Nuove opzioni terapeutiche per le infezioni fungine invasive nell'ospite compromesso

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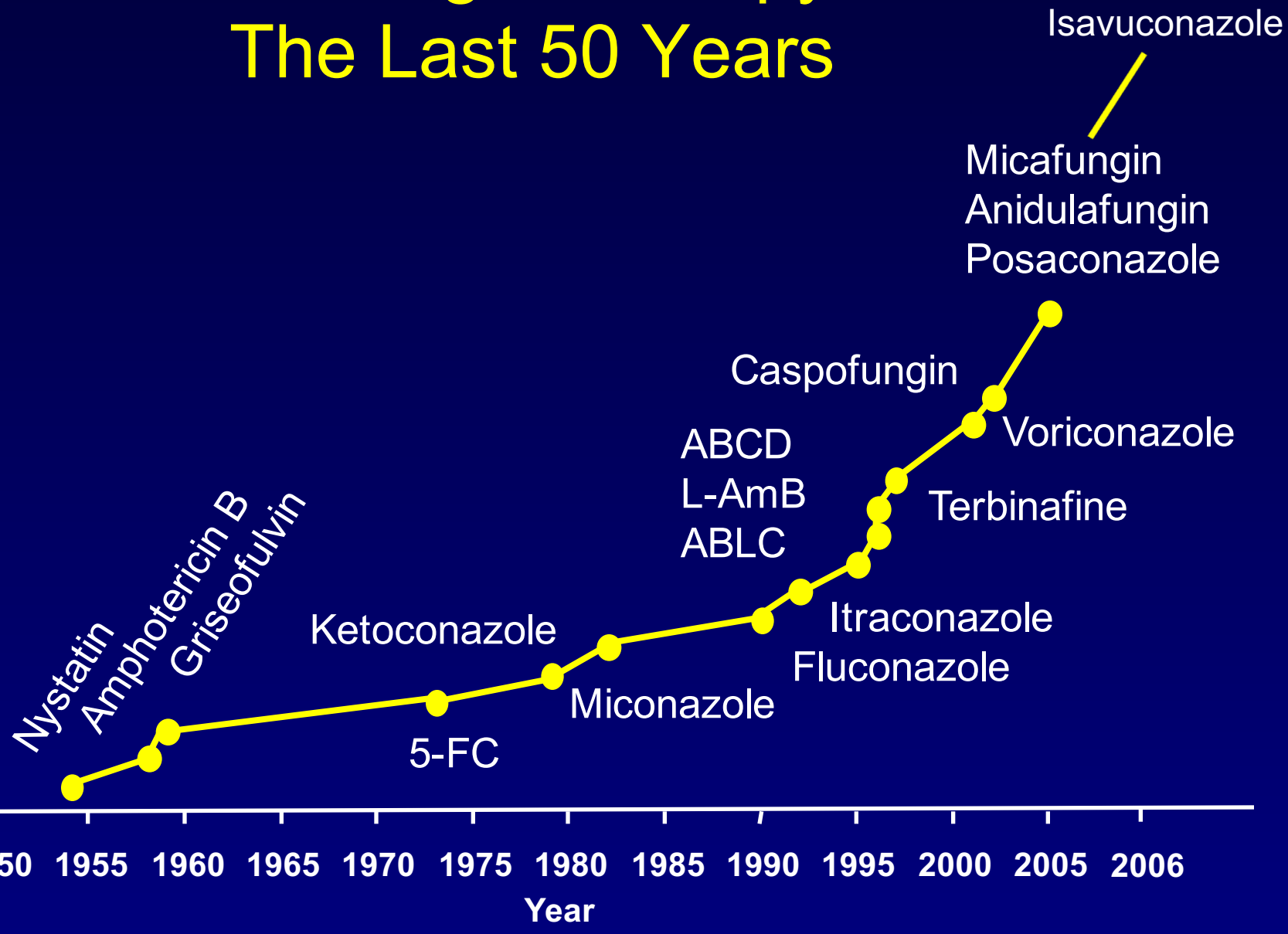
Potential conflicts of interest

- Received grants as speaker/moderator in national or international meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott, BMS, Novartis
- Received grants for participation in national or international advisory boards by Gilead, Astellas, MSD, Pfizer, Novartis
- Obtained research grants for my institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, Novartis
- Expert for the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency
- Member of several local boards (Genoa, Liguria, Italy and my hospital) (Hospital Infection Control and Antibiotic Stewardship, HIV, vaccination, Hospital Formulary)

Antifungal Therapy: The Last 50 Years



ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

Frederic Tissot,[1] Samir Agrawal,[2] Livio Pagano,[3] Georgios Petrikkos,[4] Andreas H. Groll,[5] Anna Skiada,[6] Cornelia Lass-Flörl,[7] Thierry Calandra,[1] Claudio Viscoli[8] and Raoul Herbrecht[9]

Haematologica 2017
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Table 7. ECIL-6 recommendations for first-line treatment of invasive aspergillosis.

	Grade	Comments
Voriconazole[a]	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole[a] + anidulafungin	C I	
Other combinations	C III	
Recommendation against use Amphotericin B deoxycholate	A I	Less effective and more toxic

[a]Monitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

Clinical Infectious Diseases **Clinical Infectious Diseases Advance Access published June 29, 2016**

IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,[1,a] George R. Thompson III,[2] David W. Denning,[3] Jay A. Fishman,[4] Susan Hadley,[5] Raoul Herbrecht,[6] Dimitrios P. Kontoyiannis,[7] Kieren A. Marr,[8] Vicki A. Morrison,[9] M. Hong Nguyen,[10] Brahm H. Segal,[11] William J. Steinbach,[12] David A. Stevens,[13] Thomas J. Walsh,[14] John R. Wingard,[15] Jo-Anne H. Young,[16] and John E. Bennett[17,a]

60 double-colum pages!!!!!

Table 1. Summary of GRADE recommendations on rating the strength of recommendations and quality of evidence

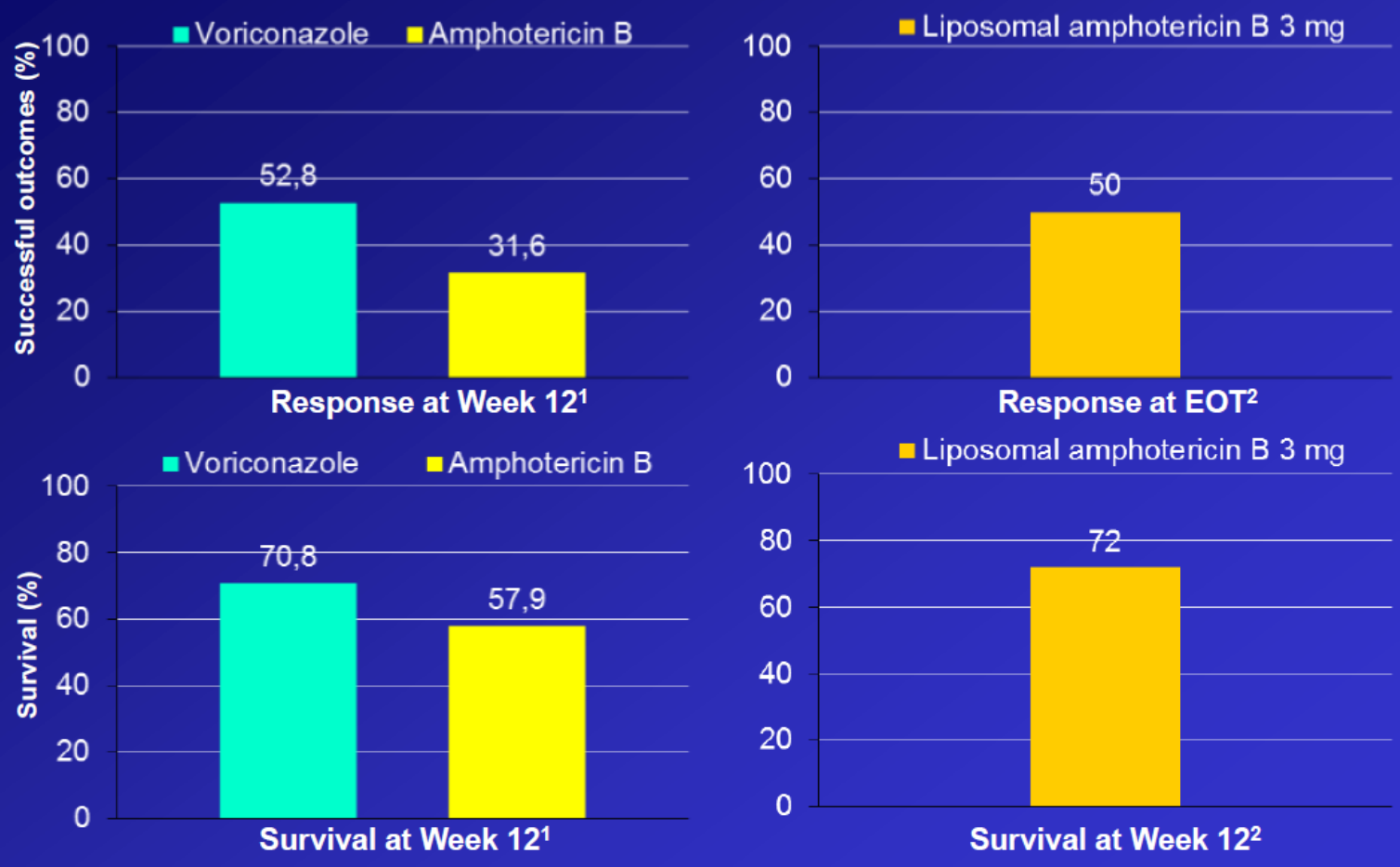
Strength of recommendation		Quality of evidence	
1 ("Strong")	Desirable effects of an intervention clearly outweigh (or clearly do not outweigh) the undesirable effects	A ("High")	Further research is unlikely to change our confidence in the estimate of effect
2 ("Weak")	Tradeoffs between desirable and undesirable effects are less certain (eg, because of low-quality evidence or evidence suggesting closely balanced effects)	B ("Moderate")	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
		C ("Low")	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
		D ("Very low")	Any estimate of effect is very uncertain

Each recommendation consists of a numerical score denoting the strength of the recommendation and a letter denoting the quality of the evidence.[12]

Condition	Primary therapy	Alternative
Invasive Pulmonary	Voriconazole	L-AmB, isavuconazole; posaconazole, itraconazole, echinocandin
Invasive sinus	" "	" "
Tracheobronchial	" "	" "
CNS	" "	" "
Bone/joint	" "	" "
Heart (endocarditis, etc)	" "	" "
Eye	Intraocular AMB	AND voriconazole
Empiric or Pre-emptive	L-AMB, itraconazole, voriconazole	
Prophylaxis	Posaconazole	Itraconazole, micafungin
Chronic necrotizing	Itraconazole, voriconazole	" "
Allergic bronchopulmonary aspergillosis (ABPA)	Itraconazole	voriconazole, posaconazole

Patterson TF, et al. *Clin Infect Dis.* 2016;64:e1-60.

