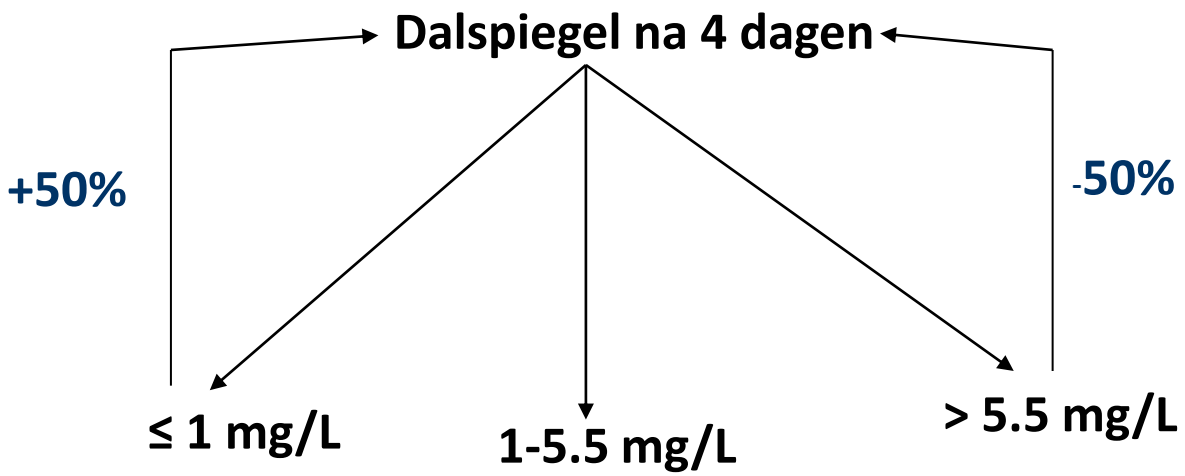
Reeds 40 in maart (5 runs)
8 per run

Praktijk


aantal stalen per dienst
30
25
20
15
10
5
0
Extramuros
HEM
IAL
ITE
BWC
PNE
REV
RAD
THO

UZ Leuven

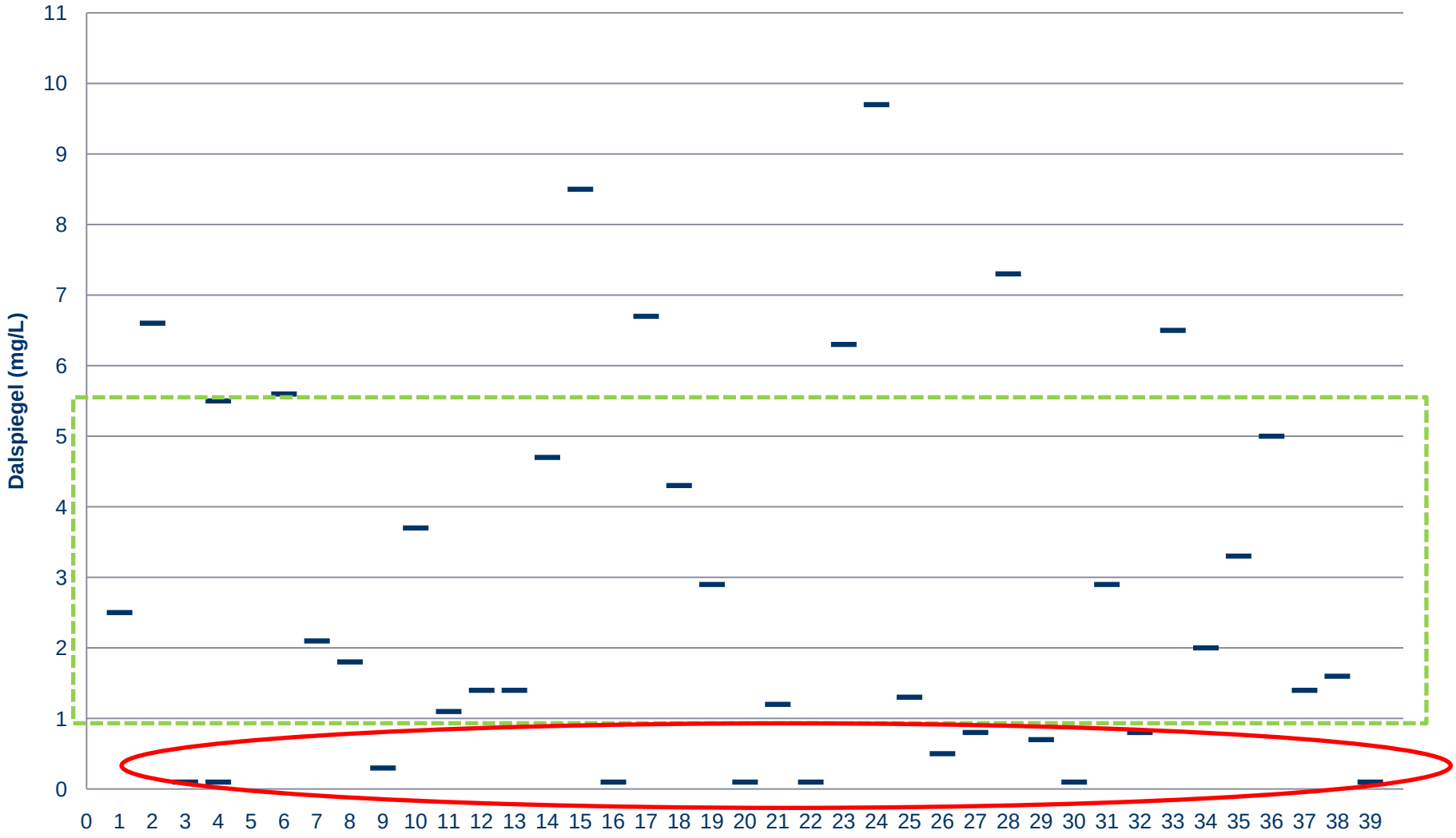
Basis: studie impact TDM voriconazole (Brüggemann)



