BEST PAPER IN INFECTIOUS DISEASE 2023

Infezioni fungine

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THE LANCET

Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

George R Thompson III, Alex Soriano, Oliver A Cornely, Bart Jan Kullberg, Marin Kollef, Jose Vazquez, Patrick M Honore, Matteo Bassetti, John Pullman, Methee Chayakulkeeree, Ivan Poromanski, Cecilia Dignani, Anita F Das, Taylor Sandison, Peter G Pappas, on behalf of the ReSTORE trial investigators

Background

- Candidemia is a **life threathening infection** with an attributed mortality of 15-20% despite effective treatment
- Echinocandins are the first line-treatment, but **they are not «perfect» drugs** (PK/PD issues, emerging resistance)
- Rezafungin is a **novel broad-spectrum echinocandin** (*Candida* spp. and *Aspergillus* spp.), with AUC/MIC-dependent activity, linear kinetics, prolonged half life (152 ± 9 hours) which allows one weekly administration, and low risk of DDI

Outline

- **Clinical question**. Can we use rezafungin for the treatment of patients with candidemia or invasive candidiasis?

- **Research question**. To compare the efficacy and safety of rezafungin once weekly iv versus caspofungin one daily iv for the treatment of candidemia and invasive candidiasis

- **Study design**. Multicentre, prospective, randomised, double-blind, double-dummy, non-inferiority, phase 3 clinical trial.

Population

Country	Patients enrolled, n	Rezafungin	Caspofungin
USA	51	26	25
Thailand	25	8	17
Spain	24	12	12
Greece	17	6	11

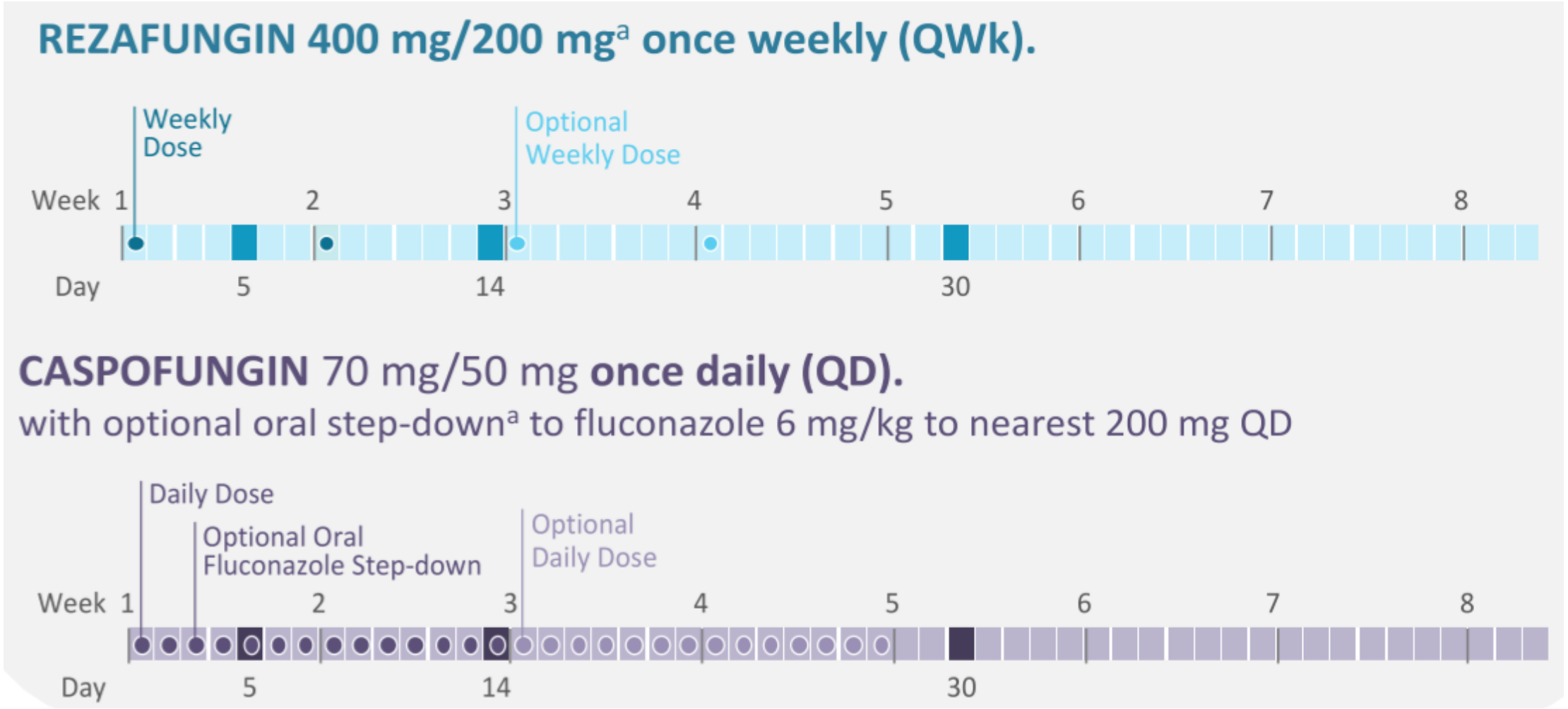
2018-2021

- **Adults** aged 18 years or older
- **Candidemia or invasive candidiasis** with mycological evidence obtained not more than 4 days before the randomization

Main exclusion criteria

- PJI, osteomyelitis, endocarditis, myocarditis, meningitis, chorioretinitis, CNS/UTI candidiasis
- Non-removable catheter or device
- Severe hepatic impairment
- Recent (< 4 days) antifungal treatment

Intervention - Comparison



All study site personnel who interacted with patients, and patients themselves, were blinded

Treatment range: 14-28 days

Outcome

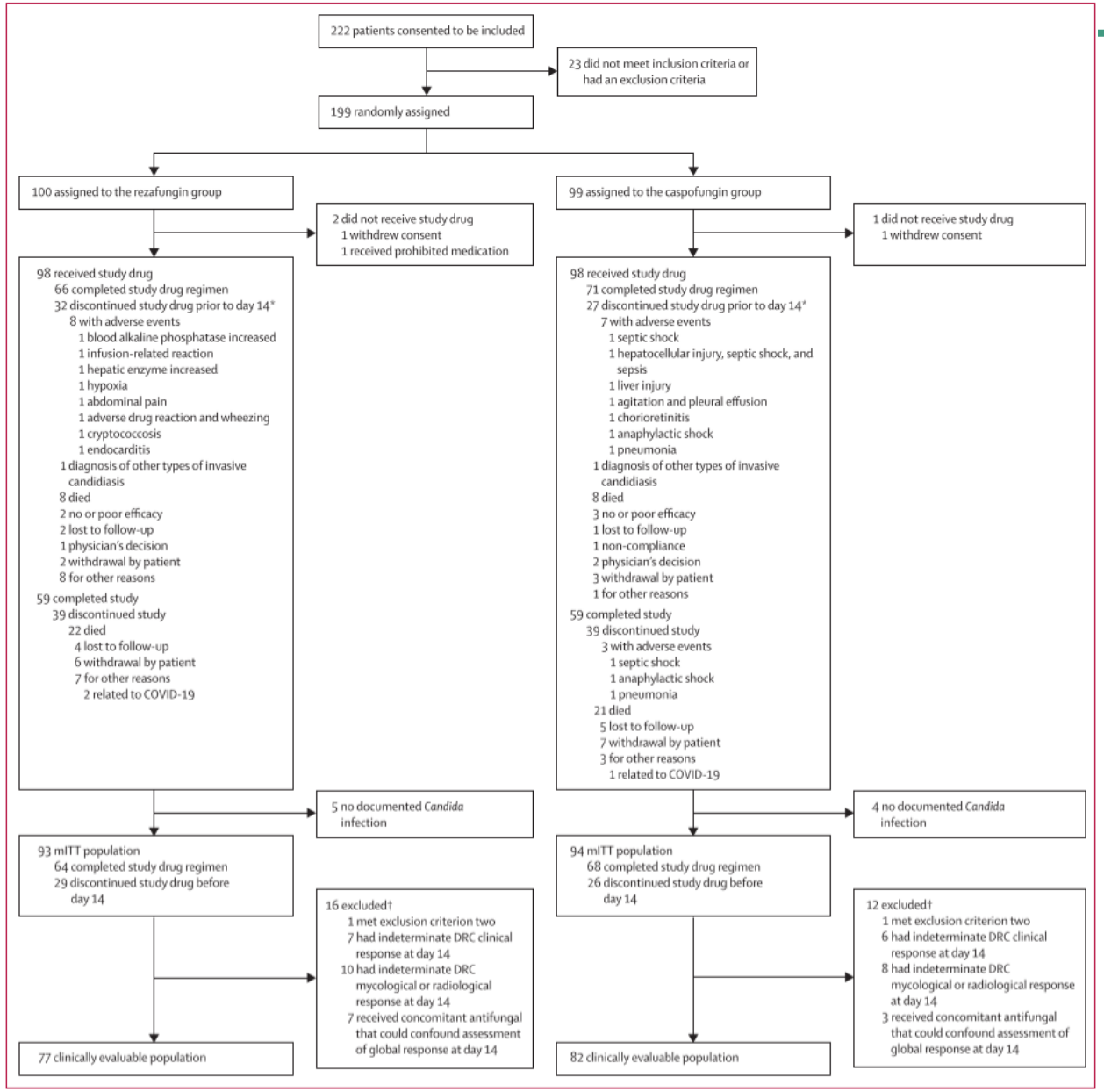
Primary endpoints

- Global cure (clinical/radilogical + mycological eradication) at the 14-day visit (EMA)
- All-cause mortality at the 30-day visit (FDA)