Primary treatment of invasive aspergillosis: response rate vs. survival



1. Herbrecht R et al. N Engl J Med 2002;347:408–15; 2. Cornely OA et al Clin Infect Dis 2007;44:1289–97.

Epidemiological analysis of IA in France

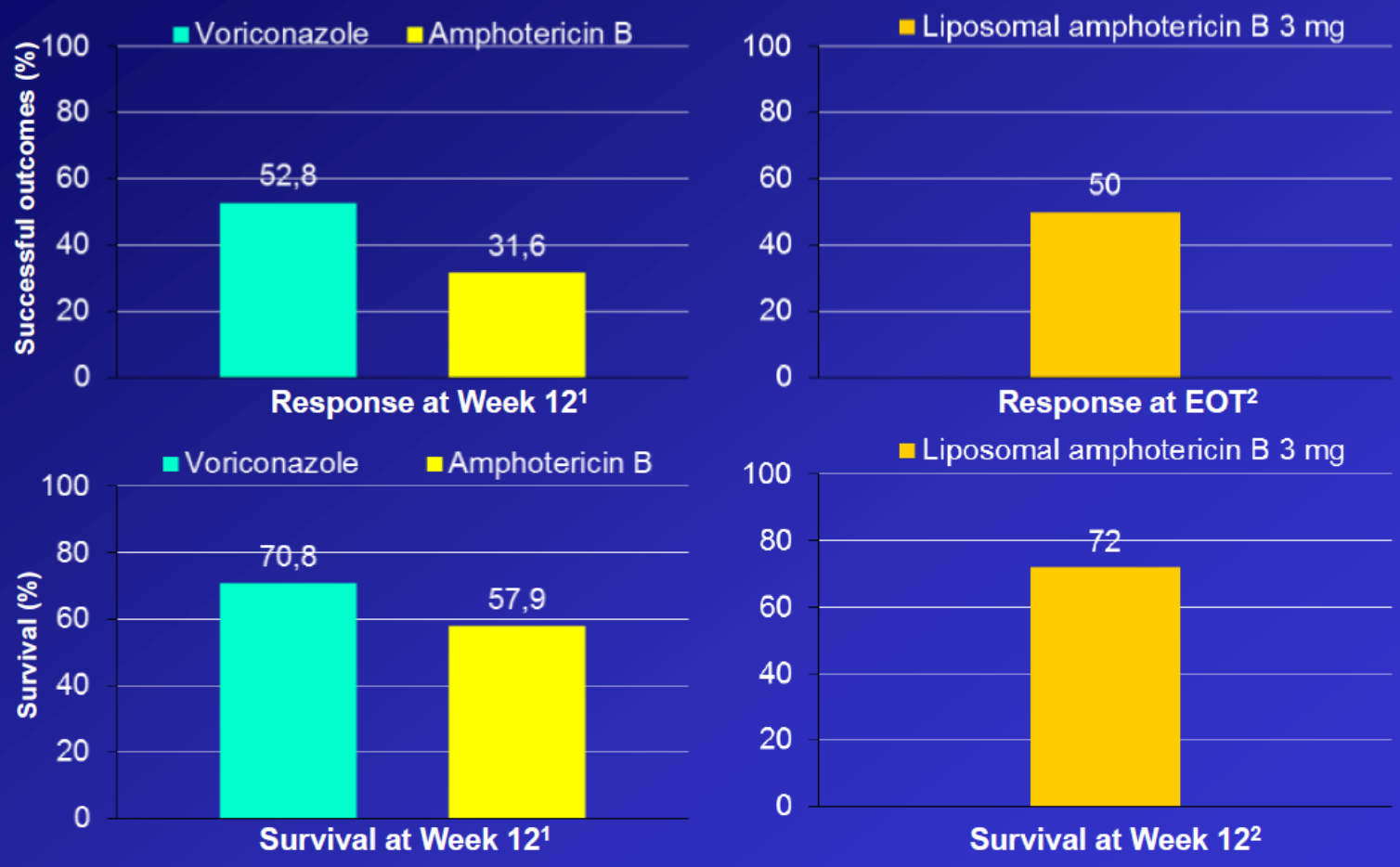
- A prospective, multicentre surveillance study in three regions of France (1/2005–12/2007)
- 424 patients were included
  - Median incidence of IA was 0.271 per 1000 admissions
- Factors associated with death within 90 days after diagnosis

Parameter	Odds ratio (95% CI)	P value
Older age	1.02 (1.00–1.03)	0.034
Positive culture and ≥ 2 positive GM	1.72 (1.07–2.74)	0.023
CNS involvement	2.01 (1.04–3.90)	0.039
Pleural effusion	2.38 (1.53–3.70)	$<10^{-3}$
Initial treatment including voriconazole	0.53 (0.34–0.82)	0.005

Gender, underlying disease and presence of nodule, halo-sign and/or cavitation were not associated in multivariate analysis

Lorthorlary O, et al. Clin Microbiol Infect 2011 DOI 10.1111/j.1469-0691.2011.03548.x

Primary treatment of invasive aspergillosis: response rate vs. survival



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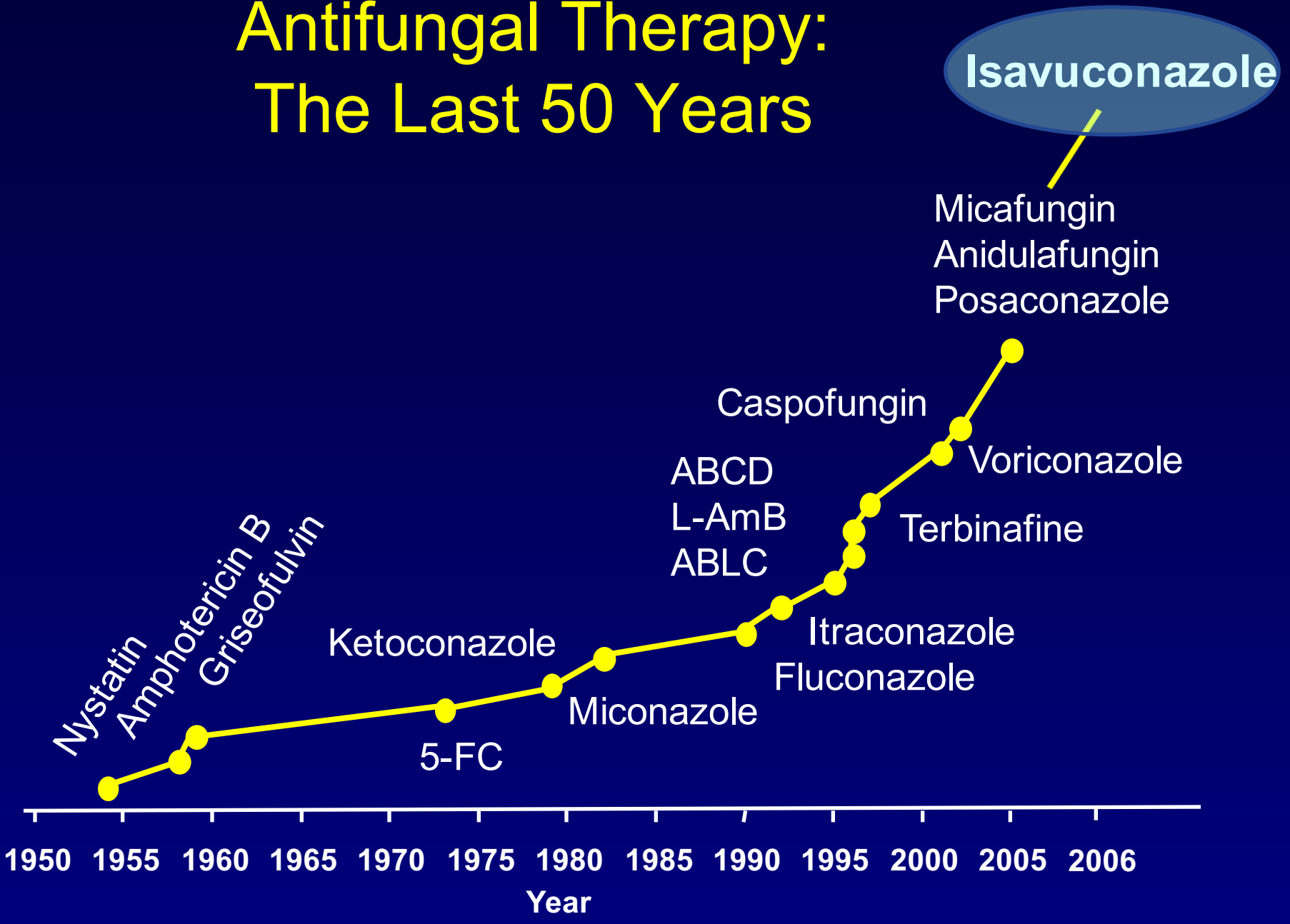
Antifungal Therapy: The Last 50 Years



Isavuconazole - In vitro activity

- *Aspergillus* spp. *Fusarium* spp. and organisms of the Mucorales order
- Yeasts such as *Candida* spp.
- *Cryptococcus* spp., *Trichosporon* and *Rhodotorula* spp.
- Dermatophytes

Falci DR, Pasqualotto AC. Infect Drug Resist 2013;6:163-74.
Lepak AJ, et al. Antimicrob Agents Chemother 2013;57:6284-9.
Luo et al., Antimicrob Agents Chemother 2014;58:2450-3

Isavuconazole

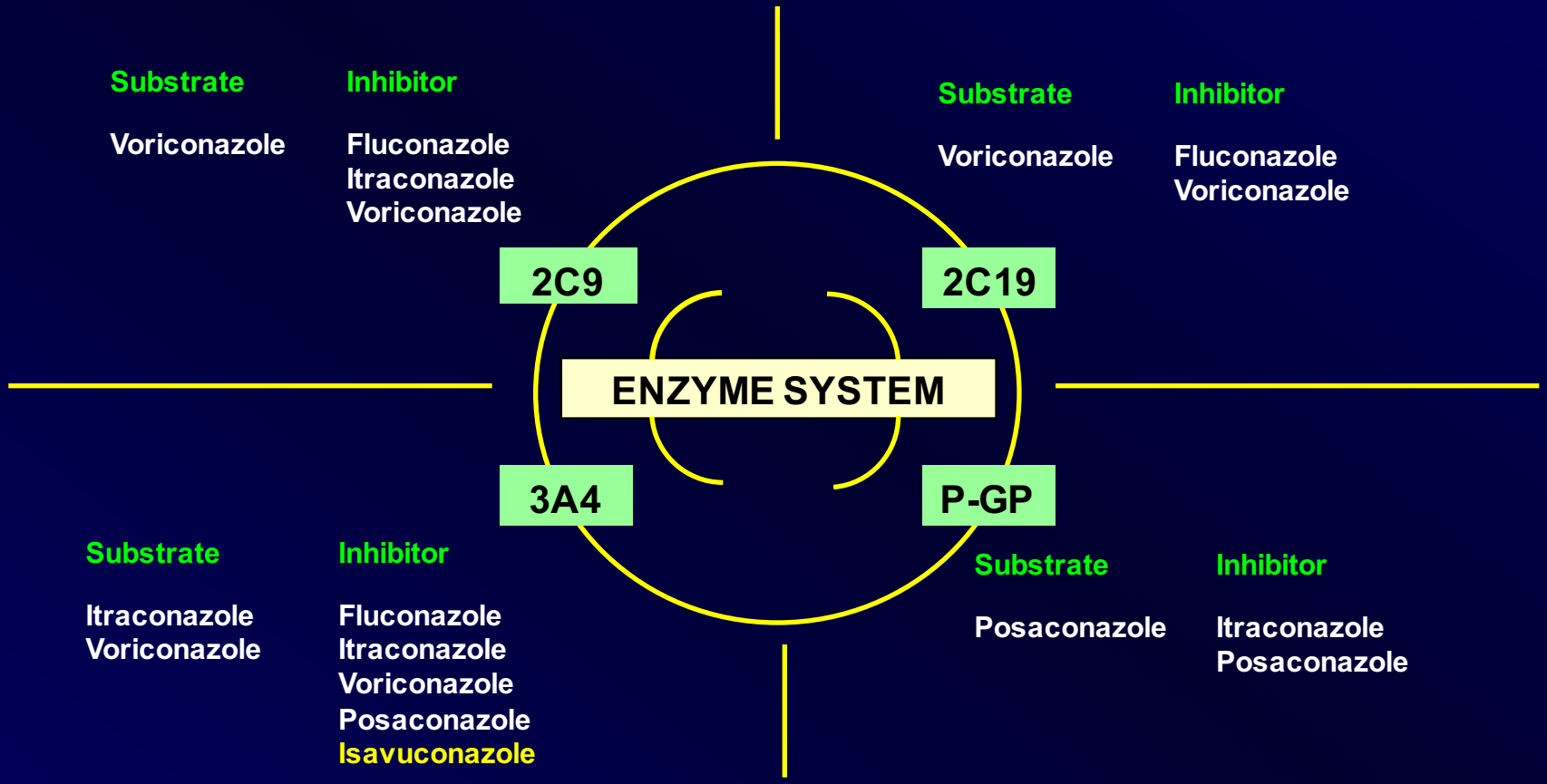
- Prodrug (isavuconazonium sulfate) that is rapidly converted to isavuconazole by plasma esterases
- Predictable linear pharmacokinetics and long half-life
- Once-daily iv or oral administration
- Protein binding 99%
- Highly bioavailable and its bioavailability is not influenced by food intake
- Does not require potentially nephrotoxic co-administration of cyclodextrin,
- Metabolized by cytochrome P-450 enzymes (CYP3A4)
- Interactions possible
- Apparently no racial differences in metabolism
- No adjustment in patients with renal impairment
- Dosing 200 mg TID for 48 hrs; then 200 mg/day

Falci DR, Pasqualotto AC. Infect Drug Resist 2013;6:163-74.
Livermore J, Hope W. Expert Opin. Drug Metab Toxicol 2012; 8:759–765.

