First-line therapy with combined antifungals for aspergillosis

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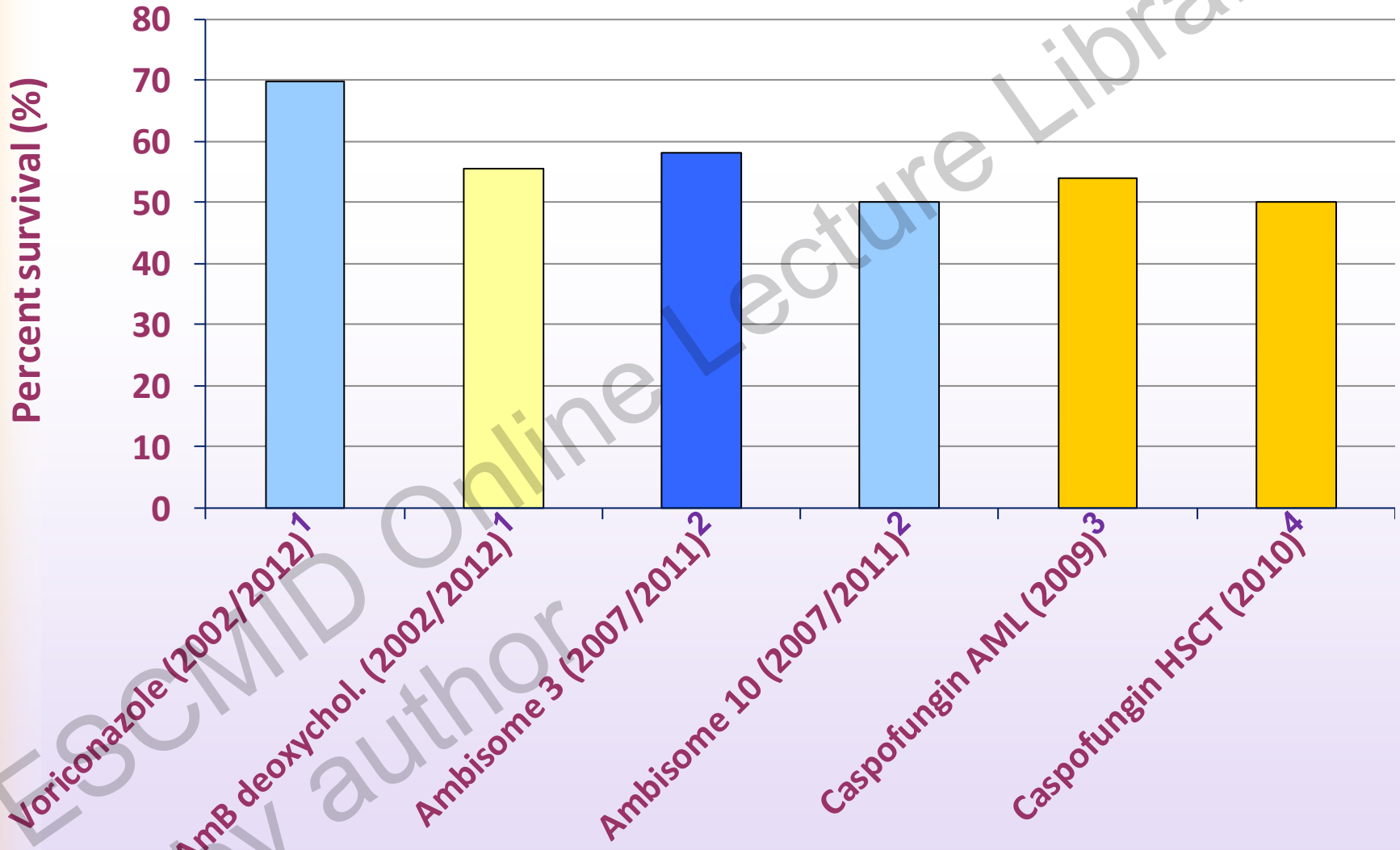
Primary monotherapy for probable / proven invasive aspergillosis according to EORTC 2008 criteria



([1]Herbrecht et al, NEJM 2002 & ICAAC, 2012; [2]Cornely et al, CID 2007 & Mycoses 2011; [3]Viscoli et al JAC, 2009; [4]Herbrecht et al, BMT 2010)

How to improve further the outcome?

- Early start of therapy
- Therapeutic drug monitoring to optimize monotherapy
- Combination therapy

What can we expect from combination therapy?

- **Combination therapy could confer**
  - **Antimicrobial synergy resulting from**
    - Inhibition of different stages of the same pathway
    - Increased intracellular penetration of an agent by action of another agent on the cell wall or membrane
    - Action on different molecular targets
  - **Complementary pharmacokinetics**
  - **Broader spectrum for empiric or pre-emptive therapy and even targeted therapy**
    - Might be critical in centers with high rate of resistance in Aspergillus till strain is isolated and tested for susceptibility
  - **Reduced acquired resistance**

What can we expect from combination therapy?