Secondary endpoints: global cure at all time points

Exploratory outcomes: time to first negative blood culture, proportion of negative blood cultures at 24-48 hours after the first dose of study drug

Results

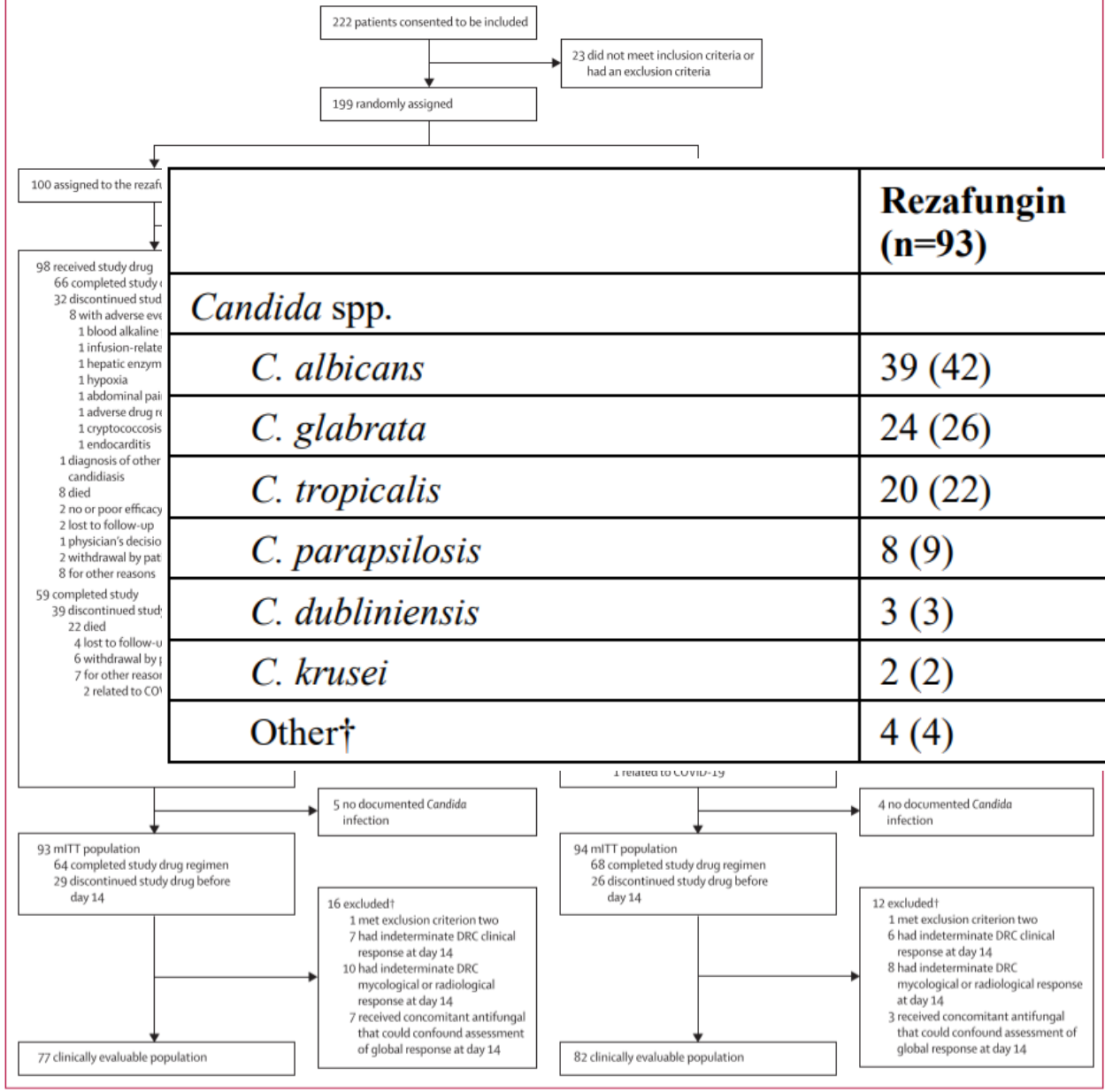


	Rezafungin group (n=100)	Caspofungin group (n=99)
Age	59·5 (15·8)	62·0 (14·6)
<65 years	60 (60%)	58 (59%)
≥65 years	40 (40%)	41 (41%)
Sex		
Male	67 (67%)	56 (57%)
Female	33 (33%)	43 (43%)
Race		
Asian	27 (27%)	31 (31%)
Black or African American	5 (5%)	4 (4%)
White	61 (61%)	60 (61%)
Other or not reported	7 (7%)	4 (4%)
Diagnosis		
Candidaemia only	70 (70%)	68 (69%)
Invasive candidiasis*	30 (30%)	31 (31%)
Mean modified APACHE II score†	12·5 (8·0)	13·1 (7·1)
≥20	15 (15%)	18 (18%)
<20	84 (84%)	81 (83%)
Body-mass index mean, kg/m²	25·4 (7·0)	24·5 (6·5)
Absolute neutrophil count, <500 cells per µL†	9 (9%)	6 (6%)

Data are n (%) or mean (SD). APACHE=Acute Physiology and Chronic Health Evaluation. *Includes patients who progressed from candidaemia to invasive candidiasis based on radiological or tissue or fluid culture assessment up to day 14. †Reported for patients with data available.

Table 1: **Demographics and baseline characteristics in the intention-to-treat population**

Results



	Rezafungin (n=93)	Caspofungin (n=94)
Candida spp.		
C. albicans	39 (42)	40 (43)
C. glabrata	24 (26)	25 (27)
C. tropicalis	20 (22)	17 (18)*
C. parapsilosis	8 (9)	17 (18)*
C. dubliniensis	3 (3)	1 (1)
C. krusei	2 (2)	2 (2)
Other†	4 (4)	2 (2)

	Rezafungin group (n=100)	Caspofungin group (n=99)
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Table 1: **Demographics and baseline characteristics in the intention-to-treat population**

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)
All-cause mortality at day 30 (US FDA primary outcome)			
Died	22 (24%)	20 (21%)	2·4 (−9·7 to 14·4)*
Known to have died	19 (20%)	17 (18%)	..
Unknown survival	3 (3%)	3 (3%)	..
All-cause mortality at day 30 by diagnosis			
Candidaemia only	18/64 (28%)	17/67 (25%)	2·8 (−12·5 to 18·0)*
Invasive candidiasis	4/29 (14%)	3/27 (11%)	2·7 (−16·7 to 21·7)*
Global response at day 14 as assessed by DRC (EMA primary outcome)			
Cure	55 (59%)	57 (61%)	−1·1 (−14·9 to 12·7)†
Failure	28 (30%)	29 (31%)	..
Indeterminate	10 (11%)	8 (9%)	..
Global response at day 14 as assessed by DRC by diagnosis			
Candidaemia only			
Cure	39/64 (61%)	43/67 (64%)	−3·2 (−19·6 to 13·3)*
Failure	21/64 (33%)	19/67 (28%)	..
Indeterminate	4/64 (6%)	5/67 (7%	..
Invasive candidiasis			
Cure	16/29 (55%)	14/27 (52%)	3·3 (−22·4 to 28·6)*
Failure	7/29 (24%)	10/27 (37%)	..
Indeterminate	6/29 (21%)	3/27 (11%)	..

Data are n (%) or n/N (%). ANC=absolute neutrophil count. APACHE II=Acute Physiology and Chronic Health Evaluation II score. DRC=data review committee. EMA=European Medical Agency. FDA=Food and Drug Administration. *Two-sided 95% CI for the observed difference (%), rezafungin group minus caspofungin group. †Two-sided 95% CI for the weighted difference (%), rezafungin group minus caspofungin group adjusted for the two randomisation strata of diagnosis (candidaemia *vs* invasive candidiasis) and high risk (APACHE II score ≥20 or ANC <500 cells per µL) versus low risk (APACHE II score <20 and ANC ≥500 cells per µL).

Table 2: **All-cause mortality at day 30 and global response at day 14 in the modified intention-to-treat population**

20% margin for non-inferiority, two-sided alfa 0.05%

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)*
Patients with negative blood culture†			
24 h	36/67 (54%)	30/65 (46%)	..
48 h	49/66 (74%)	41/64 (64%)	..
Outcomes at the day 5 visit			
Global cure as assessed by DRC	52 (56%)	49 (52%)	3·8 (−10·5 to 17·9)
Mycological eradication‡	64 (69%)	58 (62%)	7·1 (−6·6 to 20·6)
Patients with candidaemia only	50/64 (78%)	46/67 (69%)	9·5 (−5·8 to 24·4)
Investigator assessment of clinical cure	59 (63%)	70 (74%)	−11·0 (−24·0 to 2·3)
Outcomes at the day 14 visit			
Global cure as assessed by DRC§	55 (59%)	57 (61%)	−1·1 (−14·9 to 12·7)¶
Mycological eradication	63 (68%)	62 (66%)	1·8 (−11·7 to 15·2)
Patients with candidaemia only	46/64 (72%)	47/67 (70%)	1·7 (−13·9 to 17·2)
Investigator assessment of clinical cure	62 (67%)	63 (67%)	−0·4 (−13·8 to 13·1)

Data are n (%) or n/N (%). ANC=absolute neutrophil count. APACHE=Acute Physiology and Chronic Health Evaluation. DRC=data review committee. *Two-sided 95% CI for the observed difference (%), rezafungin group minus caspofungin group. †Exploratory endpoint. ‡Programmatically derived from the outcome definition described in the methods. §Primary endpoint for the European Medicines Agency (secondary endpoint for the US Food and Drug Administration). ¶Two-sided 95% CI for the weighted difference (%), rezafungin group minus caspofungin group adjusted for the two randomisation strata of diagnosis and APACHE II score and ANC.