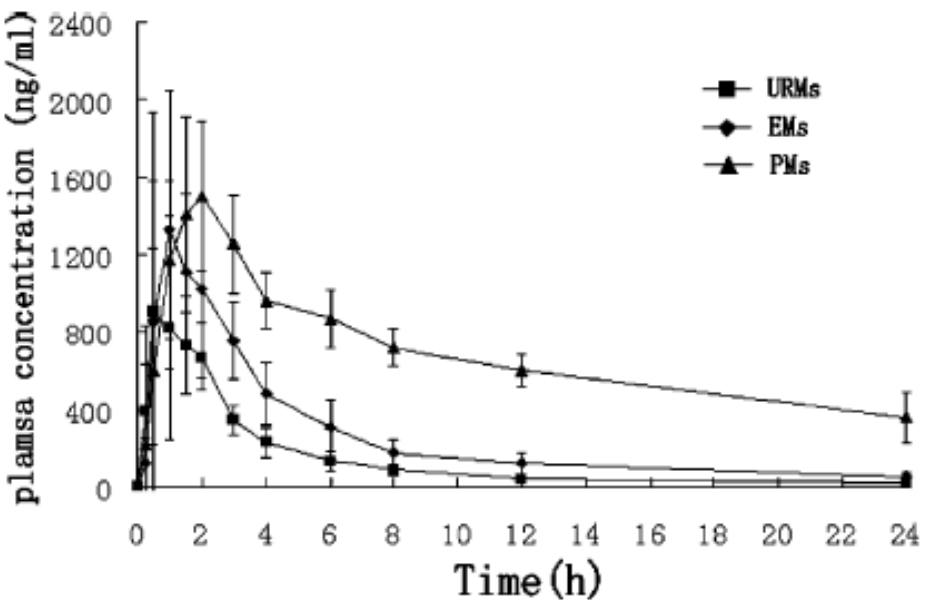
Respons
Toxiciteit
GI-dysfunctie
IV-PO
Kinderen
Interacties
IZ

Enkele gegevens

- Totaal 96 dalspiegels bij 39 patiënten tot 4 maart 2011
- 60 studiestalen
- Bij 22 patiënten opvolgspiegels (med 3 (2-7) per patiënt; med 7 d (0-83) tussen 2 spiegels, ongeveer 10% geen 3 dagen gerespecteerd)
- TAT 95% (receptie-validatie)=75 uur (sinds december)
- TAT 95% (geplande afname – validatie)= 95 uur (sinds december)
- LOQ= 0.2 mg/L