Latest triazoles: PK properties

Characteristic	Antifungal drug		
	Isavuconazole	Voriconazole	Posaconazole
Available formulations	Oral – IV	Oral – IV	Oral, iv
Bioavailability	Over 95%	Up to 95%	Low and variable with oral solution; tablets improved
Protein binding	98%	58%	99%
Food effect	No	Slightly reduced absorption; better give before or after meal	Solution absorption improved with food; tablets same effect but lower
Vd (l/kg)	High (4.4 – 7.7)	High (4.6)	High (6.5)
CNS penetration	Low in CSF, high in brain	High (> 50%)	Low
CL (l/h)	Low (1.9 – 2.8)	High (8.4)	High (21.7)
t½ (h)	56 – 104	6 – 12	16 – 35
Probability of drug interactions	Moderate	High	Moderate
Use in mild/moderate hepatic insufficiency*	Reduce dose	Reduce dose	No adjustment

Involvement of cytocrome P450 enzymes and P-glycoprotein (P-gP) in the metabolism of azole antifungal drugs



Bruggemann RJ et al., Clin Infect Dis, 2009

Courtesy Andrea Novelli

Table 4. Drug–Drug Interactions With Isavuconazole

Type of Interaction, Drug	Recommendation
Increases isavuconazole level	
Lopinavir/ritonavir	Use with caution
Decreases isavuconazole level	
Rifampin	Contraindicated
Carbamazepine	
Long-acting barbiturates	
St John's wort	
Levels increased by isavuconazole	
Sirolimus Tacrolimus Cyclosporine Mycophenolate mofetil Digoxin	Use with caution. Monitor serum levels of these drugs and adjust dose when given with isavuconazole
Colchicine Dagibatran	Use with caution. May require dose adjustment
Atorvastatin Midazolam	No dose adjustment recommended when given with isavuconazole; monitor patient
Levels decreased by isavuconazole	
Bupropion	Use with caution. Dose increase of bupropion may be necessary.
Lopinavir/ritonavir	Use with caution

ALLEGATO I

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

CRESEMBA è indicato negli adulti per il trattamento di

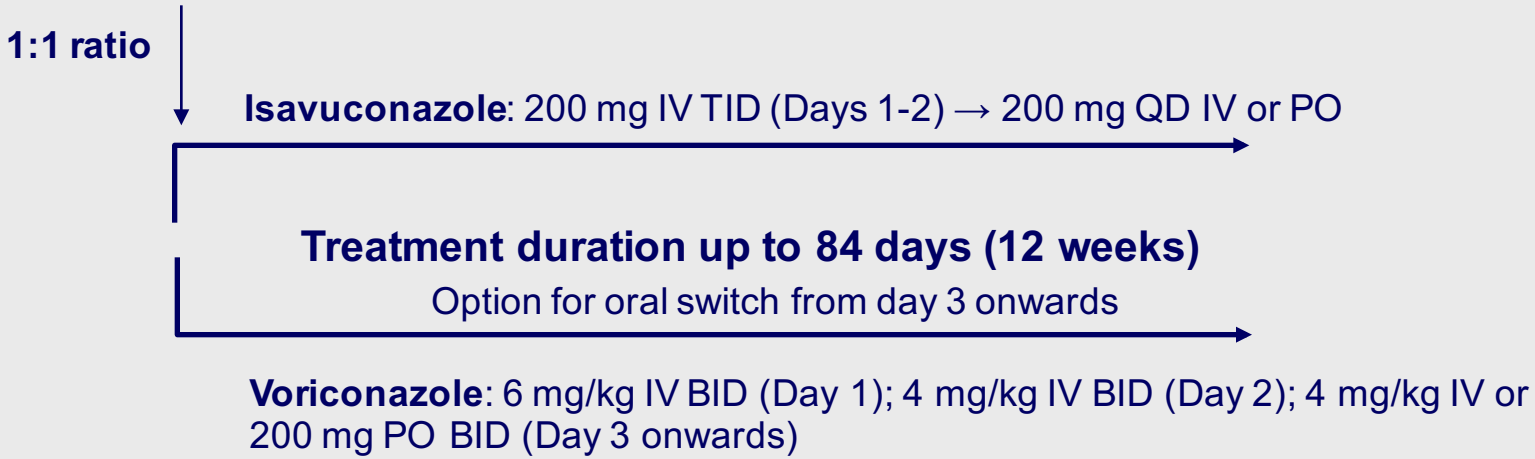
- aspergillosi invasiva
- mucormicosi in pazienti per i quali il trattamento con amfotericina B non è appropriato

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

Johan A Maertens, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P Kontoyiannis, Oliver A Cornely, Eric J Bow, Galia Rahav, Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Heinz, Raoul Herbrecht, William Hope, Meinolf Karthaus, Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag, Shmuel Shoham, George R Thompson III, Misun Lee, Rochelle M Maher, Anne-Hortense Schmitt-Hoffmann, Bernhardt Zeiher, Andrew J Ullmann

www.thelancet.com **Published online December 9, 2015**

Study design



Primary endpoint (ITT)*

All-cause mortality (ACM) through Day 42 (ITT population)

	Isavuconazole N = 258	Voriconazole N = 258
All-cause mortality, n (%)	48 (18.6)	52 (20.2)
Adjusted treatment difference, % (95% CI)[a]	–1.0 (–7.8, 5.7)	
Deaths, n (%)	45 (17.4)	50 (19.4)
Unknown survival status, n (%)[b]	3 (1.2)	2 (0.8)

*ITT = proven, probable and possible treated with at least one study drug dose

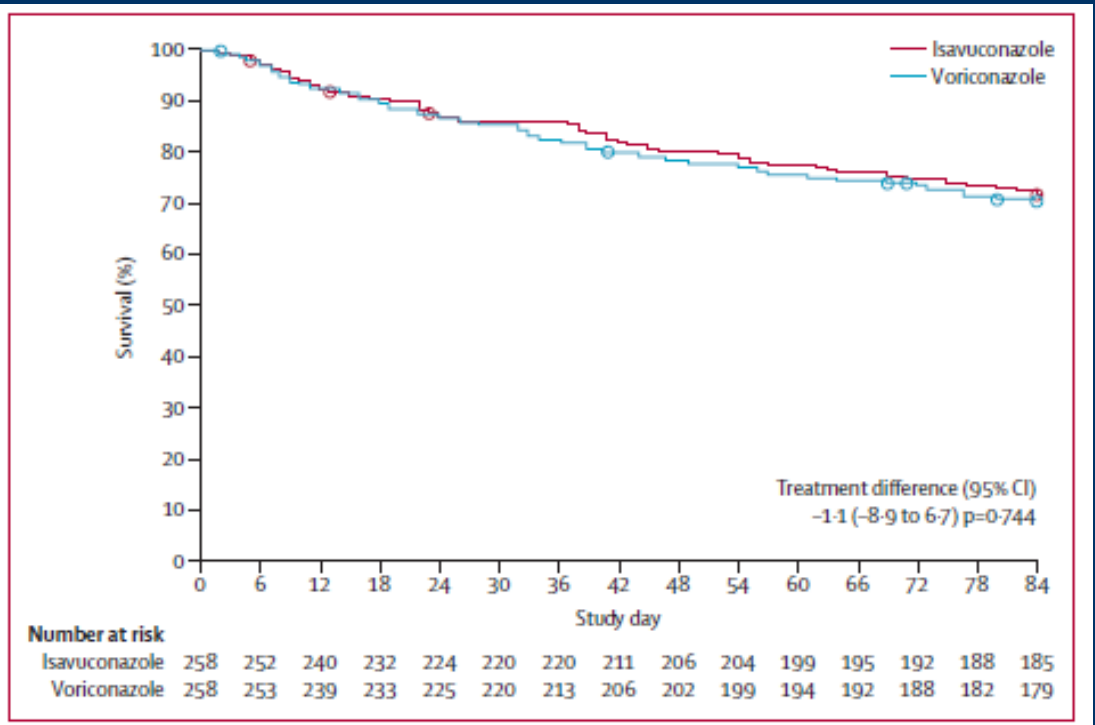


Figure 2: **Survival from first dose of study drug to day 84**

Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

System Organ Class (%)	Isavuconazole (N=257)	Voriconazole (N=259)
Patients with any AE	96.1	98.5
Skin and subcutaneous tissue disorders	33.5*	42.5
Eye disorders	15.2*	26.6
Hepatobiliary disorders	8.9*	16.2

*$p<0.05$

- Other adverse events were not significantly different between isavuconazole and voriconazole

Maertens J et al. Lancet 2016: 387; 760-9

ALLEGATO I

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CRESEMBA è indicato negli adulti per il trattamento di

- aspergillosi invasiva
- mucormicosi in pazienti per i quali il trattamento con amfotericina B non è appropriato

Mucormycosis

- Sinuses, rhinocerebral, pulmonary, wounds.
- Emergence on suppressive therapy?? (voriconazole, echinocandin)
  - Severely immunosuppressed (allo BMT), trauma, burns, uncontrolled diabetes)
- Primary therapy with high-dose lipid formulation of amphotericin B;
- Surgery
- Posaconazole also active

Isavuconazole	Mortality/Treated	(%)
All patients	14/37	38%
--Primary	7/21	33
--Salvage	7/16	44

Fungiscope	Mortality/Treated	(%)
Untreated	29/29	100
AmB treated	41/107	38
L-AmB treated*	36/116	31

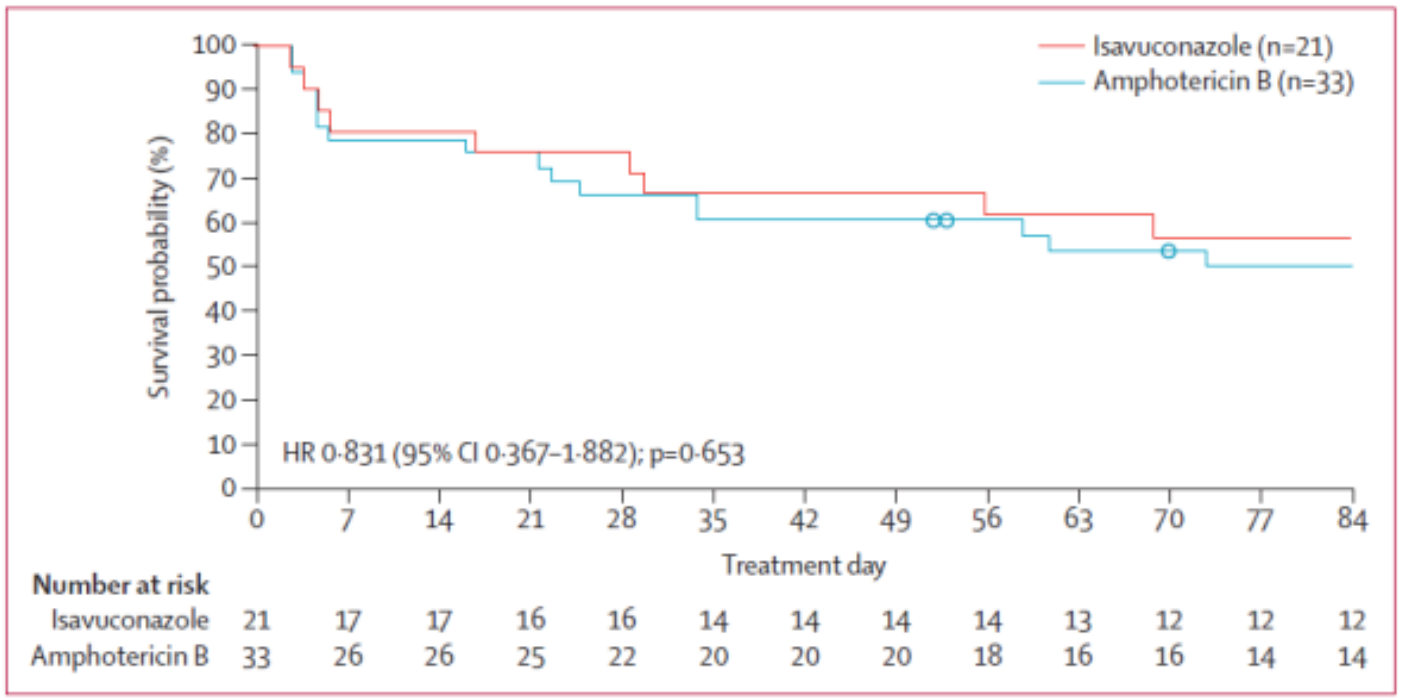


Figure 2: **Kaplan-Meier analysis of patients who received isavuconazole as primary treatment (VITAL) compared with amphotericin B-treated matched controls (FungiScope)**

Hazard ratio (HR) and 95% CI are calculated from a Cox model without covariates. Patients were censored on the day of their last known survival status, represented by the circles.