Table 3: **Secondary and exploratory endpoints of efficacy in the modified intention-to-treat population**

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)
All-cause mortality at day 30 (US FDA primary outcome)			
Died	22 (24%)	20 (21%)	2·4 (−9·7 to 14·4)*
Known			
Unkno			
All-cause			
Candi			
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Cure			
Failure			
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Indete			
Invasive			
Cure			
Failure			
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Table 2: All-cause mortality at day 30 and global response at day 14 in the modified intention-to-treat population

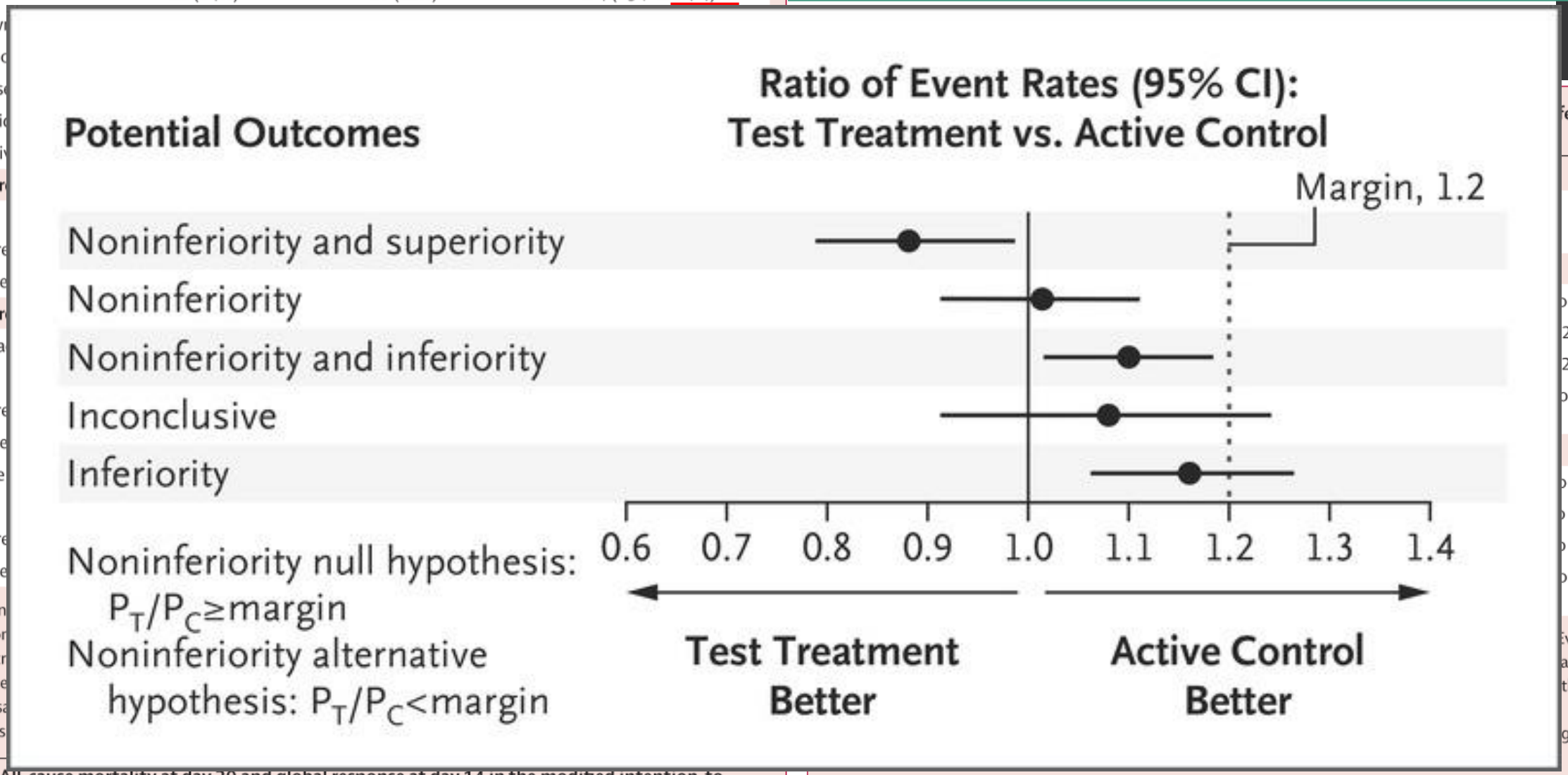

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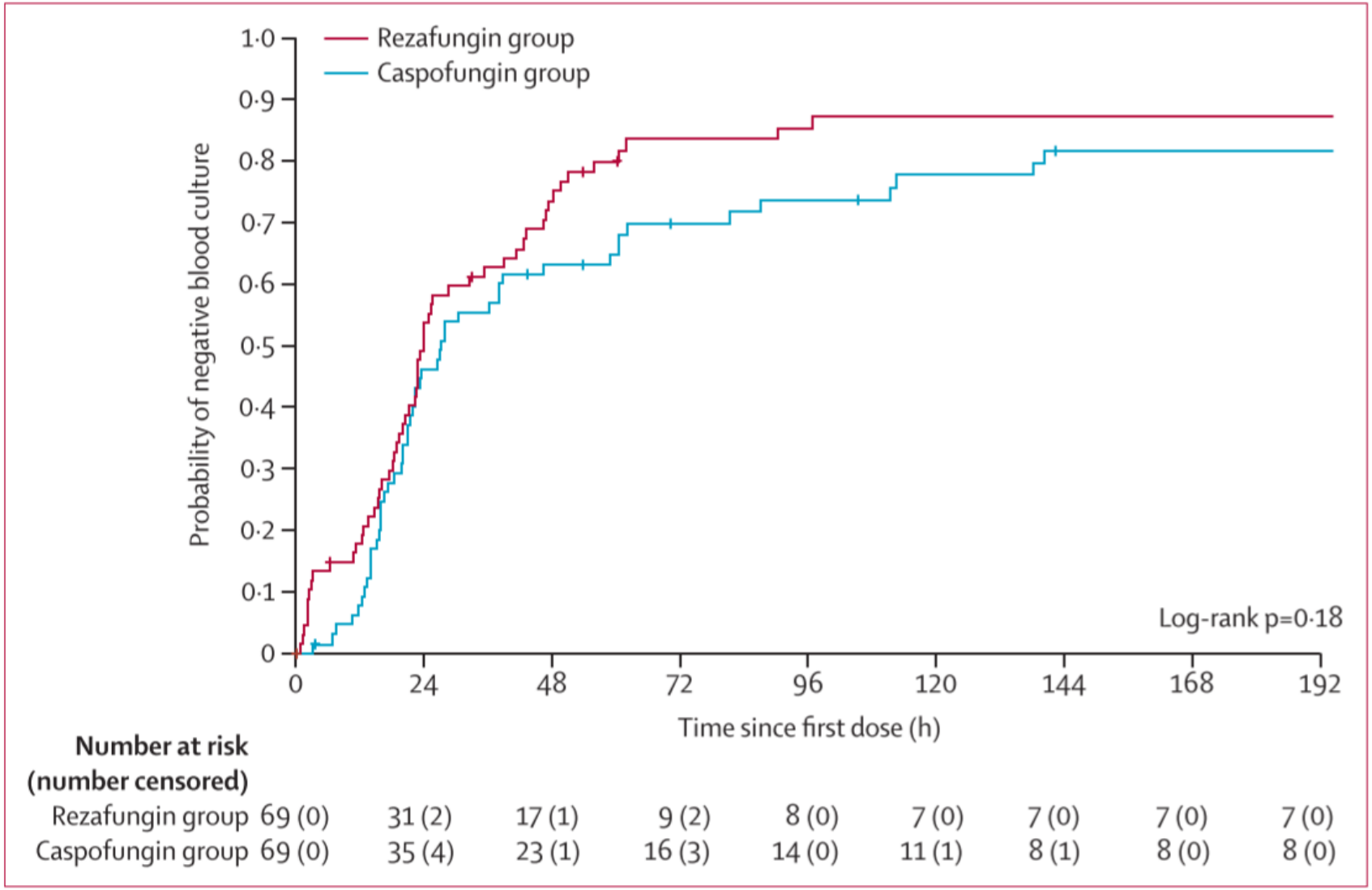
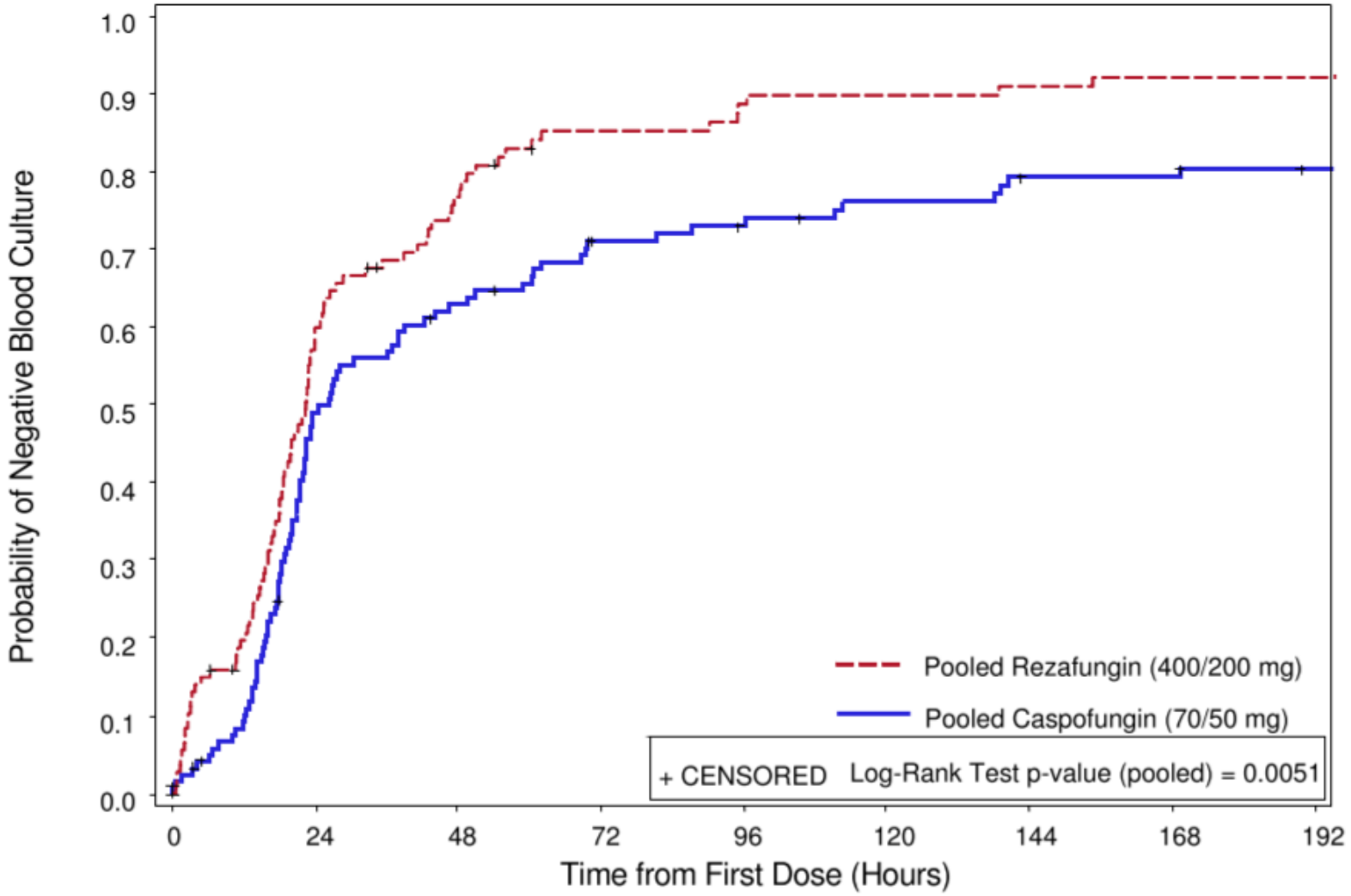
Table 3: Secondary and exploratory endpoints of efficacy in the modified intention-to-treat population