- Expected clinical results are
  - Increased response rate and survival
  - Accelerated response to therapy
- Combination of antifungal agents may also lead to
  - Antagonism
  - Increased toxicity
  - Major increase in antifungal drug acquisition costs
- Substantial amount of *in vitro* and experimental data support the assessment of antifungal combination in clinical trials

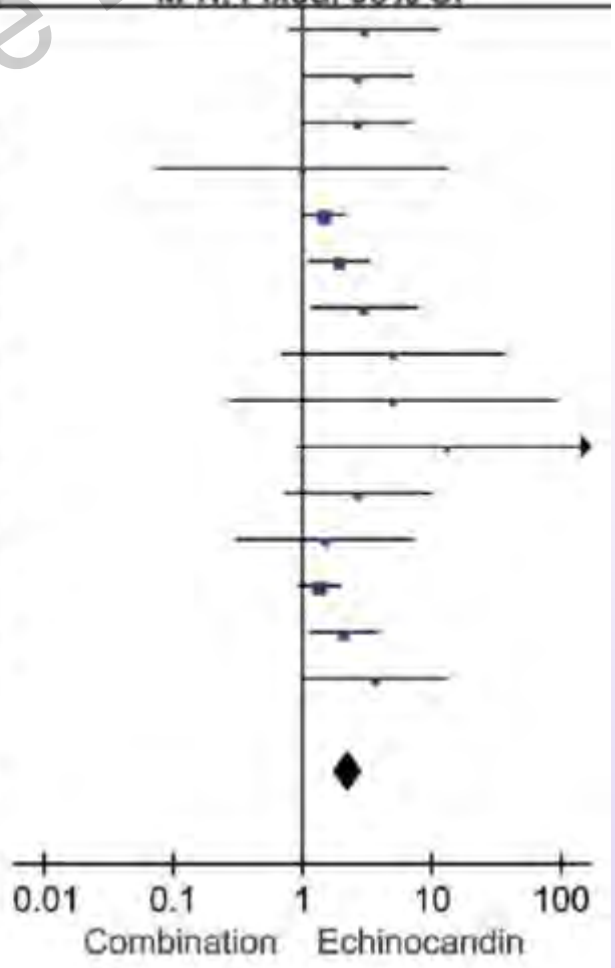
Systematic review of animal data: triazole, echinocandin or combination

Combination versus echinocandin monotherapy

Study or Subgroup	Combination Events	Combination Total	Echinocandin Events	Echinocandin Total	Risk ratio M-H, Fixed, 95% CI
Calvo 2012 (a)	6	10	2	10	3.00 [0.79, 11.44]
Calvo 2012 (b)	8	10	3	10	2.67 [0.98, 7.22]
Calvo 2012 (c)	8	10	3	10	2.67 [0.98, 7.22]
Clemons 2006	1	10	1	10	1.00 [0.07, 13.87]
Kirkpatrick 2002(a)	12	12	8	12	1.47 [0.98, 2.22]
Kirkpatrick 2002(b)	12	12	6	12	1.92 [1.10, 3.35]
Luque 2003	9	10	3	10	3.00 [1.14, 7.91]
MacCallum 2005(a)	5	12	1	12	5.00 [0.68, 36.66]
MacCallum 2005(b)	2	12	0	12	5.00 [0.27, 94.34]
Petraitis 2003	9	12	0	8	13.15 [0.87, 198.45]
Petraitis 2009(a)	6	10	2	9	2.70 [0.72, 10.14]
Petraitis 2009(b)	3	11	2	11	1.50 [0.31, 7.30]
Seyedmousavi 2013(a)	11	11	8	11	1.35 [0.92, 1.98]
Seyedmousavi 2013(b)	11	11	5	11	2.09 [1.12, 3.91]
van de Sande 2009	8	12	2	11	3.67 [0.98, 13.67]
Total (95% CI)		**165**		**159**	**2.26 [1.79, 2.87]**
Total events	111		46		

Heterogeneity: Chi² = 16.06, df = 14 (P = 0.31); I² = 13%

Test for overall effect: Z = 6.73 (P < 0.00001)



(Zhang et al., J Thorac Dis, 2014)