1e Dalspiegel alle patiënten
Dalspiegel (mg/L)
11
10
9
8
7
6
5
4
3
2
1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39

Ultra-rapid metabolizer



- 585 stalen van 273 patiënten
- 19.4% <0.2 mg/L
- 10% slechte therapietrouw
- Prevalentie UM-genotype groter in <0.2 mg/L groep dan in rest populatie
- Ethiopiërs en Zweden (18%)

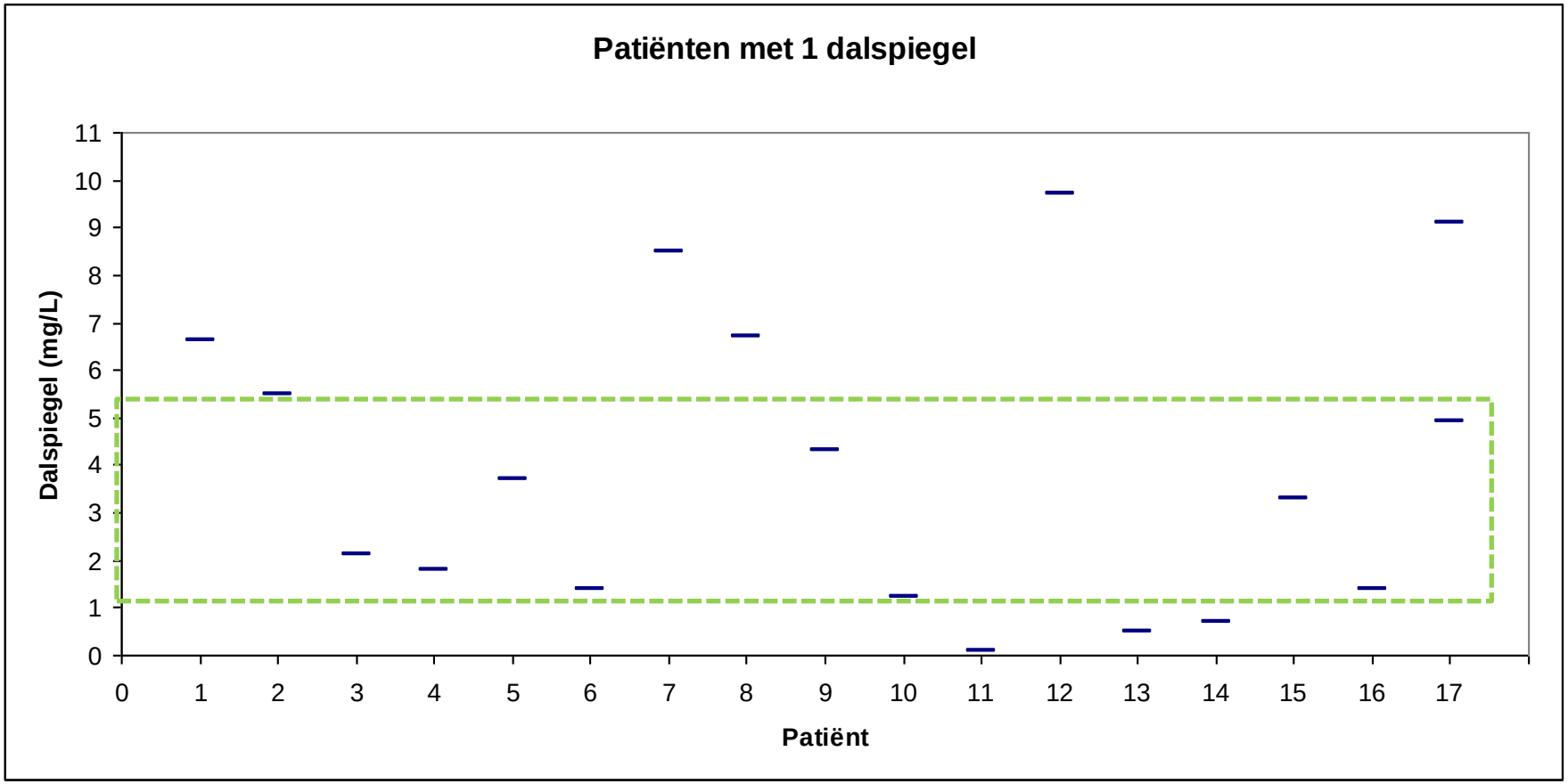
Hassan A et al. Br J Clin Pharmacol 2009;68(suppl.1):6-59

Wang G et al. Eur J Clin Pharmacol. 2009;65:281-5.