Exploratory outcomes

Time to first negative blood culture: 23.9 h (IQR 15.4-48.3) in rezafungin group and 27 h (IQR 16.4–111.3) for the caspofungin group



Exploratory outcomes



Pooled Rezafungin (400/200 mg)	109	42	23	13	10	9	8	7	7
Pooled Caspofungin (70/50 mg)	122	59	42	30	27	23	19	19	16

Conclusions

- Rezafungin once weekly was **non-inferior** to caspofungin for the treatment of candidemia and invasive candidosis
- Patients with **invasive candidiasis** were included; outcomes are less robust, as expected, but promising
- **Early efficacy outcomes** (especially time to first negative blood culture) are consistent with PK/PD data of rezafungin
- **PK** data available (low variability)
- **Limitations**: sample size, big proportion of *C. albicans*, exclusion of «difficult-to-treat» infections, no data about lenght of hospital stay

Clinical Infectious Diseases

MAJOR ARTICLE

Prevalence of Ocular Candidiasis and *Candida* Endophthalmitis in Patients With Candidemia: A Systematic Review and Meta-Analysis

Kasidis Phongkhun,[1,a] Thananop Pothikamjorn,[1,a] Karan Srisurapanont,[2] Kasama Manothummetha,[3] Anawin Sanguankeo,[4] Achitpol Thongkam,[3] Nipat Chuleerarux,[5] Surachai Leksuwankun,[1] Tanaporn Meejun,[2] Jaedvara Thanakitcharu,[6] Morgan Walker,[7,8] Shilpa Gopinath,[7] Pattama Torvorapanit,[1] Nattapong Langsiri,[3] Navaporn Worasilchai,[9] Chatphatai Moonla,[1] Rongpong Plongla,[1] Olivia S. Kates,[7] Saman Nematollahi,[10] and Nitipong Permpalung[3,7,]

Background

- The frequency of eye lesions in patients with candidemia is variable (from 2 to 20%, depending on the study design)
- Fundoscopic examination is part of bundles for candidemia management
- IDSA and AAO are in disagreement in recommending fundoscopic examination of the eye in patients with candidemia

IDSA
Infectious Diseases Society of America

AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Outline

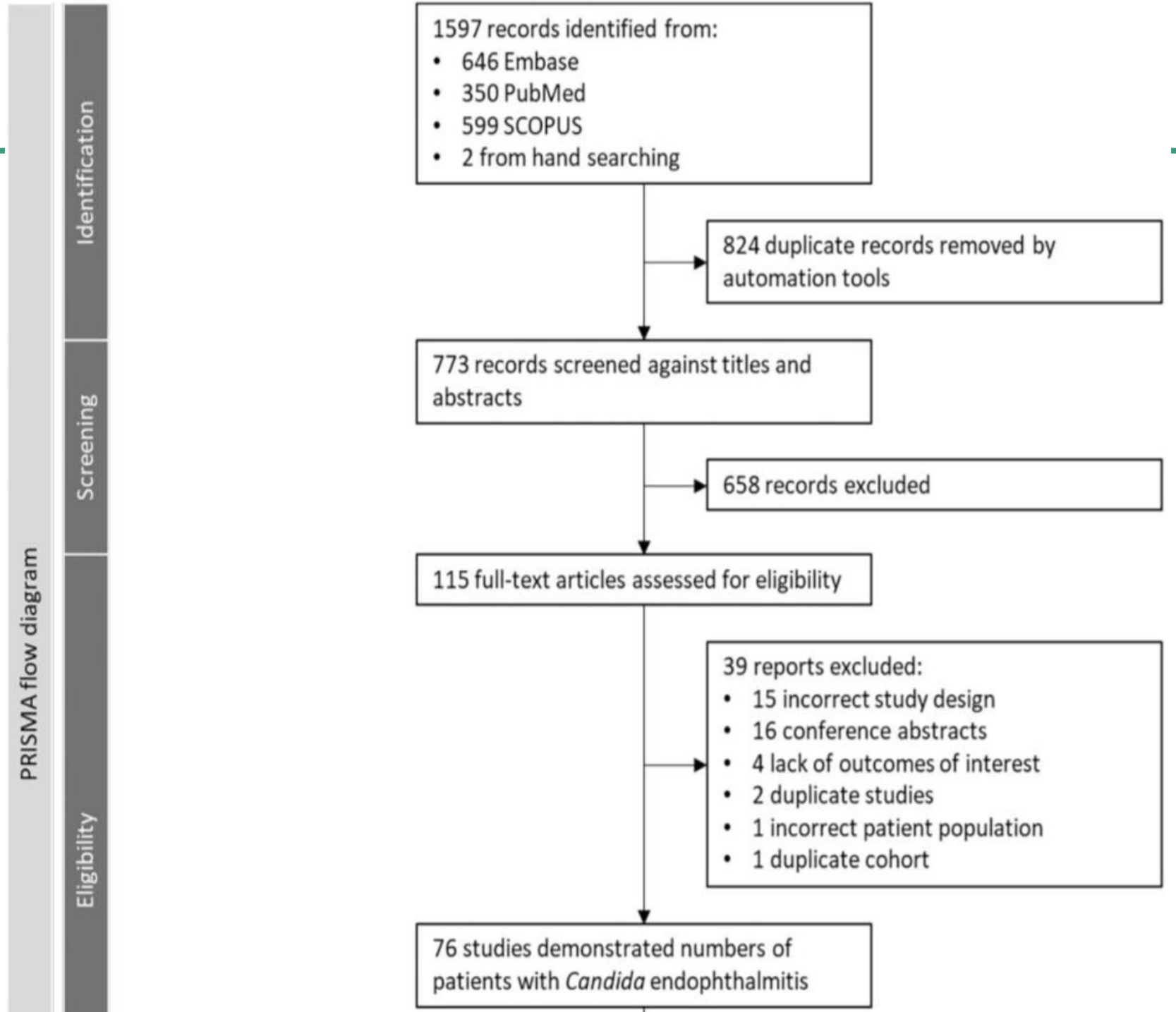
- **Research question**. What is the prevalence of *Candida* ocular involvement, both ocular candidiasis and candida endophtalmitis, in patients with candidemia?