A Study of the Safety and Efficacy of Posaconazole Versus Voriconazole for the Treatment of Invasive Aspergillosis (MK-5592-069/P06200)

This study is currently recruiting participants. (see Contacts and Locations)

Verified October 2015 by Merck Sharp & Dohme Corp.

Sponsor:
Merck Sharp & Dohme Corp.

Information provided by (Responsible Party):
Merck Sharp & Dohme Corp.

ClinicalTrials.gov Identifier:
NCT01782131

First received: January 30, 2013
Last updated: October 28, 2015
Last verified: October 2015
History of Changes

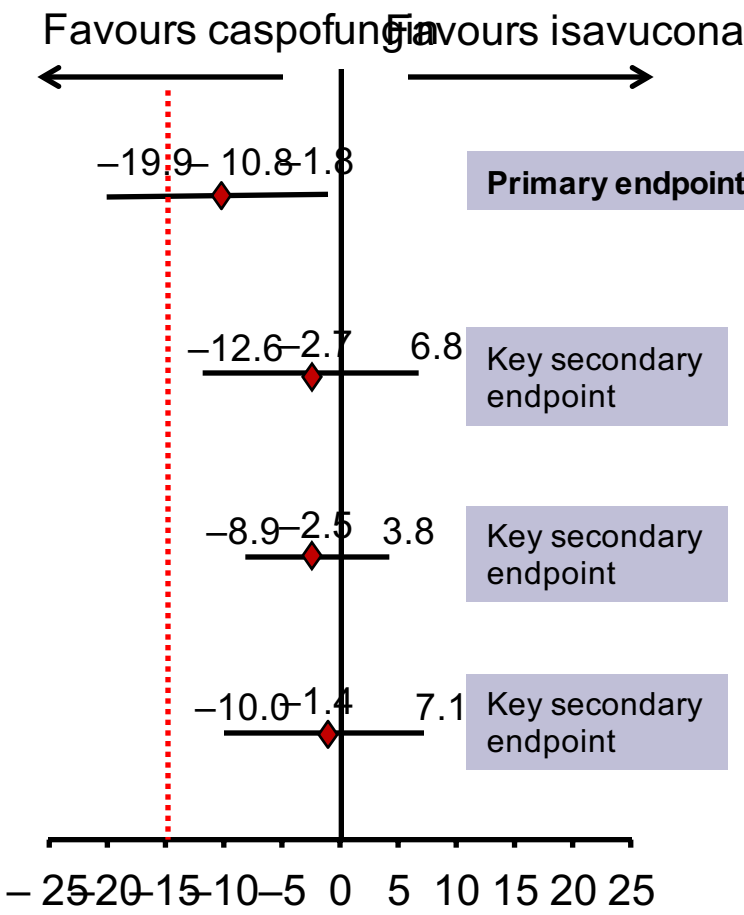
Isavuconazole versus Caspofungin in the Treatment of Candidaemia and Other Invasive *Candida* Infections: the ACTIVE Trial

Disclosure:
I was part of the DRC for this study, but I had no role in the design of the trial
I commented and approved, with others, the final version of the ESCMID presentation

Efficacy outcomes (mITT population)

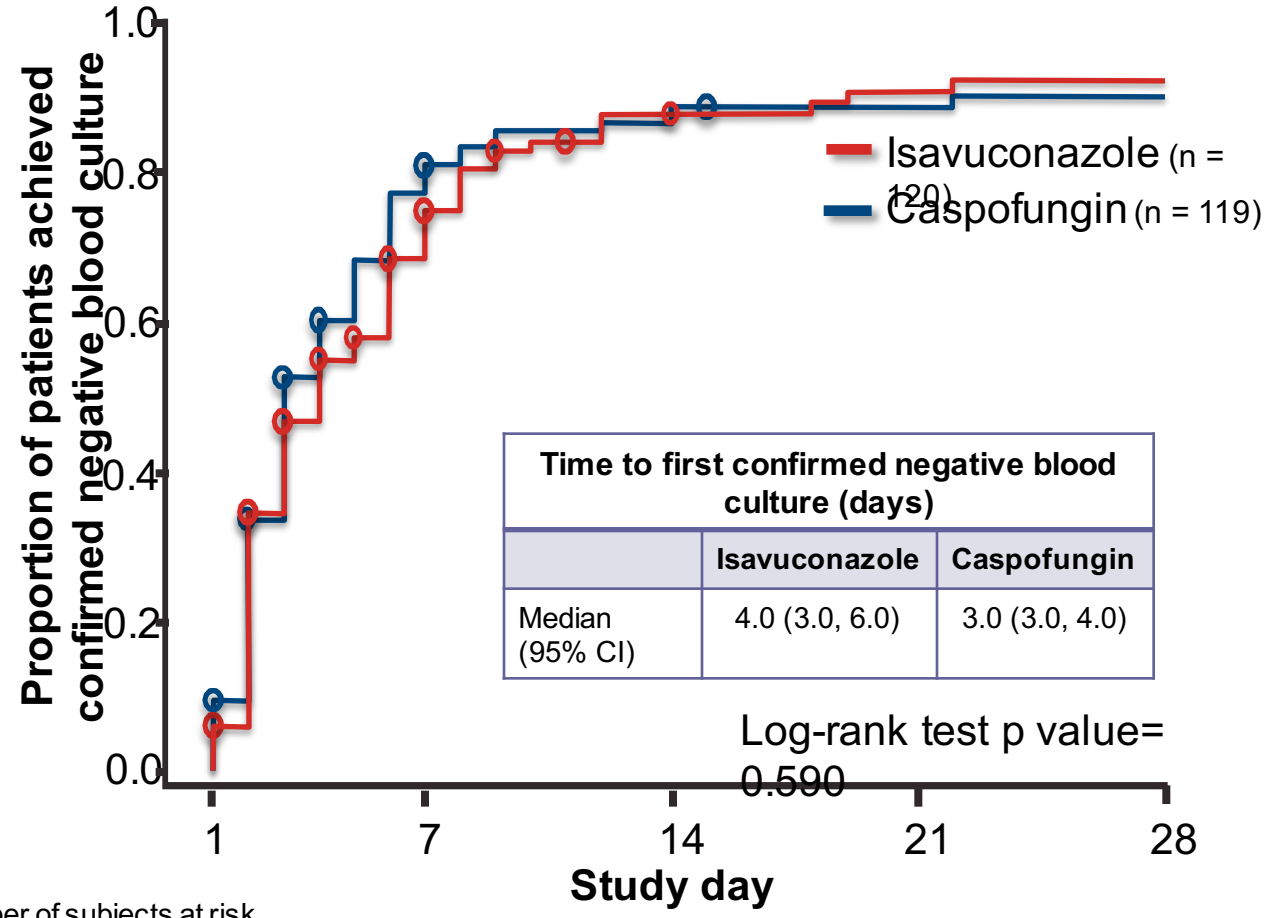
Category, n (%)	Isavuconazole (n = 199)	Caspofungin (n = 201)
Successful overall response at EOIV*	**120 (60.3)**	**143 (71.1)**
Successful overall response at EOT + 2 weeks	109 (54.8)	115 (57.2)
All-cause mortality Day 14	29 (14.6)	25 (12.4)
All-cause mortality Day 56	61 (30.7)	60 (29.9)

*Stratified by geographical region and baseline neutropenia status



Adjusted difference (%; 95% CI) between isavuconazole versus caspofungin

Time to first confirmed negative blood culture (mITT with candidaemia only)



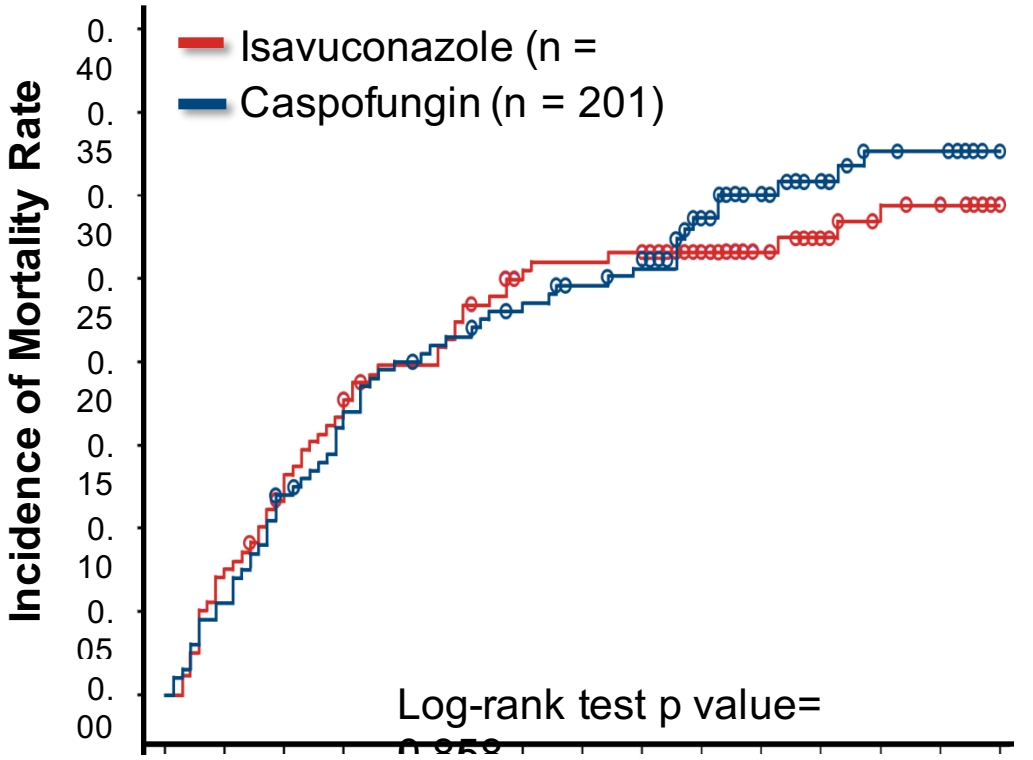
Time to first confirmed negative blood culture (days)		
	Isavuconazole	Caspofungin
Median (95% CI)	4.0 (3.0, 6.0)	3.0 (3.0, 4.0)

Number of subjects at risk

Isavuconazole	120	29	9	6	5
Caspofungin	119	23	12	9	8

Patients were censored on their last visit day, represented by the circles

All-cause mortality: time-to-event (mITT population)