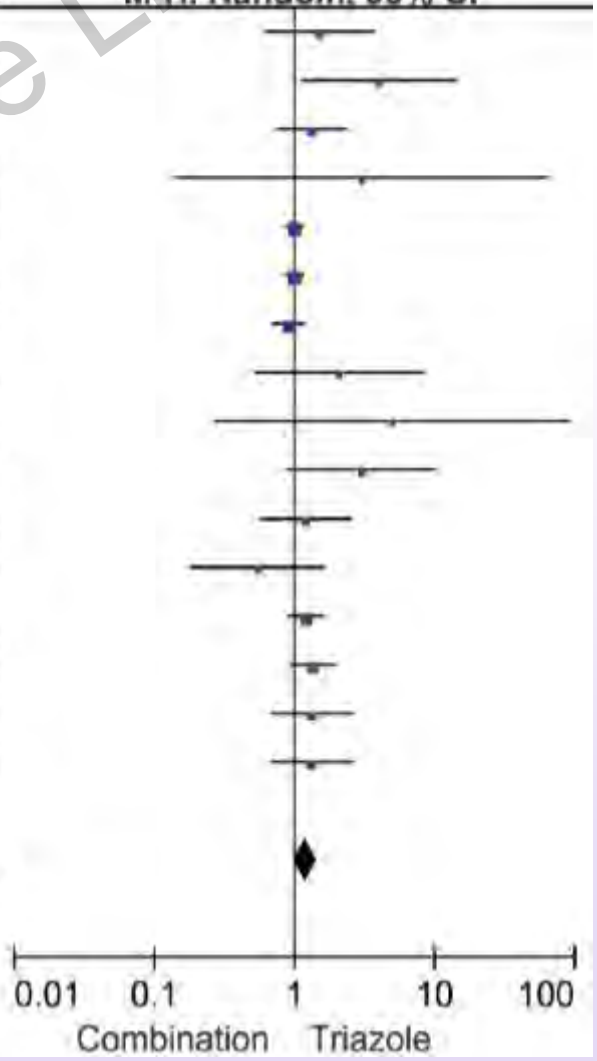
Systematic review of animal data: triazole, echinocandin or combination

Combination versus triazole monotherapy

Study or Subgroup	Combination Events	Combination Total	Triazole Events	Triazole Total	Risk ratio M-H, Random, 95% CI
Calvo 2012 (a)	6	10	4	10	1.50 [0.60, 3.74]
Calvo 2012 (b)	8	10	2	10	4.00 [1.11, 14.35]
Calvo 2012 (c)	8	10	6	10	1.33 [0.74, 2.41]
Clemons 2006	1	10	0	10	3.00 [0.14, 65.90]
Kirkpatrick 2002(a)	12	12	12	12	1.00 [0.86, 1.17]
Kirkpatrick 2002(b)	12	12	12	12	1.00 [0.86, 1.17]
Luque 2003	9	10	10	10	0.90 [0.69, 1.18]
MacCallum 2005(a)	5	12	2	10	2.08 [0.51, 8.52]
MacCallum 2005(b)	2	12	0	12	5.00 [0.27, 94.34]
Petraitis 2003	9	12	2	8	3.00 [0.86, 10.41]
Petraitis 2009(a)	6	10	6	12	1.20 [0.56, 2.56]
Petraitis 2009(b)	3	11	6	12	0.55 [0.18, 1.67]
Seyedmousavi 2013(a)	11	11	9	11	1.21 [0.88, 1.66]
Seyedmousavi 2013(b)	11	11	8	11	1.35 [0.92, 1.98]
Van de Sande 2009(a)	8	12	6	12	1.33 [0.67, 2.67]
Van de Sande 2009(b)	8	12	6	12	1.33 [0.67, 2.67]
Total (95% CI)		**177**		**174**	**1.19 [0.98, 1.44]**
Total events	119		91		

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 35.70$, df = 15 (P = 0.002

Test for overall effect: Z = 1.75 (P = 0.08)



(Zhang et al., J Thorac Dis, 2014)

Systematic review of animal data: triazole, echinocandin or combination

- The survival of animals treated with combination therapy was
  - significantly prolonged compared with echinocandin alone
    RR =2.26, (95% CI, 1.79-2.87; P<0.00001)
  - but not compared with triazole alone
    RR =1.19, (95% CI, 0.98-1.44; P=0.08)

(Zhang et al., J Thorac Dis, 2014)

My conclusion would be: if you treat (animals) with an echinocandin it make sense to add an azole but if you treat them with an azole it is useless to add an echinocandin

Disappointing first clinical trial (1997 – 1999)
Ampho B + terbinafine versus Ampho B + placebo

- **Terbinafine is effective *in vitro* on Aspergillus**
- **Controversial *in vitro* results with combination**
  - **Additive or synergistic effect with ampho. B *(Ryders et al., Med Mycol. 2001)***
  - **Antagonism with ampho B *(Mosquera et al., J Antimicrob Chemother, 2002)***
- **A few favourable case reports**
- **Results of comparative trial**
  - **Study stopped after ≈ 55 patients**
  - **Results never published**
    - More deaths is combination group

Disappointing second clinical trial (2002) Anidulafungin + Liposomal amphotericin B