- **Study design**. Systematic review and meta-analysis

Definitions

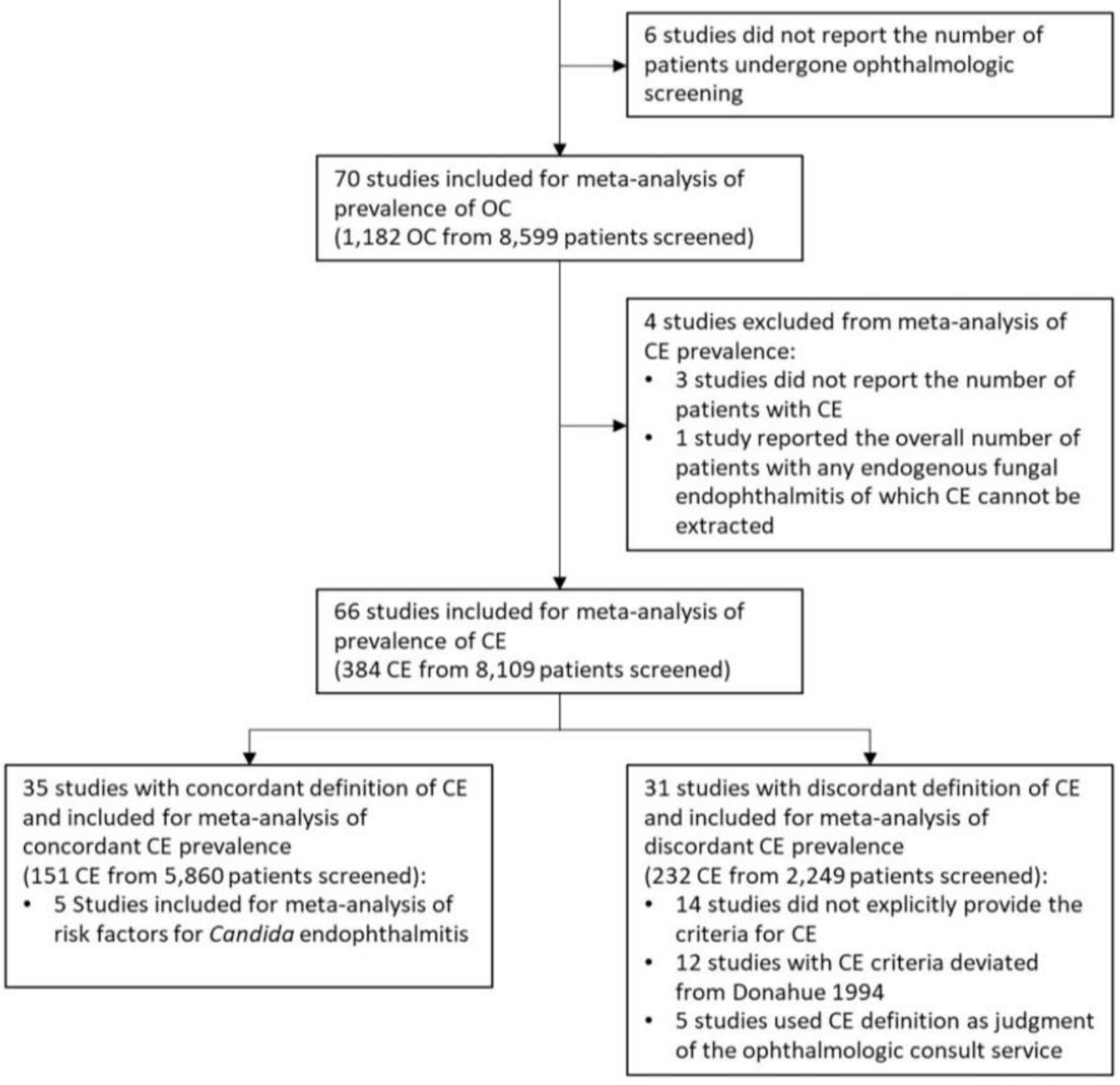
- ***Candida* endophtalmitis CE**: abnormal ocular findings specifically attributed to *Candida* infection based on the direct ophthalmologic examination performed by ophthalmologists. Patients with **concordant CE** must meet 1 of the following definitions: (1) *Candida* chorioretinitis with an extension of the surrounding inflammation into the vitreous or (2) vitreous abscess manifesting as intravitreal fluff balls. Otherwise, it is **discordant CE**.

- **Ocular candidiasis OC**: any intraocular abnormalities among patients with candidemia such as vitritis, chorioretinitis, and other nonspecific abnormal retinal findings


PRISMA flow diagram
Identification
Screening
Eligibility
1597 records identified from:
• 646 Embase
• 350 PubMed
• 599 SCOPUS
• 2 from hand searching
824 duplicate records removed by automation tools
773 records screened against titles and abstracts
658 records excluded
115 full-text articles assessed for eligibility
39 reports excluded:
• 15 incorrect study design
• 16 conference abstracts
• 4 lack of outcomes of interest
• 2 duplicate studies
• 1 incorrect patient population
• 1 duplicate cohort
76 studies demonstrated numbers of patients with Candida endophthalmitis

Flow diagram of the included studies

Included



Results – pooled prevalences

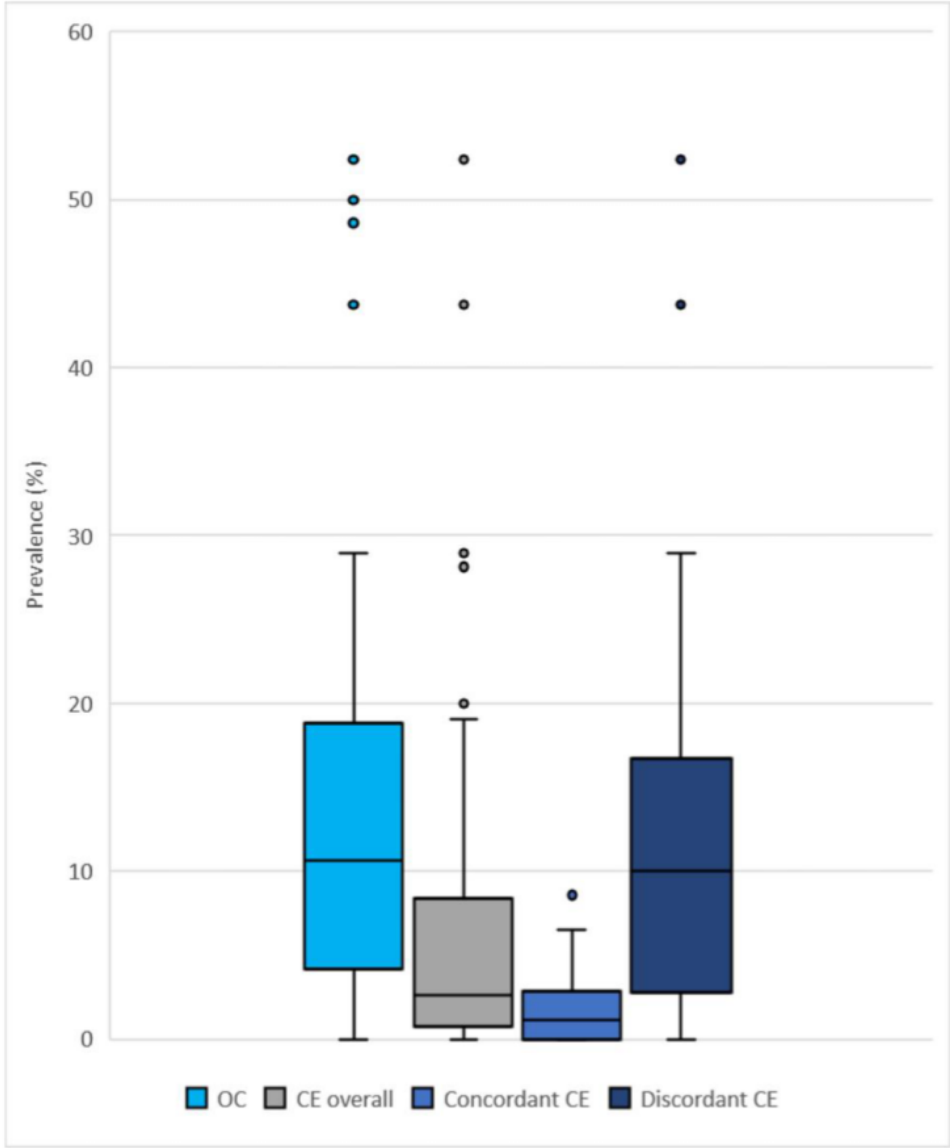
OC: 10.7% (8.41 – 13.51%; I^2 = 84%)

CE: 3.08% (2.08 – 4.54%; I^2 = 85%)

cCE: 1.83% (1.30 – 2.57%; I^2 = 24%) – 35 studies

dCE: 7.37% (4.45 – 11.97%; I^2 = 82%)