Number of subjects at risk															
	19	18	17	16	15	15	14	13	13	10	86	77	71	69	58
Isavuconazole	9	5	3	3	5	0	1	9	8	2	94	83	74	70	62
Caspofungin	20	19	17	16	15	15	15	14	14	10					
	1	0	6	7	9	5	0	5	2	5					

Voriconazole	Posaconazole	Isavuconazole
Non linear metabolism; genetic influence; TDM indicated	Linear metabolism; no genetic influence; TDM in some cases	Linear metabolism; no genetic influence; TDM uncertain
Oral and IV	Oral and IV	Oral and IV
Loading dose	Loading dose	Loading dose
Ma Generic	Less interactions than vori	Few interactions
Toxicity is an issue	Well tolerated; high dose?	Well tolerated
Very well absorbed	Oral absorption is an issue with solution: improved with tablets	Very well absorbed
Approved for prophylaxis of IFI in given populations and therapy of Aspergillus, Candida and rare molds	Approved for prophylaxis of IFI in given populations and salvage therapy (Aspergillus); no Candida)	Approved for therapy (Aspergillus and Mucor); no Candida)
Approved in children	No children	No children
IV formulation with cyclodextrin (renal toxicity)	IV formulation with cyclodextrin (renal toxicity)	Prodrug; no renal issues
Large clinical experience	Large clinical experience in prophylaxis; not in therapy	Little experience

I’ll stop here
Thank you for your attention

Combination therapy: potential advantages and disadvantages

Advantages	Disadvantages
Increased rate and extent of fungal killing (*synergy*)	Decreased rate and extent of fungal killing (*antagonism*)
Enhanced spectrum of activity	Increased toxicity
Decreased likelihood of resistance or fungal tolerance	Increased drug interactions
[Minimized toxicity]	Increased cost

Kontoyiannis DP and Lewis RE. Br J Haematol 2004; 126: 165-175

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

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Other combinations	C III	
Recommendation against use Amphotericin B deoxycholate	A I	Less effective and more toxic

[a]Monitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

IDSA Guidelines

Combination antifungal therapy with voriconazole and an echinocandin may be considered in select patients with documented IPA (*weak recommendation; moderate-quality evidence*)

Annals of Internal Medicine

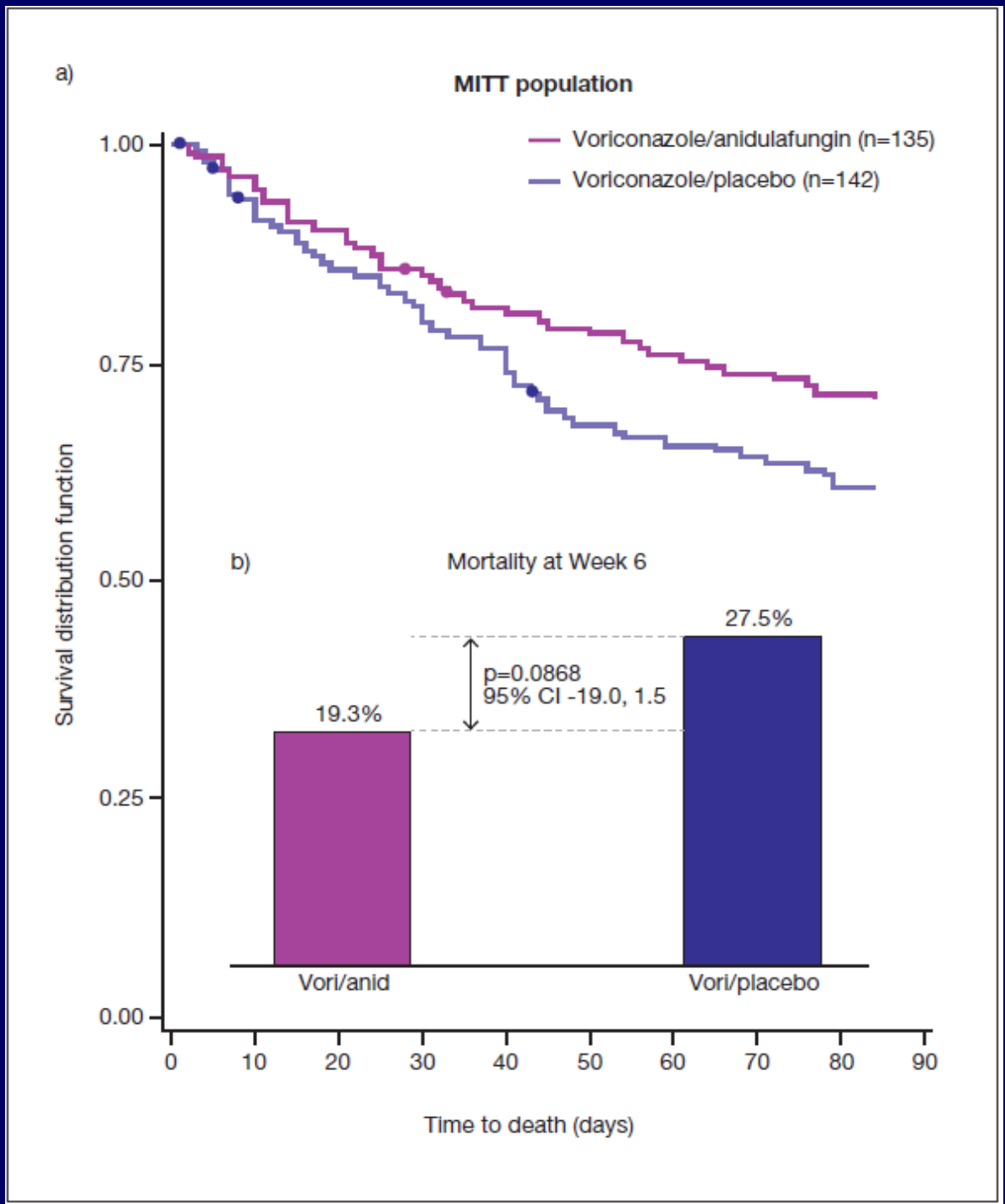
ORIGINAL RESEARCH

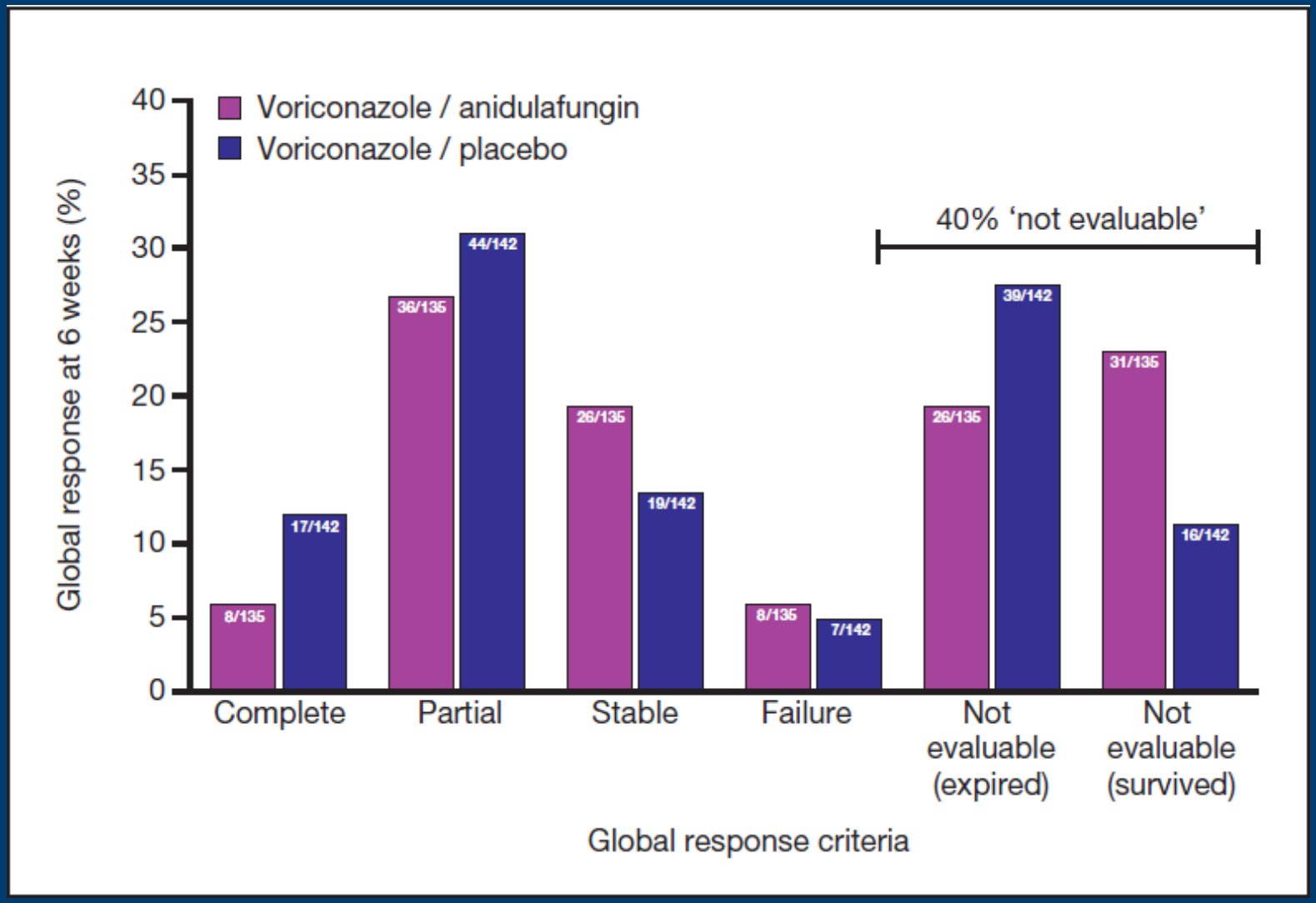
Combination Antifungal Therapy for Invasive Aspergillosis

A Randomized Trial

Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc; Oliver A. Cornely, MD; Werner J. Heinz, MD; Shyla Jagannatha, PhD; Liang Piu Koh, MBBS; Dimitrios P. Kontoyiannis, MD; Dong-Gun Lee, MD; Marcio Nucci, MD; Peter G. Pappas, MD; Monica A. Slavin, MD; Flavio Queiroz-Telles, MD, PhD; Dominik Selleslag, MD; Thomas J. Walsh, MD; John R. Wingard, MD; and Johan A. Maertens, MD, PhD

Ann Intern Med. 2015;162:81-89. doi:10.7326/M13-2508


a)
MITT population
Voriconazole/anidulafungin (n=135)
Voriconazole/placebo (n=142)
1.00
0.75
0.50
0.25
0.00
Survival distribution function
b)
Mortality at Week 6
27.5%
p=0.0868
95% CI -19.0, 1.5
19.3%
Vori/anid
Vori/placebo
0
10
20
30
40
50
60
70
80
90
Time to death (days)


Voriconazole / anidulafungin
Voriconazole / placebo
40% 'not evaluable'
Global response at 6 weeks (%)
40
35
30
25
20
15
10
5
0
8/135
17/142
36/135
44/142
26/135
19/142
8/135
7/142
26/135
39/142
31/135
16/142
Complete
Partial
Stable
Failure
Not evaluable (expired)
Not evaluable (survived)
Global response criteria

DOSAGGI

NOXAFIL OS SOSP 105 ML 40 MG/ML	POSACONAZOLO	200 MG 4 VOLTE AL GIORNO
NOXAFIL TABLETS 100 MG	POSACONAZOLO	300 MG DUE VOLTE AL GIORNO IL PRIMO GIORNO (6 COMPRESSE) 300 MG AL GIORNO I GIORNI SUCCESSIVI (3 COMPRESSE
VFEND INF EV FL 200 MG 10 MG/ML	VORICONAZOLO	6 MG/KG 2 VOLTE AL GIORNO IL PRIMO GIORNO 4 MG/KG 2 VOLTE AL GIORNO I GIORNI SUCCESSIVI
VFEND CPS 200 MG	VORICONAZOLO	400MG 2 VOLTE AL GIORNO IL PRIMO GIORNO 200 MG 2 VOLTE AL GIORNO I GIORNI SUCCESSIVI
CRESEMBA EV FL 200MG 10ML	ISAVUCONAZOLO	200MG OGNI 8 0RE PER 48 ORE 200MG 0GNI 24 ORE GIORNI SUCCESSIVI
CRESEMBA CPS 100MG	ISAVUCONAZOLO	200MG EV OGNI 8 0RE PER 48 ORE 100MG 0GNI 24 ORE GIORNI SUCCESSIVI

If the patient was on an aspergillus-active prophylaxis (low probability of aspergillus) what to do?