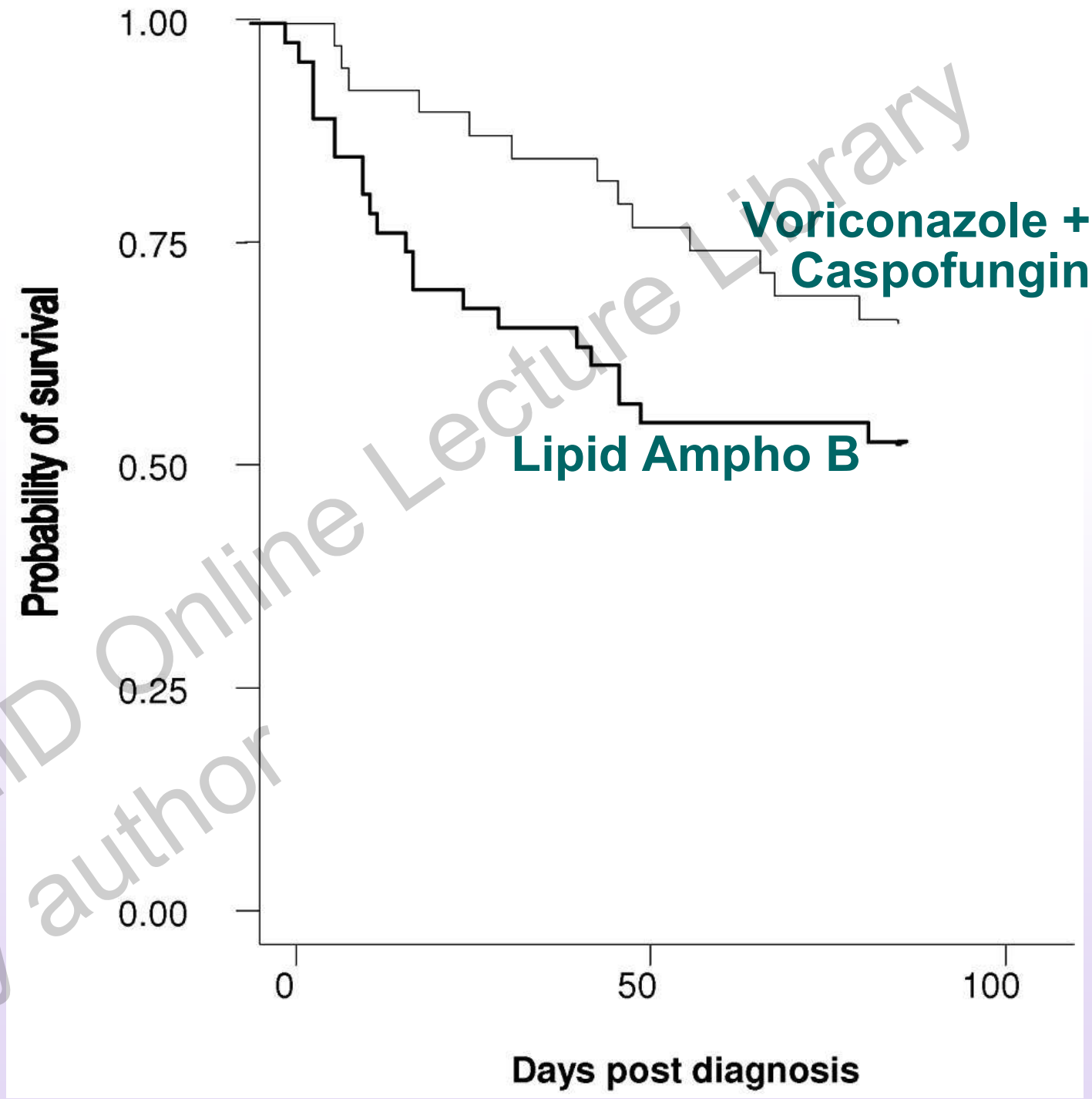
- Non-comparative; Anidulafungin 200 mg on day 1 then 100 mg/day + Liposomal amphotericin B 3 to 5 mg/kg/d
- 30 patients (mostly haematological and HSCT patients)
- Safety data and PK presented
  - "The patterns of AE's and laboratories abnormalities were not unexpected for this ill population" *(Herbrecht et al., Tandem Meeting of the American Society for Blood and Marrow Transplantation and of the Center for International Blood and Marrow Transplant Research, 2004, Orlando)*
  - "Co-administered liposomal amphotericin B does not affect the pharmacokinetics of anidulafungin" *(Dowell et al., Focus on Fungal Infections 14, 2004, New Orleans)*
  - 17 (57%) deaths within 3 months
- Efficacy results never presented

Two promising clinical trials

Antifungal agents	N	Success rate	12-week survival
Prospective randomized:			
Caspofungin+L-AmB (3mg/kg)	15	67%	100%
Liposomal AmB (10mg/kg)	15	27%	80%
Historical control group:			
Lipid amphotericin B	47	-	51%*
Voriconazole + caspofungin	40	-	67.5%*

* Difference is significant in patients with renal failure and in patient with *A. fumigatus* infection