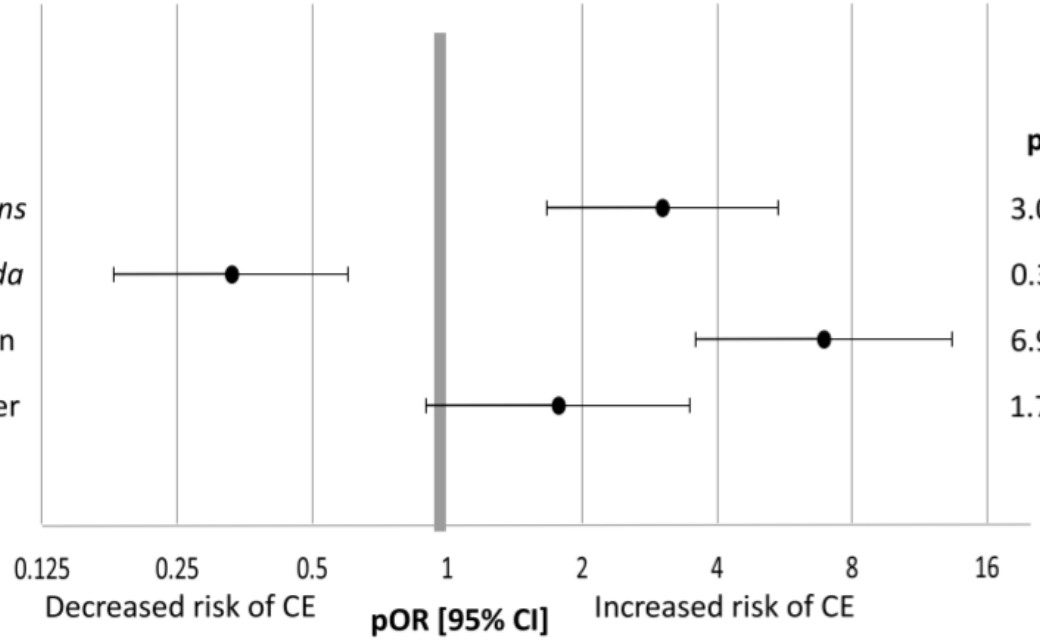
Subgroup analyses of cCE: higher prevalence in Asian patients (3.64%), no differences between adults and pediatric patients.



Results – risk factor for CE

Candida species, total parenteral nutrition and the presence of a central venous catheter were assesed as risk factors for CE:

- *C. albicans* candidemia and TPN are risk factors
- The presence of a CVC is not a risk factor



Potential risk factor	pOR [95% CI]	No. of studies	No. of participants	I^2	GRADE
Candida albicans	3.02 [1.67 - 5.46]	4	1129	52%	Very low
Non-albicans *Candida*	0.33 [0.18 - 0.60]	4	1129	53%	Very low
Total parenteral nutrition	6.92 [3.58 - 13.36]	4	982	0%	Very low
Central venous catheter	1.77 [0.90 - 3.49]	3	1097	60%	Very low

Conclusion

- Major **differences** in pooled prevalence according to the definition of ocular involvement; cCE is the most stringent and, probably, the most relevant clinically
- Higher prevalence in **Asian** patients: genetic susceptibility (CARD9 deficit involved in Candida immune response)? Differences in screening procedures?
- No data about ocular **symptoms** and **timing** of eye examination
- **Risk factor** analysis should be interpreted with cautions (few studies), but the results are plausible
- Large **prospective** observational studies are warranted

Clinical Infectious Diseases

MAJOR ARTICLE

Single High-dose of Liposomal Amphotericin B in Human Immunodeficiency Virus (HIV)/AIDS-related Disseminated Histoplasmosis: A Randomized Trial

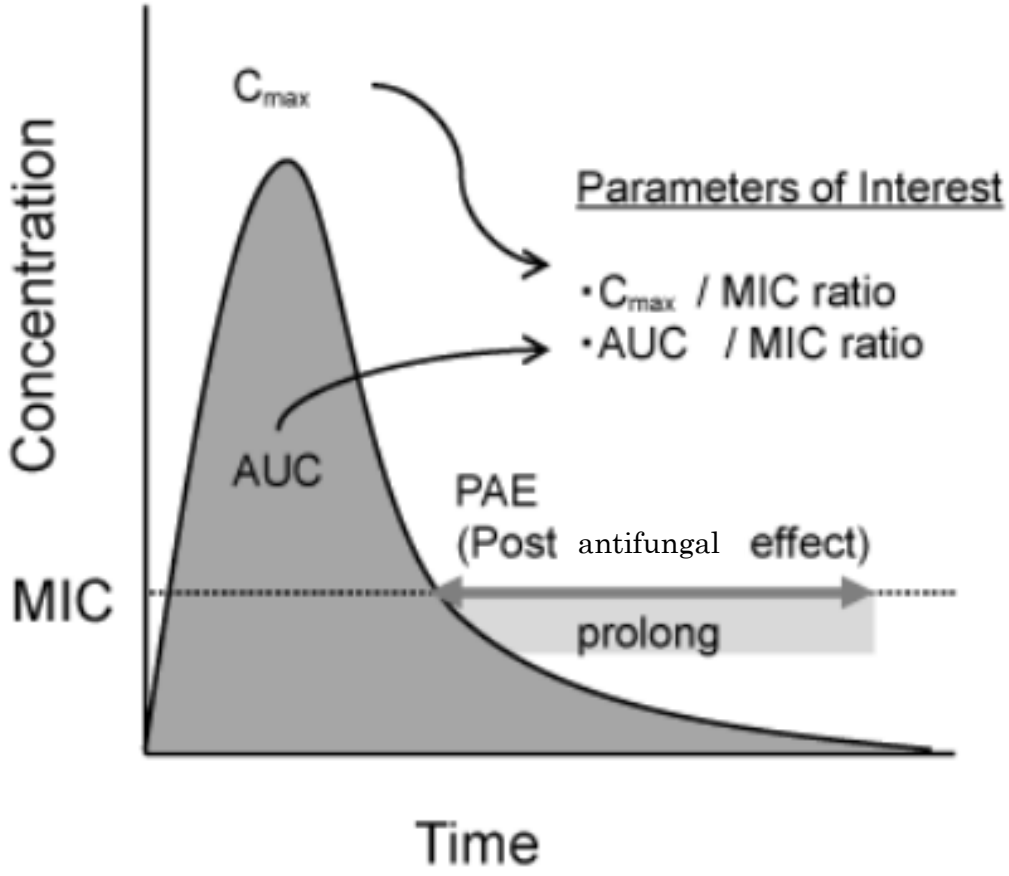
Alessandro C. Pasqualotto,[1,2] Daiane Dalla Lana,[1] Cassia S. M. Godoy,[3,4] Terezinha do Menino Jesus Silva Leitão,[5,6] Monica B. Bay,[7,8] Lisandra Serra Damasceno,[5,6] Renata B. A. Soares,[3,4] Roger Kist,[2] Larissa R. Silva,[1] Denusa Wiltgen,[1,2] Marineide Melo,[9] Taiguara F. Guimarães,[3] Marilia R. Guimarães,[10] Hareton T. Vechi,[7] Jacó R. L. de Mesquita,[5] Gloria Regina de G. Monteiro,[7,8] Antoine Adenis,[11] Nathan C. Bahr,[12] Andrej Spec,[13] David R. Boulware,[14] Dennis Israelski,[15] Tom Chiller,[16] and Diego R. Falci[17,18]

Background

- Disseminated histoplasmosis DH is a **major AIDS-defining illness** in the Americas
- The real **burden** of DH is not known yet
- Liposomal amphotericin B (L-AmB) is the **cornerstone** of treatment, but access to this drug in endemic countries is seldom limited
- **Single dose L-AmB** strategies have been validated for some diseases (leishmaniosis, cryptococcal meningitis) and could improve access to treatment and costs

Rationale

- L-AmB has a dose-related, non-linear, saturation-like PK
- PK/PD parameter: **Cmax/MIC**
- Time-kill studies proved the concentration-dependent fungicidal activity and prolonged post-antifungal effects for a duration of up to 12 hours



Clin Infect Dis 2019; 68:S260–74

Outline

- **Clinical question**. Can we use a single dose L-AmB strategy in patients with DH and HIV infection?