- Check if the patient was taking prophylaxis (compliance)
- Check blood levels
  - Posaconazole oral absorption (tablets?
  - Appropriate antibacterial therapy
  - Antifungal: change family
- Not a fungal infection? Negative GM
- Probably a fungal infection, but another mold (GM negative: Mucor?)

The anti-mold azoles: a comparison

Voriconazole

- Metabolism complicated
- Loading dose
- Interactions
- Toxicity not negligible
- logical
- n
- on
- ent)
- ed
- Changed the prognosis of aspergillosis
- Approved for prophylaxis and therapy
- Approved for *Candida, Aspergillus, Scedosporium and Fusarium*
- Approved in children
- Becoming generic
- i.v. formulation (not the oral) controindicated in GFR<50%

Going generic

Posaconazole

- Easier metabolism
- Loading dose
- Pretty well tolerated
- Few interactions
- Limited approval
  - Anti-mold prohylaxis
  - Salvage therapy (second line)
- Oral absorption erratic with the solution (food), but improved (not completely) with capsules
- No i.v. formulation in Italy
- Not approved for children
- Not approved for *Candida*
- No problem in renal insufficiency with the oral formulation
- Same problem as iv vorico

Isavuconazole

- Easy metabolism
- Loading dose
- Few interactions
- Better tolerated than vorico in a face-to-face study
- Oral absorption reliable
- No cyclodextrine for i.v. formulation, but prodrug (isavuconazonium sulphate converted to isavuconazole)
- Approved for *Aspergillus* and *Mucor*
- Not approved for Candida
- Not approved in prophylaxis
- Little experience

Clinical Infectious Diseases 2012;54(8):1110–22

Impact of Treatment Strategy on Outcomes in Patients with Candidemia and Other Forms of Invasive Candidiasis: A Patient-Level Quantitative Review of Randomized Trials

David R. Andes,[1] Nasia Safdar,[1] John W. Baddley,[2] Geoffrey Playford,[6] Annette C. Reboli,[3] John H. Rex,[4] Jack D. Sobel,[5] Peter G. Pappas,[2] and Bart Jan Kullberg[7] for the Mycoses Study Group[a]

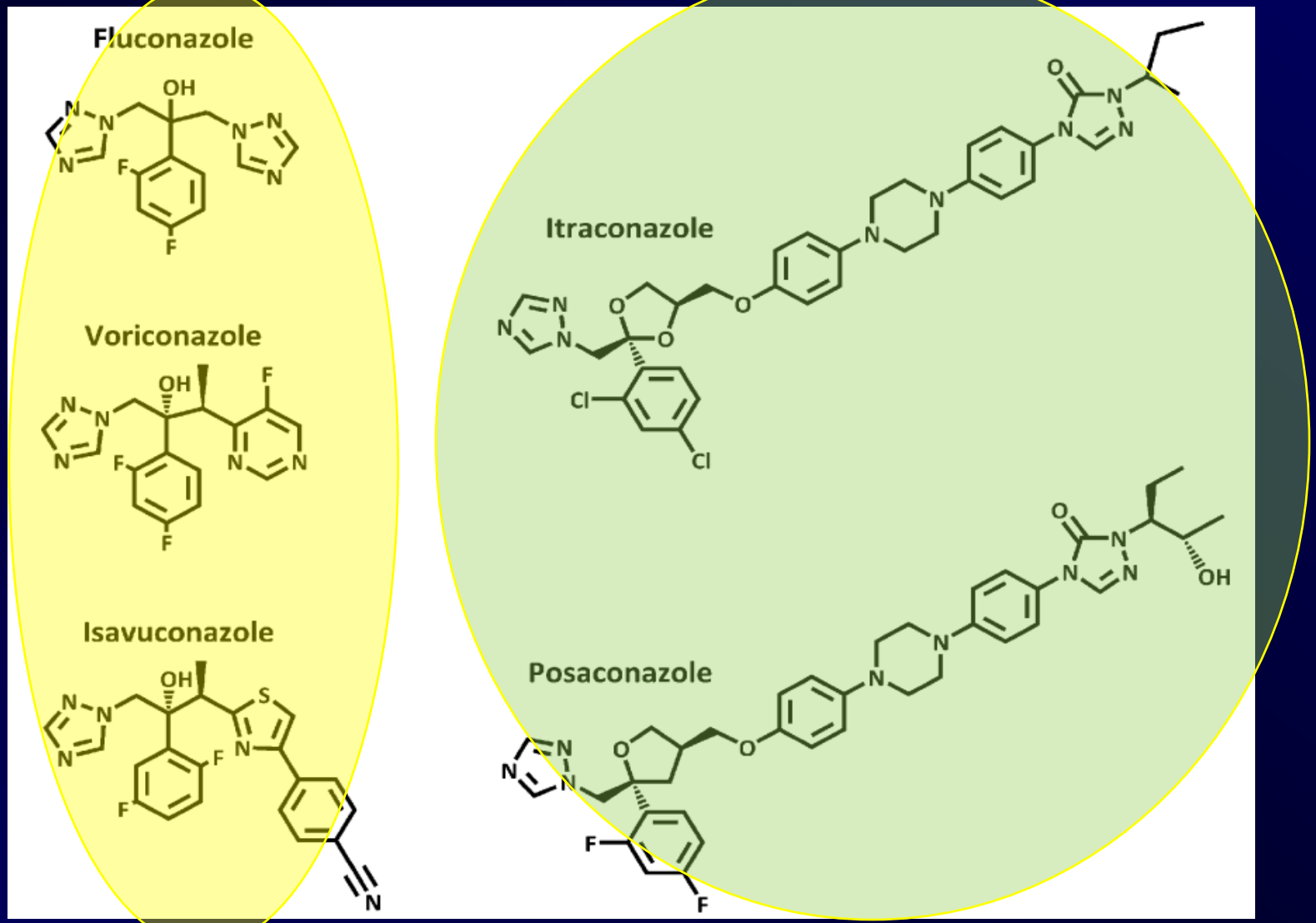
Factors Associated With Mortality and Treatment Response

The overall 30-day mortality was 31.4%, and composite treatment success at the end of treatment was 67.4%. Univariate

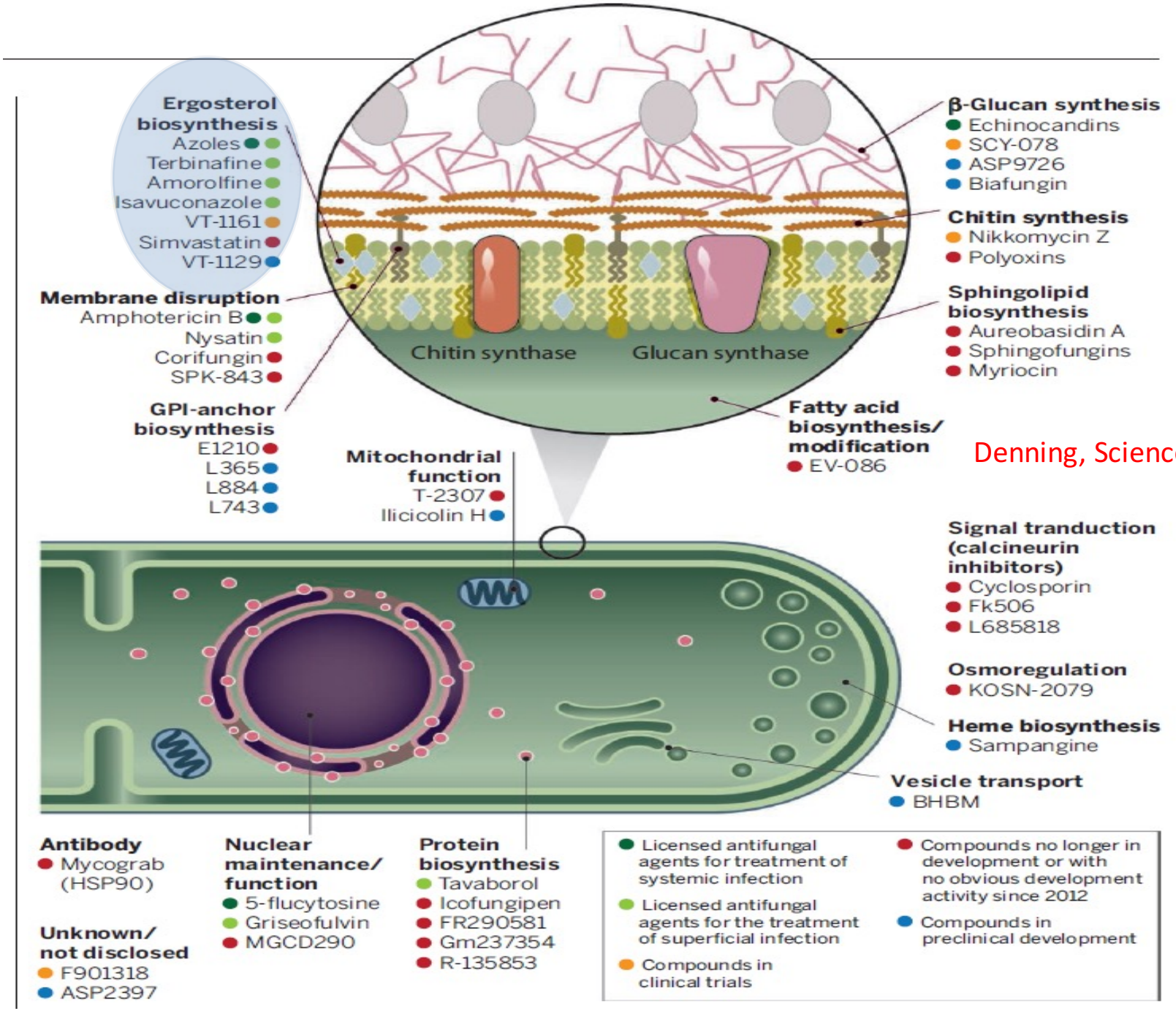
Table 4. Multivariate Analysis of Host, Disease, and Treatment Factors and Outcome in Patients With Invasive Candidiasis

		Mortality				Success		
Organisms[a]	Factor	*P*	OR	95% CI	Factor	*P*	OR	95% CI
All organisms (n = 978)	Age	.02	1.01	1.00–1.02	APACHE II	.0001	0.94	.93–.96
	APACHE II score	.0001	1.11	1.08–1.14	Echinocandin	.01	2.33	1.27–4.35
	Immunosuppressive therapy	.001	1.69	1.18–2.44	CVC removed	.001	1.69	1.23–2.33
	Candida tropicalis	.01	1.64	1.11–2.39	Study	NS		
	Echinocandin	.02	0.65	.45–.94				
	CVC removed	.0001	0.50	.35–.72				
	Study	NS						
Candida albicans (n = 408)	APACHE II score	.0001	1.09	1.05–1.13	APACHE II score	.005	0.92	.92–.99
	Immunosuppressive therapy	.002	2.22	1.30–3.70	Echinocandin	.005	3.70	1.49–9.09
	Surgery	.05	0.58	.34–.98	Study	NS		
	Malignancy	.03	1.89	1.05–3.45				
	Echinocandin	.03	0.55	.32–.95				
	CVC removed	.01	0.52	.31–.90				
	Study	NS						
Non-*albicans* species (n = 570)	APACHE II score	.0001	1.14	1.1–1.17	Age	.004	1.02	1.01–1.03
	Echinocandin	.04	0.52	.36–.78	APACHE II score	.0001	0.93	.91–.96
	CVC removed	.05	0.69	.48–.98	CVC removed	.007	1.74	1.16–2.61
	Study	NS			Study	NS		
Candida glabrata (n = 104)	CVC removed	.001	0.13	.04–.45	APACHE II score	.05	0.95	.90–.99
	Study	NS			Echinocandin	.05	2.63	1.10–625
					Study	NS		
Candida tropicalis[b]	APACHE II score	.0001	1.13	1.08–1.18	Age	.04	0.98	.96–.99
	Study	NS			APACHE II score	.0001	0.93	.89–.96
					CVC removed	.02	1.97	1.10–3.52
					Study	NS		
Candida parapsilosis[c]	APACHE II score	.001	1.11	1.04–1.19	APACHE II score	.01	0.95	.90–.99
	ICU admission	.02	2.63	1.12–6.25	Study	NS		
	Study	NS						