Caillot, Cancer, 2007; Singh et al, Transplantation 2006

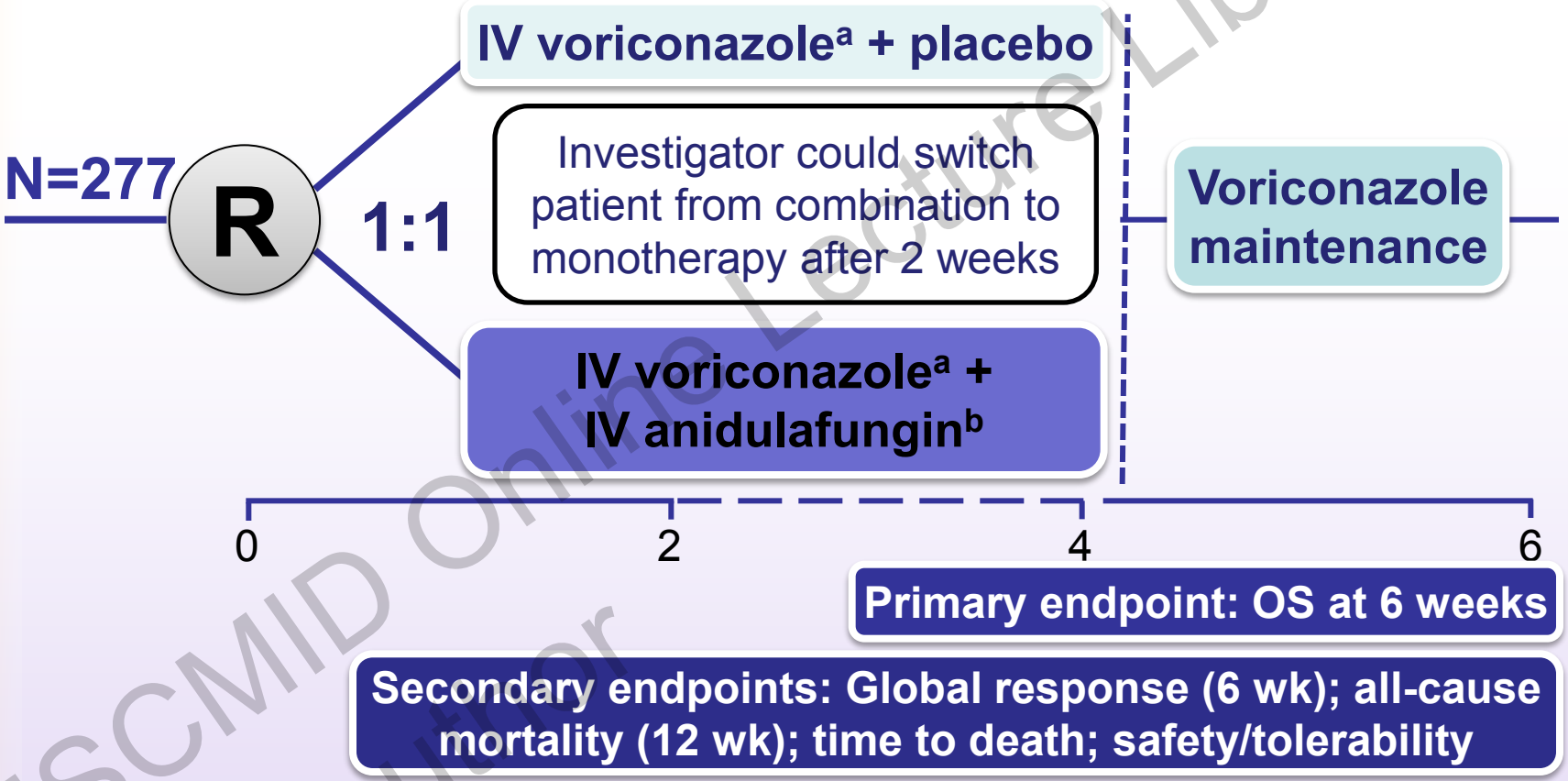


Singh et al, Transplantation 2006

Combination for primary therapy of IA

AlloHSCT /hematological malignancies with proven or probable IA

(Marr et al, ECCMID, London, 2012)



[a] 6 mg/kg q12h Day 1, then 4 mg/kg q12h (a switch to oral voriconazole [300 mg q12h] was allowed after ≥7 days of IV therapy) [b] 200 mg on Day 1, then 100 mg q24h

(Marr et al, ECCMID, London, 2012)

Baseline demographics and treatment history

Characteristic	Combination	Voriconazole monotherapy
Modified ITT, n	135	142
Mean age, years	52.2	51.6
Male, %	55	58
Host factor, n (%)		
Allogenic HSCT	44 (33)	42 (30)
Non-allogenic/no HSCT	91 (67)	100 (70)
Prolonged steroids, n (%)	12 (9)	10 (7)
T-cell immunosuppressant, n (%)	22 (16)	17 (12)
Neutropenic, n (%)	77 (57)	86 (61)

(Marr et al, ECCMID, London, 2012)