- **Research question**. To establish safety, clinical and mycological response of a high dose L-AmB regimen for the treatment of DH in PLWH

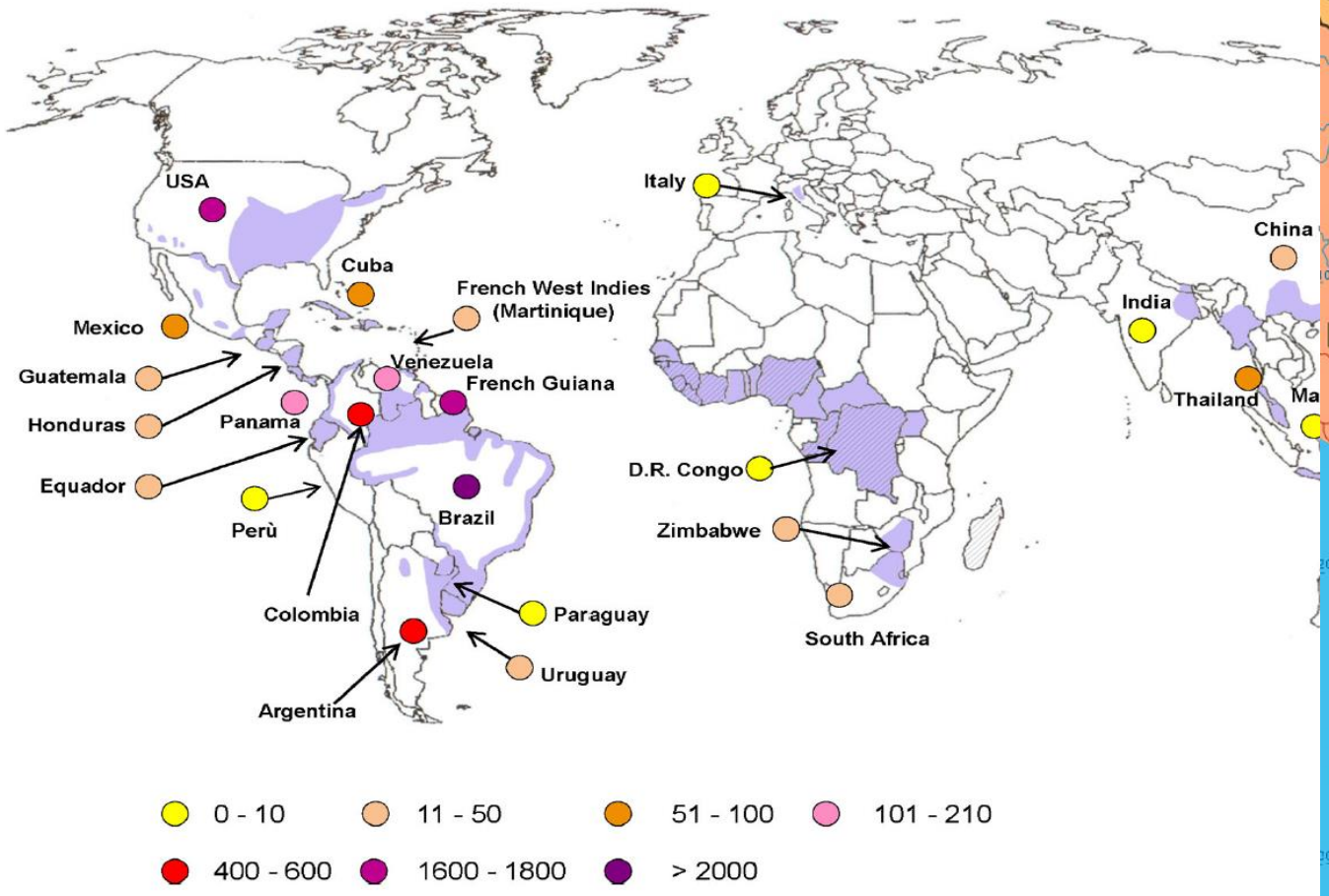
- **Study design**. Phase II, randomized, open label, non-inferiority trial

Population

- **Adults** ≥ 18 year old, hospitalized
- HIV infection
- Diagnosis of **histoplasmosis** by urine antigen (Sn/Sp 98/97%), classical mycology (microscopy, culture, histopathology) or PCR in BAL, bone marrow or tissue samples.

Exclusion criteria: previous histoplasmosis, active TB, pregnancy/lactation, creatinine > 1.5x URL, CNS involvement, receipt of polyenes in the last 48h, expected survival < 48h

Population



Curr Trop Med Rep. 2015;2(2):70-80.

Intervention - Comparison

Single dose L-Amb
10 mg/Kg one-shot

2 doses L-Amb
5 mg/Kg (D1) +
2 mg/Kg (D3)

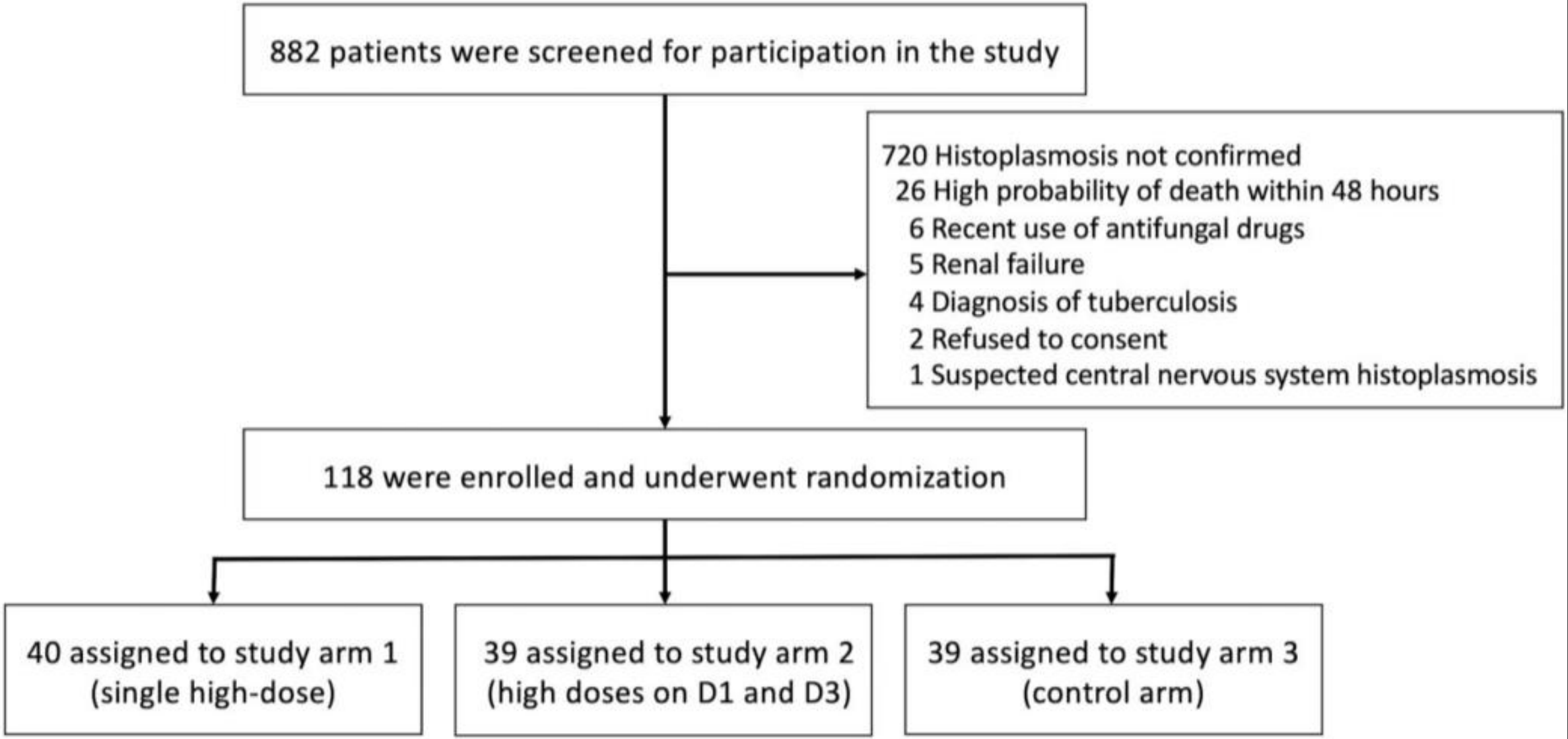
Control arm
3 mg/Kg qd 14 days

- 1:1:1 centralized randomization, unblinded
- Itraconazole capsules 400 mg q24h within 24 hours after induction and continued for 1 year
- ART initiation as soon as possible, at physician's discretion

Outcomes

Primary outcome. Clinical resolution on day 14, defined as resolution of fever and signs/symptoms attributable to histoplasmosis, except for manifestations that are expected to last for more than 14 days after treatment initiation: skin lesions, hepatosplenomegaly, jaundice, and pancytopenia.

Secondary outcomes. Overall survival (day 14 and 1 year), renal function abnormalities (KDIGO), anemia, and liver function abnormalities on day 14.


882 patients were screened for participation in the study
720 Histoplasmosis not confirmed
26 High probability of death within 48 hours
6 Recent use of antifungal drugs
5 Renal failure
4 Diagnosis of tuberculosis
2 Refused to consent
1 Suspected central nervous system histoplasmosis
118 were enrolled and underwent randomization
40 assigned to study arm 1 (single high-dose)
39 assigned to study arm 2 (high doses on D1 and D3)
39 assigned to study arm 3 (control arm)