	Type dalspiegel		P (two tailed)
Dalwaarde	1e spiegel (%)	Opvolgspiegel (%)	
< 0.2 mg/L	7/39 (17.9)	2/57 (3.5)	**0.04** (Fisher exact)
Laag (< 1 mg/L)	12/39 (30.8)	18/57 (31.6)	0.93 (Chi square)
Hoog (> 5.5 mg/L)	8/39 (20.5)	6/57 (10.5)	0.28 (Fisher exact)
Totaal buiten interval	20/39 (51.3)	24/57 (42.1)	0.38 (Chi square)

Dalwaarde 1e spiegel	Opvolging (%)	Eerstvolgende spiegel binnen interval (kwantificeerbaar)	Eindspiegel binnen interval (kwantificeerbaar)
< 0.2 mg/L	6/7 (85.7)	2/6 (6/6)	3/6 (5/6)*
Laag (< 1 mg/L)	9/12 (75)	4/9 (8/9)	5/9 (8/9)*
Hoog (> 5.5 mg/L)	4/9 (44.4)	3/4	3/4
Totaal buiten interval	13/21 (61.9)	7/13 (11/13)	8/13 (11/13)*
Binnen interval	9/18 (50)	6/9	7/9

* Overgang van niet-kwantifeerbaar naar kwantificeerbaar als goed (niet noodzakelijk binnen interval)


Patiënten met 1 dalspiegel
Dalspiegel (mg/L)
11
10
9
8
7
6
5
4
3
2
1
0
0
1
2
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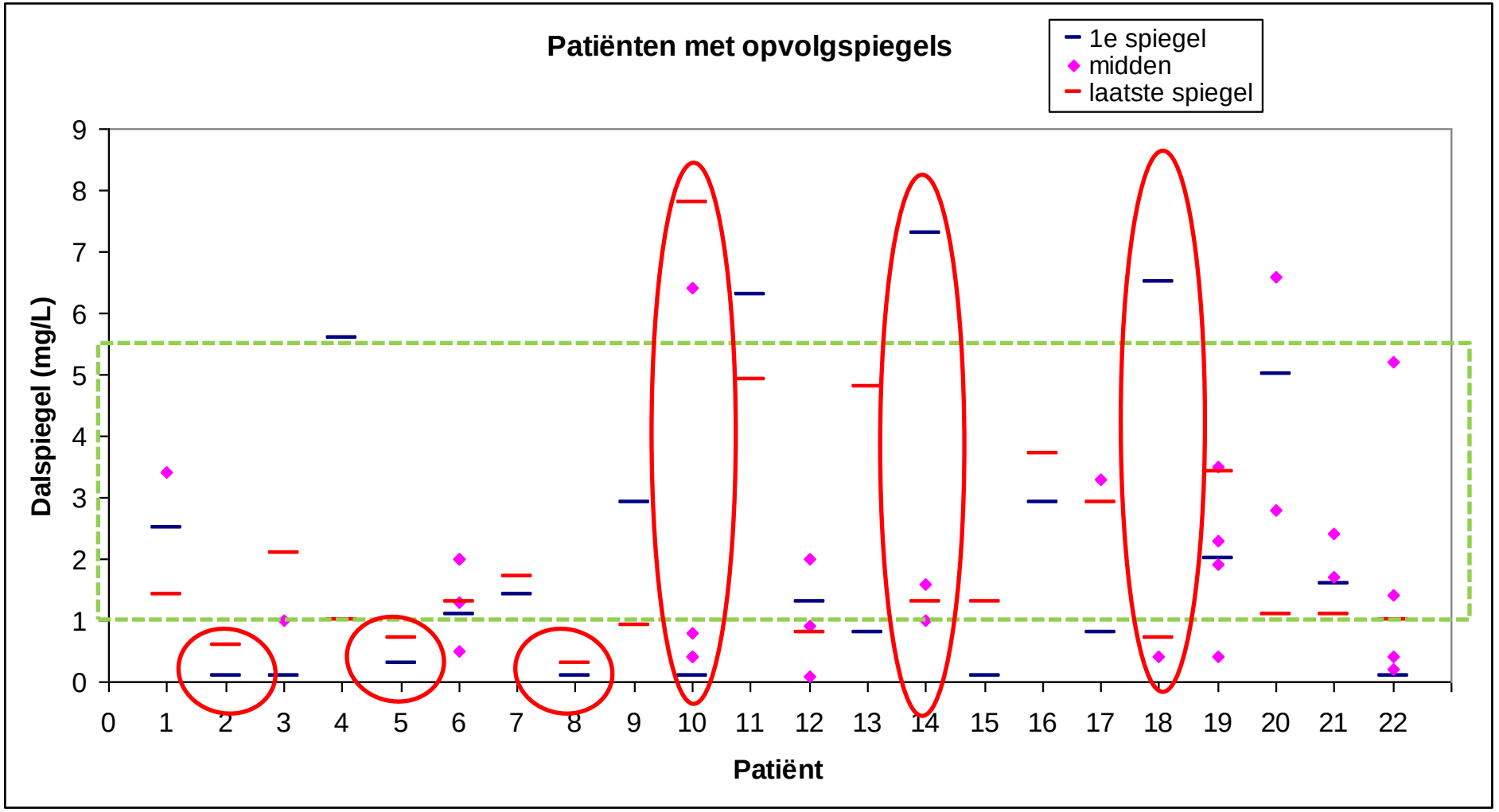
Patiënt