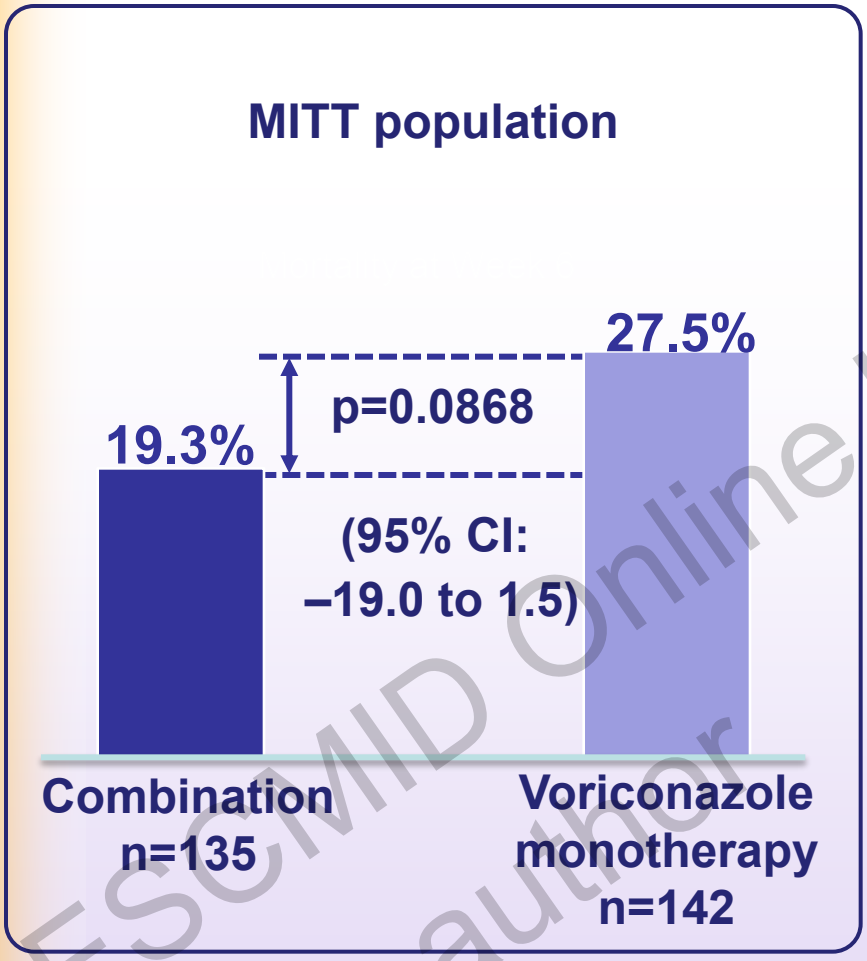
IA diagnoses at baseline

Probable IA, n (%)	Combination	Voriconazole monotherapy
Histopathology without culture	4 (3)	0
Culture or cytology of BAL	20 (15)	30 (21)
Positive GM only	**108 (80)**	**110 (77)**
Positive BAL GM and serum GM	7 (5)	12 (8)
Positive serum GM only	61 (45)	64 (45)
Positive BAL GM only	40 (30)	34 (24)
Proven IA, n (%)		
Histopathology with culture	1 (1)	0
Culture of tissue	2 (1)	0
Histopathology without culture	0	2 (1)

GM: galactomannan

(Marr et al, ECCMID, London, 2012)