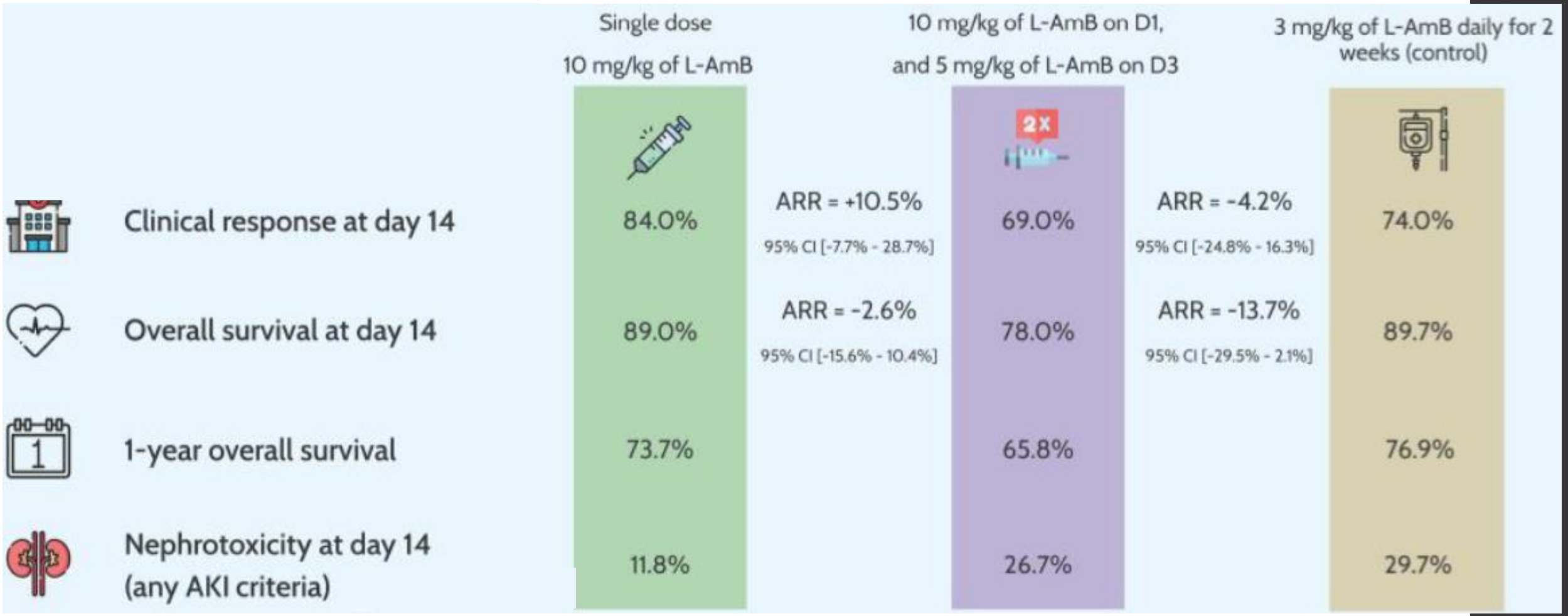
Results

Histoplasmosis was the AIDS-defining illness for 51% (60/118) patients in the study

Urine antigen was positive in 97% of patients; other diagnostic tools were less commonly used (< 40%)

	Arm 1	Arm 2	Arm 3
Age in years (median)	40	39	39
Male sex	88%	72%	87%
On antiretroviral therapy	32%	38%	26%
CD4 count cells/μL (median)	27	27	22
Viral load, $\log_{10}$ (median)	5.3	5.2	5.6
Histoplasma antigen, EIV (median)	47.6	30.7	31.0
Karnofsky score ≤70	52%	49%	51%
Fever	70%	58%	69%
Weight loss	80%	56%	74%
Pulmonary symptoms	75%	69%	56%
Oral lesions	42%	33%	31%
Skin lesions	42%	31%	41%
Hemoglobin (median)	8.80	9.10	9.35
Leukocytes (median)	2930	3030	2850
Neutrophils (median)	2025	2363	2285
Lymphocytes (median)	443	313	431
Platelets (median)	90 000	135 000	93 000
Serum creatinine (median)	0.80	0.78	0.77
Lactate dehydrogenase (median)	496	618	691
Ferritin (median)	5193	8250	8250
Aspartate aminotransferase (median)	43	102	88
Alanine aminotransferase (median)	43	58	59

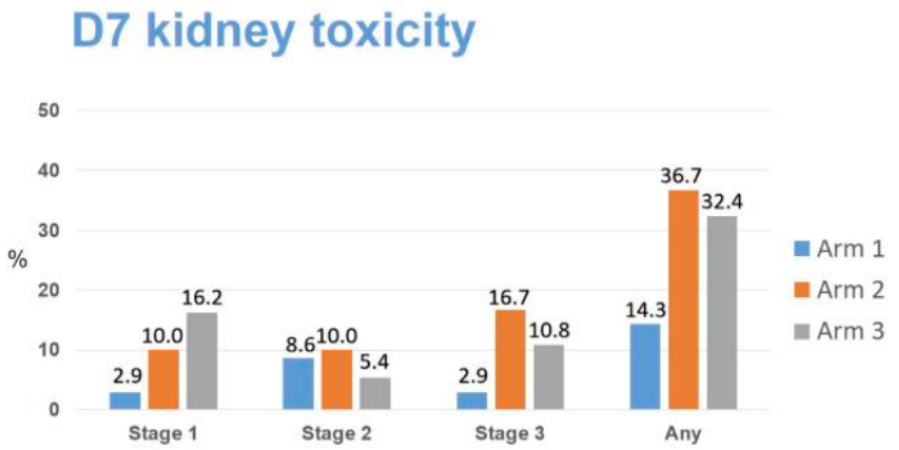
20% margin for non-inferiority, 1-side alfa: 0.05%

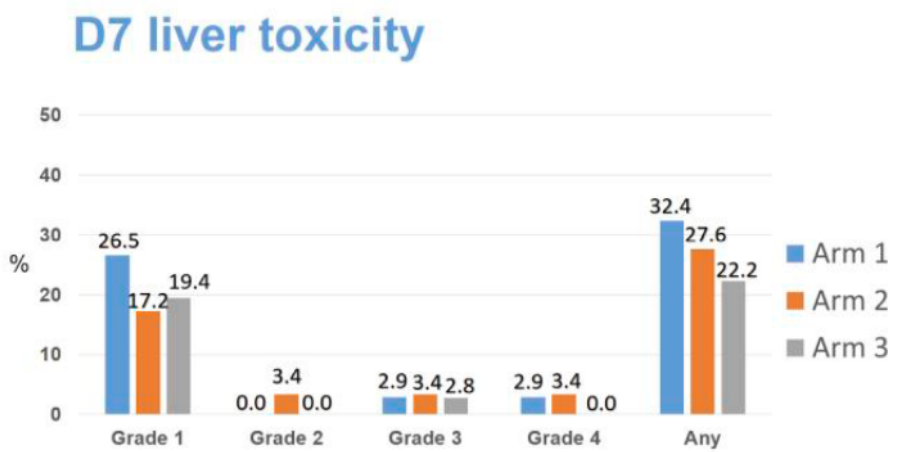


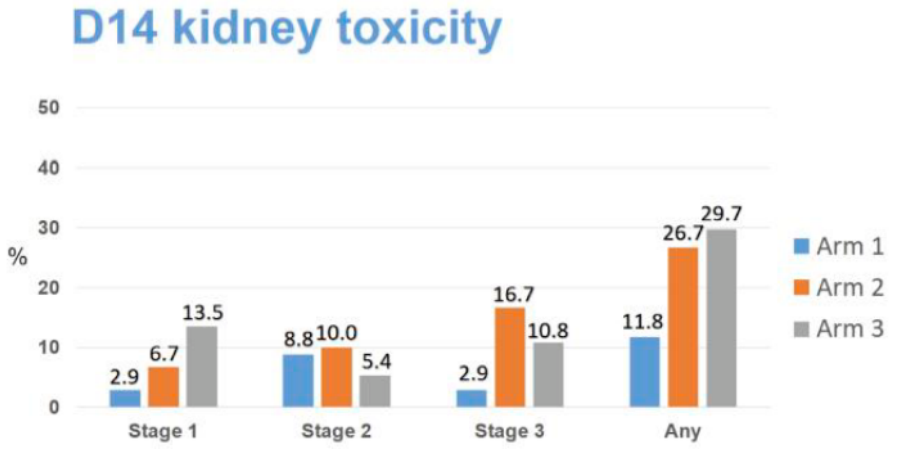
Clinical response and survival are similar to data obtained from the only clinical trial on the use of L-AmB in DH

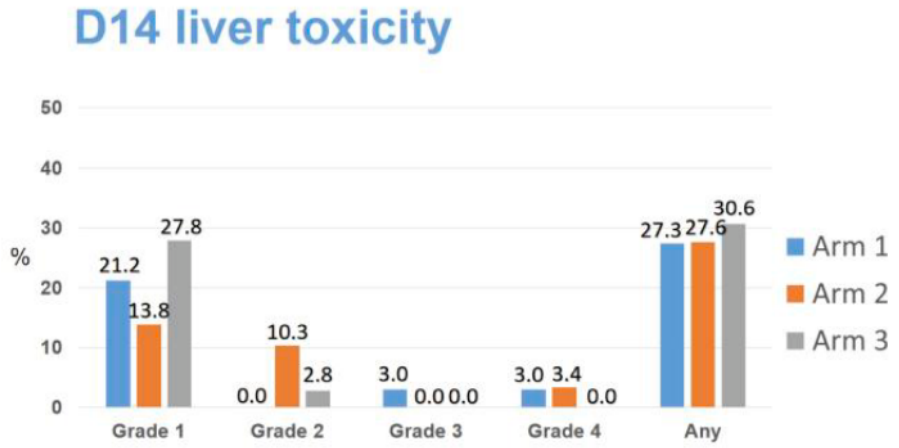
Ann Intern Med 2002; 137:105–9.

Safety









- Infusion-related toxicity: 19% in the high dose arm
- No safety concerns in terms of anemia, liver function, and electrolytes
- Acute kidney injury occured twice as often in the control arm

Clinical question. Can we use a single dose L-Amb strategy in patients with DH and HIV infection? **Probably we will**

Research question. Is a single high dose L-Amb strategy safe and effective in the treatment of DH in PLWH? **Yes, but data from a phase III trial are necessary**

Limitations: sample size, DH diagnosis details (probable vs. proven), urine antigen titer dynamics after treatment not reported, ART timing/IRIS data not reported

Grazie per l’attenzione