Patiënten met opvolgspiegels
1e spiegel
midden
laatste spiegel
Dalspiegel (mg/L)
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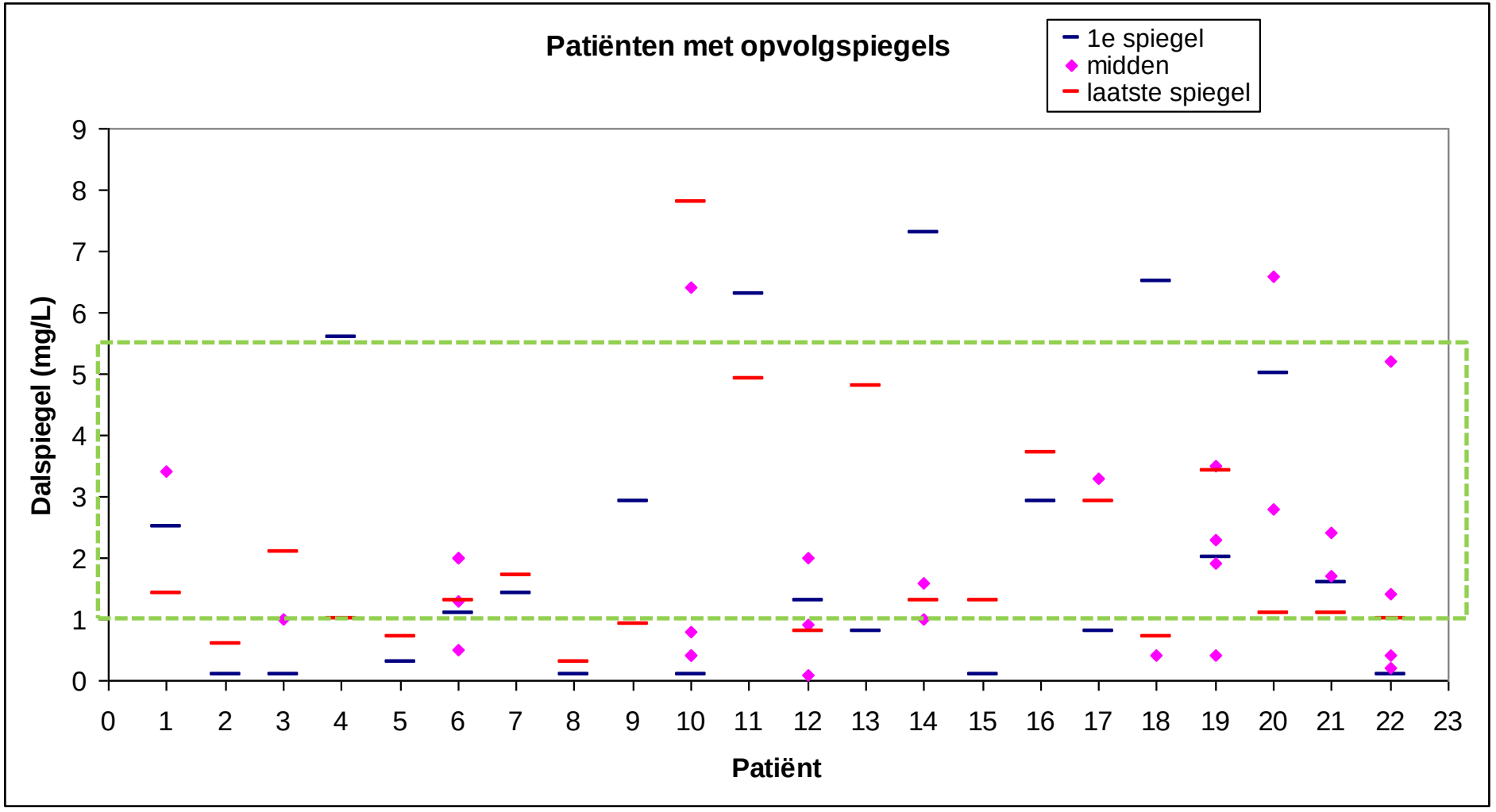
Patiënt