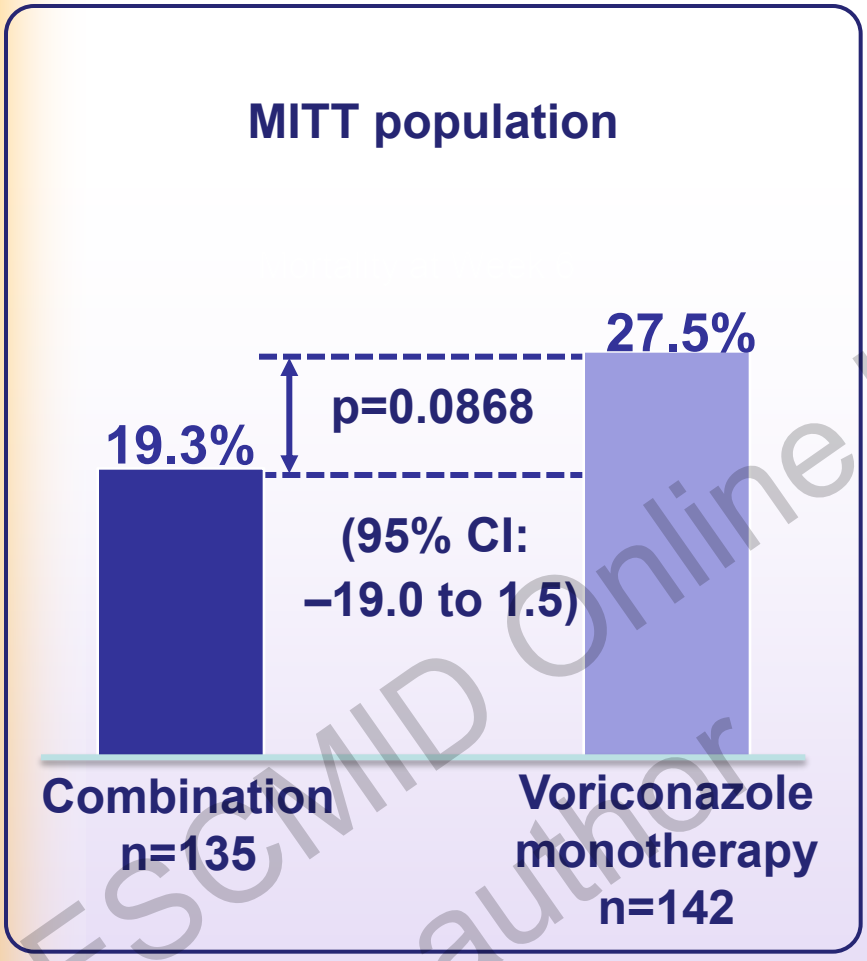
Mortality at Week 6

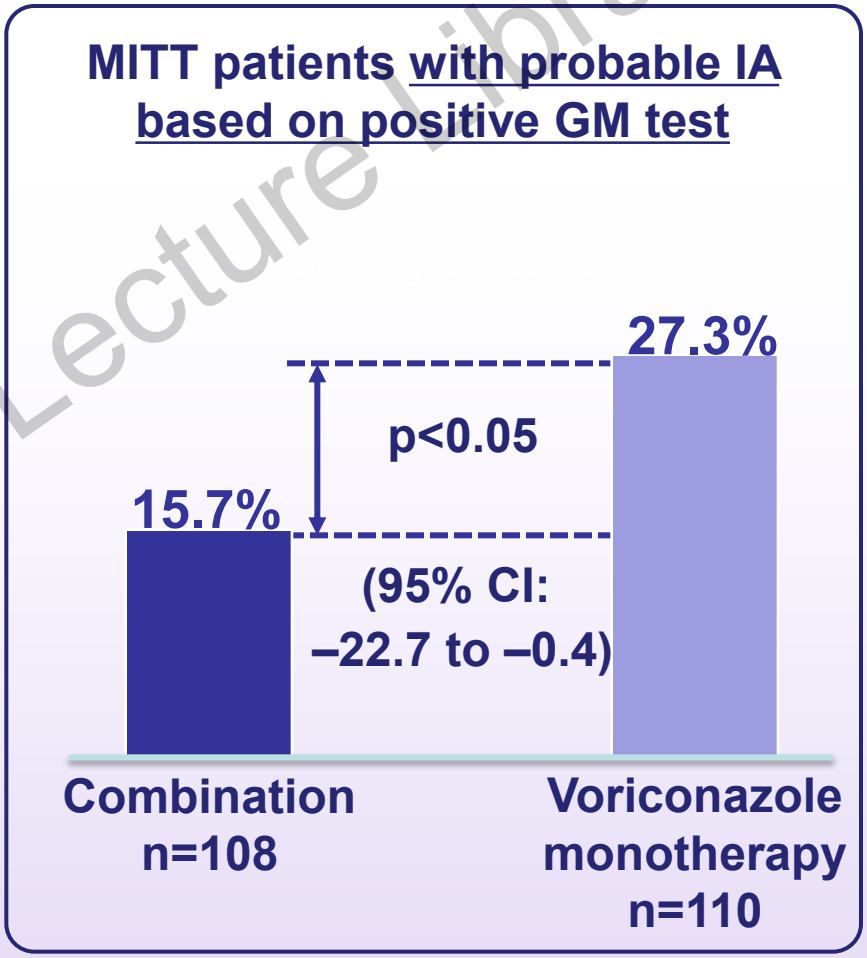


p-value for mortality estimates adjusted for randomisation strata

(Marr et al, ECCMID, London, 2012)

Mortality at Week 6





p-value for mortality estimates adjusted for randomisation strata

(Marr et al, ECCMID, London, 2012)