Currently available triazoles



Rybak JM et al., Pharmacother, 2015



Denning, Science, 2015

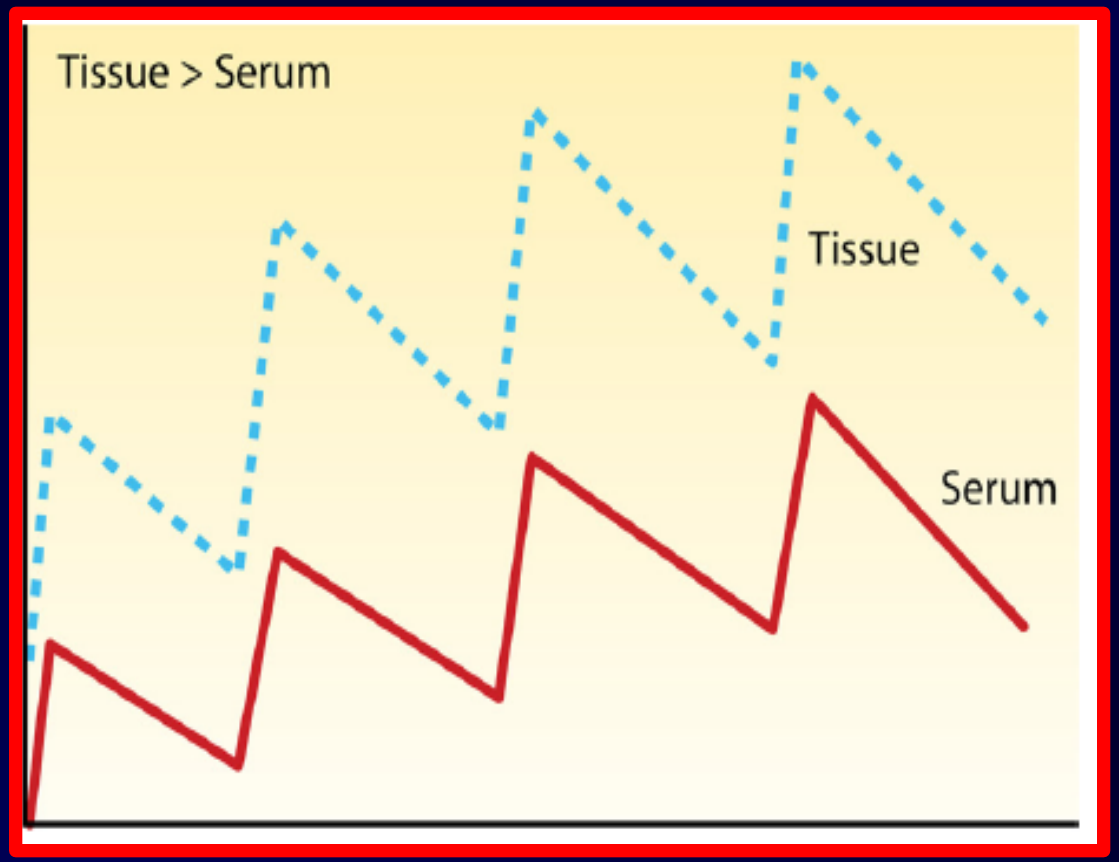
PK/PD indices of antifungals

Classification	PK/PD index	Explanation	Example of antifungals	PAFE
TIME-DEPENDENT	T > MIC	Efficacy is related to maintaining the concentration above the MIC for a certain period of time	Flucytosine	No
CONCENTRATION-DEPENDENT	C_{max}/MIC (AUC_{0-24}/MIC)	Efficacy is optimised by achieving high peak concentrations	Amphotericin B Echinocandins	Yes (prolonged)
CONCENTRATION-INDEPENDENT	AUC_{0-24}/MIC	Efficacy is optimised by increasing total drug exposure	Triazoles	Yes (prolonged)

Sinnoallareddy M et al., Int J Antimicrob Agents, 2012, mod

Triazoles

Potential plasma and tissue concentrations



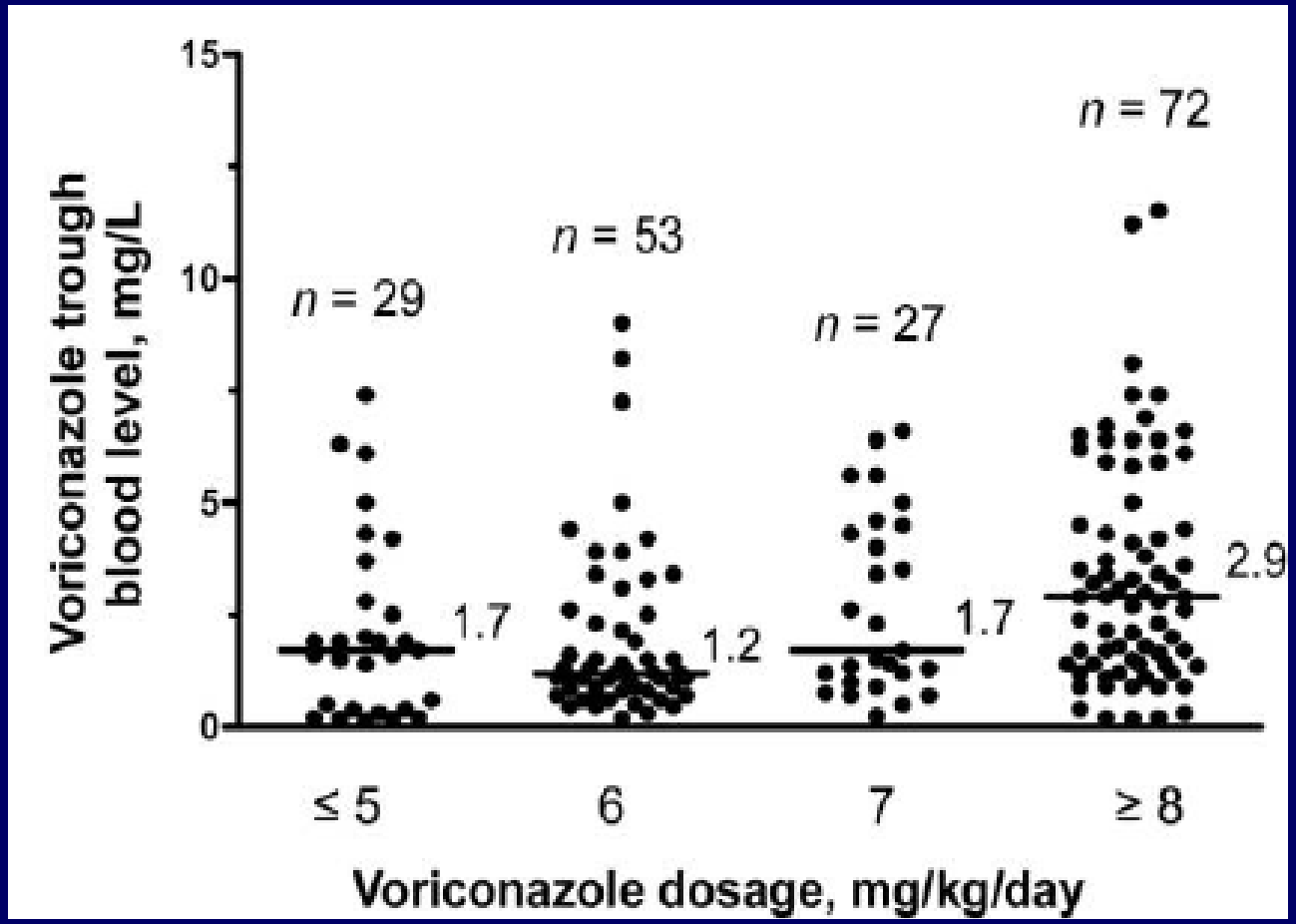
Felton T et al., Clin Microbiol Rev, 2014

Voriconazole metabolism

- CYP2C19 genetic polymorphism results in significant inter-subject variation in plasma levels and drug exposure
- Genotype, age and gender result in wide inter-subject variability in exposure

Patterson BE et al., ICAAC, 1995; Flockhart DA, Clin Pharmacokinet, 1995;
Dest Z et al.,
Clin Pharmacokinet, 2002; Lat A & Thompson GR Infection and Drug Resistance 2011

Voriconazole: variability of blood concentrations



Pascual A et al. CID 2008; 46:201-211

Voriconazole trough blood levels and clinical response to antifungal therapy

Variable	Voriconazole trough blood level ≤1 mg/L (*n* = 13)	Voriconazole trough blood level >1 mg/L (*n* = 39)	*P*
Route of voriconazole administration			.05
Intravenous	4 (31)	24 (61)	
Oral	9 (69)	15 (39)	
Voriconazole dosage, median mg/kg/day (range)			
Overall	7 (2.5–9)	8 (2–11)	NS
Intravenous	7.5 (7–8)	8 (6–11)	NS
Oral	6 (2.5–9)	7 (2–11)	NS
Response to antifungal therapy			
Interval between start of voriconazle therapy and assessment, median days (range)	21 (10–120)	17.5 (10–180)	NS
Treatment success			
Overall	7 (54)[a]	34 (88)	.02
Complete response	5	27	
Partial response	2	7	
Lack of response	6 (46)	5 (12)	
Persistence	3 (23)	0 (0)	
Progression	3 (23)	4 (10)	
Breakthrough IFI	0 (0)	1 (2)	

Pascual A et al. CID 2008; 46:201-211

Voriconazole trough blood levels and safety of antifungal therapy

Variable	Vor trough blood level ≤5.5 mg/L (*n* = 36)	Vor trough blood level >5.5 mg/L (*n* = 16)	*P*
Vor route			.07
Intravenous	15 (42)	13 (81)	
Oral	21 (58)	3 (19)	
Vor dosage, median mg/kg/day (range)			
Overall	7 (2–11)	8 (6–11)	.13
Intravenous	7.5 (6–10)	8 (6–11)	NS
Oral	6 (2–11)	7 (6–8)	NS
Serious adverse event			
Encephalopathy			
Incidence	0	5 (31)	.002
Interval after start of Vor, days (range)	NA	9 (5–30)	
Cholestatic hepatopathy			
Incidence	3 (8)	3 (19)	NS
Interval after start of Vor, days (range)	50 (5–150	13 (6–20)	NS
Concomitant therapy			
Omeprazole	6 (17)	7 (44)	.04
Tacrolimus	0	1 (6)	NS

Pascual A et al. CID 2008; 46:201-211

Factors associated with a significant change in voriconazole concentration

Dolton MJ et al., AAC, 2012

Model term	Coefficient	95% Confidential Interval		P-value
		Lower	Upper	
Oral administration[a]	-1.348	-1.741	-0.955	< 0.01
Age (years)[b]	0.026	0.017	0.036	< 0.01
Weight (kg)	-0.028	-0.038	-0.018	< 0.01
Daily dose (mg)	0.005	0.003	0.006	< 0.01
Concomitant CYP2C19 inducer[c]	-2.367	-3.181	-1.553	< 0.01
Concomitant Prednisone/ Prednisolone	-1.012	-1.346	-0.678	< 0.01
Concomitant Methylprednisolone	-1.833	-2.445	-1.221	< 0.01
Concomitant Dexamethasone	-1.245	-1.991	-0.5	< 0.01
Concomitant PPI (range)	0.685 – 1.414	0.33 – 0.8	1.041 – 2.028	< 0.05 - < 0.01