Werkzaam?

		Einddalspiegel	
		Goed	Slecht
1e dalspiegel	Goed	7	2
	Slecht	11 (8)*	2 (5)*

* Overgang van niet-kwantifeerbaar naar kwantificeerbaar als goed (niet noodzakelijk binnen interval)


Patiënten met opvolgspiegels
1e spiegel
midden
laatste spiegel
Dalspiegel (mg/L)
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Patiënt
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23

Stabiliteit spiegels

		Volgende dalspiegel	
		Goed	Slecht
Begindalspiegel	Goed	20	7
	Slecht	17 (12)*	7 (12)*

* Overgang van niet-kwantifeerbaar naar kwantificeerbaar als goed (niet noodzakelijk binnen interval)

Benchmarking

		Einddalspiegel	
		Goed	slecht
Begindalspiegel	Goed	5	3
	slecht	3	7

Miyakis S, van Hal SJ, Solvag CJ, Ray JR, Marriot D. Clinician Ordering Practices for Voriconazole Therapeutic Drug Monitoring: Experiences of a Referral Laboratory. Ther Drug Monit 2010;32:661-4

Take Home Messages

1. Routinematig doseren van dalspiegels is zinvol om werkzame (kwantificeerbare) concentraties te staven, zowel bij aanvang als doorheen therapie

2. TDM in combinatie met dosisaanpassing in staat dalspiegels aan te passen (UZ Leuven)

3. Voorlopig nog geen hard bewijs voor preventieve dosisaanpassing (studie lopende)

Voriconazole-Induced Musical Hallucinations

A.K. Agrawal, L.K. Sherman

group. The patient's chief complaint was hearing Christmas music for the past 5 days. Onset of this phenomenon was described as very sudden, and he stated never having had such an episode in the past. The music was so realistic that he even wrote a letter to the administration of the hospital complaining of this constant music and asking for remediation of the problem. The patient

Agrawal AK, Sherman LK. Infection. 2004 Oct;32(5):293-5.

Hallucinations during Voriconazole Therapy

Dimitrios I. Zonios,[1] Juan Gea-Banacloche,[2] Richard Childs,[3] and John E. Bennett[1]

On the first day of treatment, patient 6 saw a figure bending over him when he closed his eyes. The figure looked large and hairy but not threatening, like the character Chewbacca from the *Star Wars* films. That day, the patient also had the impression that his bed was moving around the room, and he

Zonios DI, Gea-Banacloche J, Childs R, Bennett J. Clin Infect Dis. 2008; 47(1):e7-e10.