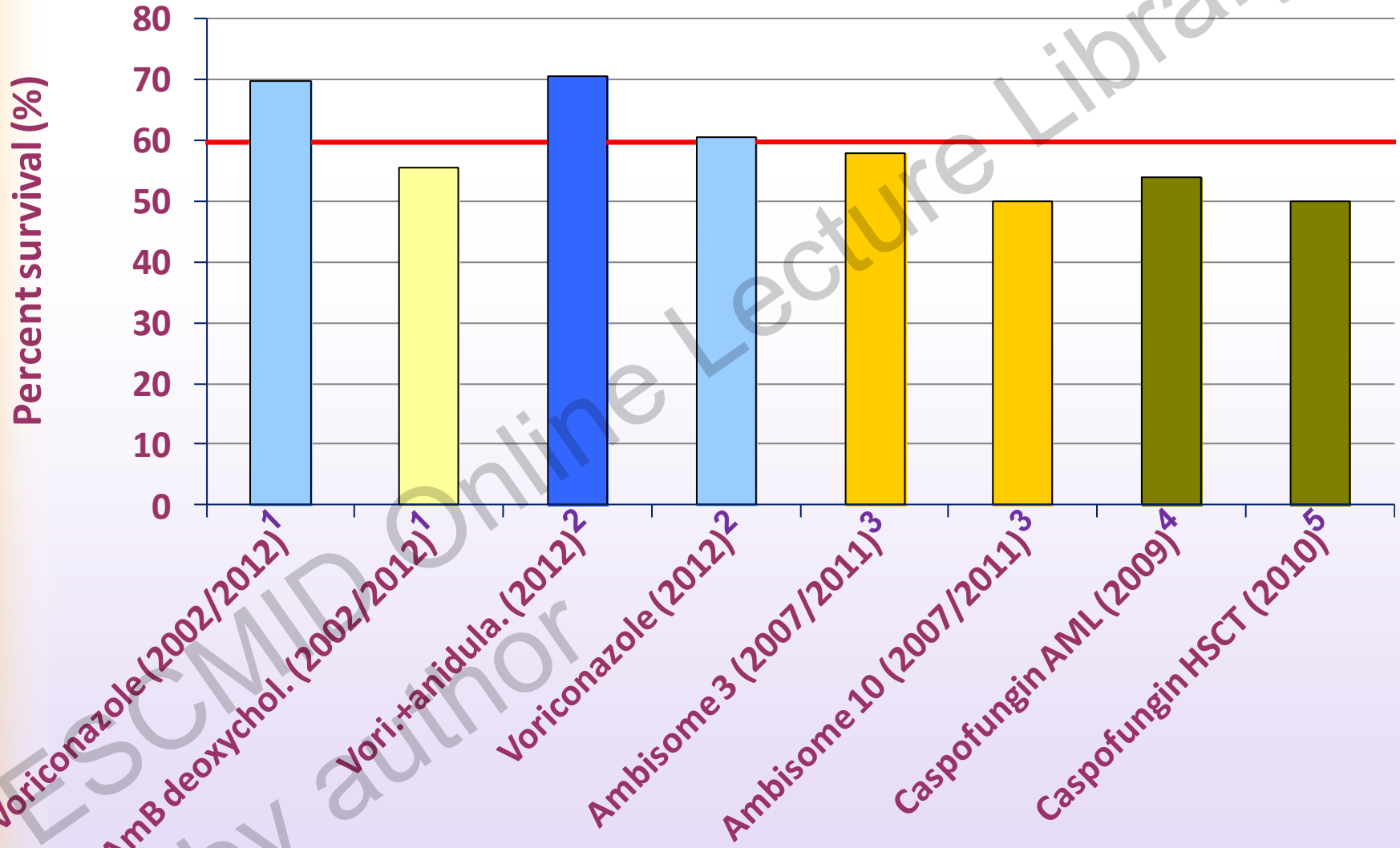
Conclusions for the combination study

- Voriconazole plus anidulafungin resulted in a trend towards improved overall 6-week survival compared with voriconazole monotherapy in patients with proven or probable IA diagnosed after allo-HSCT or treatment of haematological malignancies

- In a subset of patients with antigen-diagnosed disease, overall 6-week survival was significantly improved with combination versus monotherapy

(Marr et al, ECCMID, London, 2012)

Twelve week survival in probable / proven invasive aspergillosis according to EORTC 2008 criteria



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Invasive aspergillosis: First-line

Agent	Grade	Comments
Caspofungin	C II	
Itraconazole	C III	
ABCD	C I	
Combination voriconazole + anidulafungin	C I [1]	
Other combinations	C III	
AGAINST THE USE		
Amphotericin B deoxycholate	A I	

Similar grading for combination in the ESCMID guidelines

(Ullmann et al, ECCMID, Barcelona, 2014)

A: strong evidence
B: moderate evidence
C: poor evidence
to support a recommendation

[1] *provisional*

In the absence of data in 1st line, posaconazole has not been graded

IDSA Guidelines 2008
Primary Therapy of Invasive Aspergillosis

Products		Comments
Voriconazole	Preferred therapy	Primary combination therapy is not routinely recommended based on lack of clinical data; addition of another agent for salvage therapy may be considered in individual patients
Liposomal amphotericin B	Alternative	

(Walsh et al., Clin Infect Dis, 2008)

Monotherapy or combination ?

- No convincing demonstration that combination is doing much better than monotherapy
- However, no suggestion of increased toxicity
- Major increase in costs
- Optimization of monotherapy is still another approach to explore
- New drugs
  - Isavuconazole ?
    - *Maertens et al, ECCMID 2014, abstract O230a; oral presentation: May 13, 13:30 Hall F*