R^2 = 0.24; n = 736 concentration measurements; [a] compared to IV administration; [b] age at time of first voriconazole concentration measurement; [c] phenytoin or rifampicin

Voriconazole TDM

Practical indications

- Suspected treatment failure
- Suspected suboptimal dosing (interaction with other drugs, children, cerebral infections)
- Suspected suboptimal absorption
- Suspected non-compliance
- Suspected neurologial or other toxicity possibly related to overdosing

Mikulska M et al., J Chemother, 2012

Treatment response in Therapeutic Drug Monitoring (TDM) vs Non-TDM groups

	TDM (n =37)	Non-TDM (n = 34)	P value
Treatment success	30 (81)*	20 (59)	0.04
Complete response	21 (57)	13 (38)	0.12
Partial response	9 (24)	7 (21)	0.71
Stable response	1 (3)	2 (6)	0.60
Treatment failure	6 (16)	12 (35)	0.07

* = %

Park WB et al., Clin Infect Dis, 201

Current recommendations of voriconazole dosing

Patient age/wt	Recommended dose by treatment type			
	Intravenous (mg/kg/12h)		Oral	
	Loading	Maintenance	Loading	Maintenance
< 2 yr*	9	8		9 mg/kg/12h
2 – 12 yr or 12- 14 yr/ <50 kg	9	8		9 mg/kg/12h (max 350mg/12h)
> 14 yr/<40 kg	6	4	200 mg/12h	100 mg/12h
> 12 – 14 yr/>40 kg	6	4	400 mg/12h	200 mg/12h

* For patients <2 years of age, the dose as recommended in the summary of product characteristics for patients 2 to 12 years of age was used

Bartelink IH et al., Antimicrob Agents Chemother, 2013; Pfizer Limited. 2012. Vfend summary of product information. Pfizer Limited, London, United Kingdom

Posaconazolo oral solution

- Variable and erratic absorption
- Absorption improved
  - With fat meal
  - With any meal or nutritional supplement
  - Coke-like drink
  - By subdividing doses (4x)
  - Avoiding proton pump inhibitors
- Absorption seems to worsen if drug administered through naso-gastric tube

Table 8. Posaconazole plasma concentration versus global response in patients with invasive aspergillosis (MITT subset).

Quartile	No. of subjects[a]	Plasma C_{max} Mean ng/mL	Plasma C_{max} CV, %	Plasma C_{avg} Mean ng/mL	Plasma C_{avg} CV, %	No. (%) of responders
1	17	142	51	134	45	4 (24)
2	17	467	27	411	21	9 (53)
3	17	852	15	719	12	9 (53)
4	16	1480	16	1250	28	12 (75)

Walsh et al, CID 2007

mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Original article

Optimising absorption of posaconazole

Myke R. Green[1,2] and Joseph E. Woolery[3,4]

Table 1 'Posaconazole bundle'.

1. Ascorbic acid 500 mg *per os* with each dose of posaconazole.
2. 4–6 ounces (120–180 ml) carbonated soda beverage (i.e.: cola or ginger ale) or acidic fruit juice (e.g.: cranberry or orange juice) with each dose of posaconazole.
3. Dividing daily dose of 600 mg (prophylaxis) into TID or 800 mg (treatment) into QID dosing. Maximum of 200 mg per administration.
4. Heavy snack or food with each dose, preferably high-fat.
   (a) Includes commercially available nutritional supplements.
5. Proton pump inhibitors and cimetidine strictly forbidden.
   (a) Use of other histamine$_2$-antagonist allowed, if needed.
   (b) Use of aluminium/magnesium-containing antacid allowed, if needed.
6. Co-administration of rifamycin derivatives and phenytoin strictly forbidden.

FEASIBLE???

Journal of Antimicrobial Chemotherapy Advance Access published November 26, 2015

J Antimicrob Chemother
doi:10.1093/jac/dkv380

Journal of Antimicrobial Chemotherapy

Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease

Oliver A. Cornely[1]*, Rafael F. Duarte[2], Shariq Haider[3], Pranatharthi Chandrasekar[4], David Helfgott[5], Javier López Jiménez[6], Anna Candoni[7], Issam Raad[8], Michel Laverdiere[9], Amelia Langston[10], Nicholas Kartsonis[11], Marlou Van Iersel[12], Nancy Connelly[13]† and Hetty Waskin[13]

Serum posaconazole levels among haematological cancer patients taking extended release tablets is affected by body weight and diarrhoea: single centre retrospective analysis

Marisa H. Miceli,[1] Anthony J. Perissinotti,[2] Carol A. Kauffman[1,3] and Daniel R. Couriel[4]

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- **Posaconazole tablets are absorbed in the small intestine in an elevated pH environment**
- **This leads to improved exposure and less absorption variability**
- **No effect of PPI on absorption**
- **Still some problems in hematological patients**

Posaconazole gastroresistant tablet and IV formulations

ECIL VI, Russel Lewis

- Pending further data, TDM is still recommended in patients receiving posaconazole tablets or IV formulation for prophylaxis **(CIII)**
- TDM is recommended in patients receiving posaconazole tablets or IV formulation receiving treatment for suspected or documented fungal infection **(CIII)**
- TDM is indicated for patients receiving tablets or IV formulation in the setting of breakthrough or progressing infection unresponsive to treatment, treatment of pathogens with reduced susceptibility, or drug interactions **(CIII)**

additional data are needed

1. Cumpston et al. Antimicrob Agent Chemother 2015;59:4424-4428
2.Durani et al. Antimicrobial Agent Chemother 2015;59:4914-4918
3. European Medicine Agency. Assessment report: Noxafil. 2014. Accessed 30 April 2015.

DOSAGE AND ADMINISTRATION

Indication	Dose and Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	**Injection*:** Loading dose: 300 mg Noxafil injection intravenously twice a day on the first day. Maintenance dose: 300 mg Noxafil injection intravenously once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.1)
	Delayed-Release Tablets†: Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.2)
	Oral Suspension‡: 200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.3)

A new entry: isavuconazole

Isavuconazole-concentration efficacy

Isavuconazole package labelling:

12.2 Pharmacodynamics

Pharmacokinetic/Pharmacodynamic Relationship

In patients treated with CRESEMBA for invasive aspergillosis in a controlled trial, there was no significant association between plasma AUC or plasma isavuconazole concentration and efficacy.

TDM is indicated for patients receiving tablets or IV formulation in the setting of breakthrough or infection unresponsive to treatment, treatment of pathogens with reduced susceptibility, or in the setting of drug interactions **(CIII)**

additional data are needed

Clinical indications

ECIL V 2013 in AML

Type of drug	Grading
Fluconazole	BI
Itraconazole	BI
Voriconazole	BII
Posaconazole	AI
L-AmB aerosol and oral fluco	BI

ECIL V 2013 in HSCT

Type of Drug	Pre-engraftment and low risk for moulds	Pre-engraftment and high risk for moulds	GVHD
Fluconazole	AI	AIII against	AIII against
Itraconazole	BI	BI	BI
Voriconazole	BI	BI	BI
Posaconazole	BII	BII	AI
Mikafungin	BI	CI	CII
Caspo/anidula L-AmB	No data	No data	No data
Aerosol AmB + fluco	CIII	BII	No data
L-AmB	CII	CII	CII

Similar strenght of recommendation and quality of evidence for ESCMID guidelines

Invasive aspergillosis

• Voriconazole	A I
• Isavuconazole	A I
• Ambisome	B I
• ABLC	B II
• Caspofungin	C II
• Itraconazole	C III
• ABCD	C I
• Vorico+Anidula	C I
• Other combinations	C III
• AmB deoxycholate	A I against

ECIL-5
A: Good evidence to support a recommendation for use
B: Moderate evidence to support a recommendation for use
C: Poor evidence to support a recommendation for use

Thank you for your attention

TABLE 3. Evidence for and against monitoring of blood levels during azole therapy

Evidence for monitoring of blood levels during azole therapy	Evidence against monitoring of blood levels during azole therapy
Large and unpredictable variability of blood levels	Real-time measurements not routinely available
Multiple factors influencing drug absorption, distribution, and elimination, including age, genetic background, compliance and gastrointestinal function, comedication, and liver and/or renal dysfunction	Target blood levels not established; lacking data from prospective controlled studies systematically exploring efficacy and toxicity associated with drug over- or underdosing
Emergence of fungal pathogens with decreased susceptibility requiring optimal adjustment of drug exposure	Drug blood concn might not reflect exposure and efficacy in infected tissues
Multiple clinical reports of failure associated with drug underdosing and toxicity associated with drug overdosing	

TABLE 4. Tentative recommendations for monitoring of blood levels during antifungal therapy

Drug	Indication	Time of first measurement after start of therapy (days)	Target blood concn[a] (μg/ml) for:	
			Efficacy	Safety
Flucytosine	Routine during first wk of therapy, renal insufficiency, lacking response to therapy	3–5	Peak of >20	Peak of <50
Itraconazole	Routine during first wk of therapy, lacking response, gastrointestinal dysfunction, comedication	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >1 to 2	NA
Voriconazole	Lacking response; gastrointestinal dysfunction; comedication; children; intravenous-to-oral switch; severe hepatopathy; unexplained neurological symptoms/signs	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >1 to 2	Trough of <6
Posaconazole	Lacking response; gastrointestinal dysfunction, therapy with proton pump inhibitors; comedication	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >0.5 to 1.5	NA

[a] Total or bound and unbound drug concentrations. NA, not applicable.

Isavuconazole: Recommendations

Contraindications	Used with caution	No interaction
Carbamazepine	Aprepitant	Caffeine
Efavirenz	Bupropion	Dextromethorphan
Etravirine	Clarithromycin	Esomeprauole
High dose ritonavir	Colchicine	Ethinyl estradiol
Ketoconazole	Cyclophosphamide	Methadone
Long-acting barbiturates	Ciclosporin	Methotrexate
Nafcillin	Dabigatran etexilate	Norethindrone
Phenytoin	Digoxin	Omeprazole
Rifabutin	Metformin	Repaglinide
Rifampicin	Midazolam	Warfarin
St. John's wort	Mycophenolate mofetil	
	Other anticancer agents	
	Other NNRTIs	
	Pioglitazone	
	Prednisone	
	Other protease inhibitors	
	Short-acting opiates	
	Sirolimus	
	Statins	
	Tacrolimus	
	Vinca alcaloids	

NNRTI = Non-nucleoside reverse transcriptase inhibitors

ISAVUCONAZOLE VERSUS VORICONAZOLE

	Voriconazole	Isavuconazole*
Active against Mucorales	No	Yes
Food/ph effect	Yes/yes	No clinically relevant/no
ß-cyclodextrin	Yes	No
Administration	Twice/d following loading dose	Once/d following loading dose
Predictable PK in adults	No	Yes (at least up to 600 mg)
Need for TDM	Yes	Unlikely
Drug interactions	+++	++
Safety (visual)	++	+ (no visual)
Renally impaired patients	Avoid IV creatinine clearance <50	No dose adaptations (ind ESRD)
Clinical experience	Extensive	Limited

*Miceli MH and Kauffman CA. Clin Infect Dis 2015 Jul 15

Courtesy Andrea Novelli

Voriconazole metabolism: expression of different CYP2C19 genotypes for different ethnic groups

Phenotype	Population frequencies				
	White	African-American	Hispanic	Ashkenazi Jewish	Asian
Ultrarapid metabolizers	31.2%	33.3%	18.3%	24.6%	~ 1%
Extensive metabolizers	42%	39%	58%	46%	35-43%
Intermediate metabolizers	19%	15%	20%	22%	43-46%
Poor metabolizers	2.8%	6.7%	0.87%	1.8%	14-19%

*1 = normal function;
*2, *3, *4, *5, *6, *8 = loss of funcion or null alleles;
*17 = increased function

Owusu Obeng A et al., Pharmacotherapy, 2014