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Comparative effectiveness of azoles, amphotericin B, and echinocandins in the treatment of invasive aspergillosis: A systematic review and meta-analysis

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SUPPLEMENTARY MATERIAL

Table 1. Search strategy.

Component	Details of the search strategy
Review question	Which antifungal treatment is more effective in treating patients with invasive aspergillosis?
Population	Patients with invasive aspergillosis
Intervention	Any new triazoles (e.g. voriconazole, posaconazole, isavuconazole), echinocandins either as monotherapy or in combination with azole or amphotericin b to treat patients with invasive aspergillosis
Comparison	Monotherapy of voriconazole or amphotericin b
Outcomes	Efficacy, including mortality rate survival rate or response rate
Study design	RCTs and cohort
Database	PubMed, Scopus, ProQuest

Table 2. Search algorithms from databases.

Database	Query
Pubmed	(("invasive aspergillosis"[Title/Abstract] OR "invasive pulmonary aspergillosis"[Title/Abstract]) AND ("posaconazole"[Title/Abstract] OR "isavuconazole"[Title/Abstract] OR "echinocandin"[Title/Abstract] OR "caspofungin"[Title/Abstract] OR "micafungin"[Title/Abstract] OR "anidulafungin"[Title/Abstract]) AND ("amphotericin b"[Title/Abstract] OR "voriconazole"[Title/Abstract] AND ("efficacy"[Title/Abstract] OR "mortality rate"[Title/Abstract] OR "survival rate"[Title/Abstract] OR "success"[Title/Abstract] OR "effectiveness"[Title/Abstract] OR "treatment efficacy"[Title/Abstract] OR "response"[Title/Abstract] OR "end of treatment"[Title/Abstract]))
Scopus	TITLE-ABS-KEY (invasive AND aspergillosis OR invasive AND pulmonary AND aspergillosis) AND TITLE-ABS-KEY (posaconazole OR isavuconazole OR echinocandin OR caspofungin OR micafungin OR anidulafungin) AND TITLE-ABS-KEY (amphotericin AND b OR voriconazole) AND TITLE-ABS-KEY (efficacy OR mortality AND rate OR survival AND rate OR success OR effectiveness OR treatment AND efficacy OR end AND of AND treatment OR response)
ProQuest	abstract(invasive aspergillosis OR invasive pulmonary aspergillosis) AND abstract(posaconazole OR isavuconazole OR echinocandin OR caspofungin OR micafungin OR anidulafungin) AND abstract(amphotericin b OR voriconazole) AND abstract(efficacy OR mortality rate OR survival rate OR success OR effectiveness OR treatment efficacy OR end of treatment OR response)

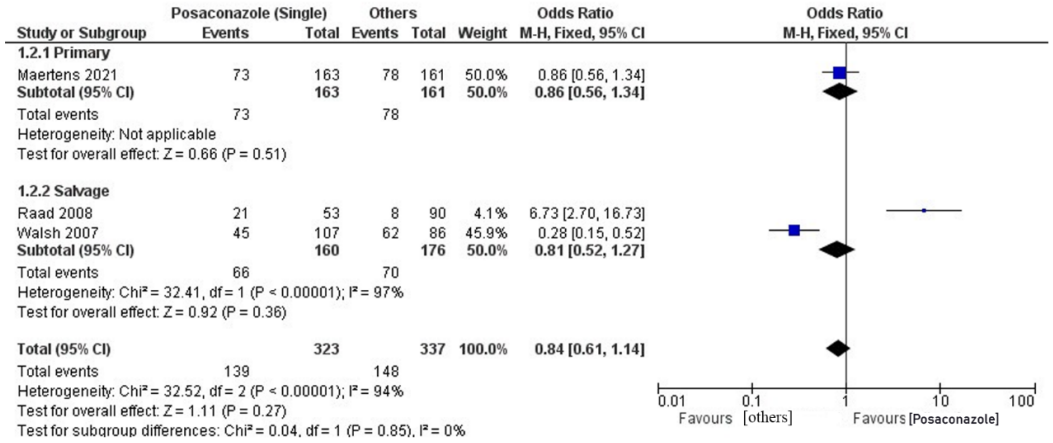
Table 3. Characteristics of the 10 included studies with details of each drug comparison.

Study	IA status	Female/ male (n)	Underlying condition	Intervention	Control	Outcome	Follow up duration	Adjusted effect estimates
Herbrecht et al., 2002	Definite, probable IA (EORTC/MSG 2002)	90/ 187	Allogeneic HCT, autologous HCT, acute leukemia, other hematologic cancer, solid-organ transplantation, AIDS, solid-organ transplantation	Voriconazole 6 mg/kg BID IV (1 day) --> 4 mg/kg BID IV (1 week) --> switch to 200 mg bid PO	AmB deoxycholate 1.0-1.5 mg/kg/day IV	Response, survival	12 weeks	HR: 0.59 (0.40-0.88)
Caillot et al., 2007	Definite, probable IA (EORTC/MSG 2002)	9/ 21	Acute myeloid leukemia, chronic lymphocytic leukemia, myeloproliferative disorders, acute lymphoid leukemia	LAmB 3 mg/kg QD IV (at least 14 weeks) + caspofungin 70 mg QD IV (1day) --> 50mg QD IV	LAmB 10 mg/kg QD IV	Response, survival	12 weeks	NA
Cornely et al., 2015	Proven, probable IA (EORTC/MSG 2008)	6/ 11	Acute myelogenous leukemia, myelodysplastic syndrome, HSCT	Micafungin 300 mg QD IV	AmB (liposomal/ colloidal dispersion/ lipid complex) 5 mg/kg QD IV 3-12 wk or voriconazole 6 mg/kg BID IV (1 day) --> 4 mg/kg BID IV or caspofungin 70 mg QD IV (1 day) --> 50 mg QD IV for 3-12 weeks	Response, mortality	12 weeks	NA
Marr et al., 2015	Proven, probable, possible IA (EORTC/ MSG 2008)	121/ 156	Allogeneic HCT, autologous HCT, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, aplastic anemia, chronic lymphocytic leukemia, chronic myelogenous	Voriconazole 6 mg/kg BID IV (1 day) --> 4 mg/kg BID IV (1 week) --> 300 mg BID PO (6 weeks) + anidulafungin 200 mg QD IV (1 day) --> 100mg QD IV/	Voriconazole 6 mg/kg BID IV (1 day) --> 4 mg/kg BID IV (1 week) --> 300 mg BID PO (6 weeks)	Response, mortality	6 & 12 weeks	Adjusted treatment difference (mortality): −8.3% (−19.0 to 1.5) −10.1% (−21.4 to 1.1)

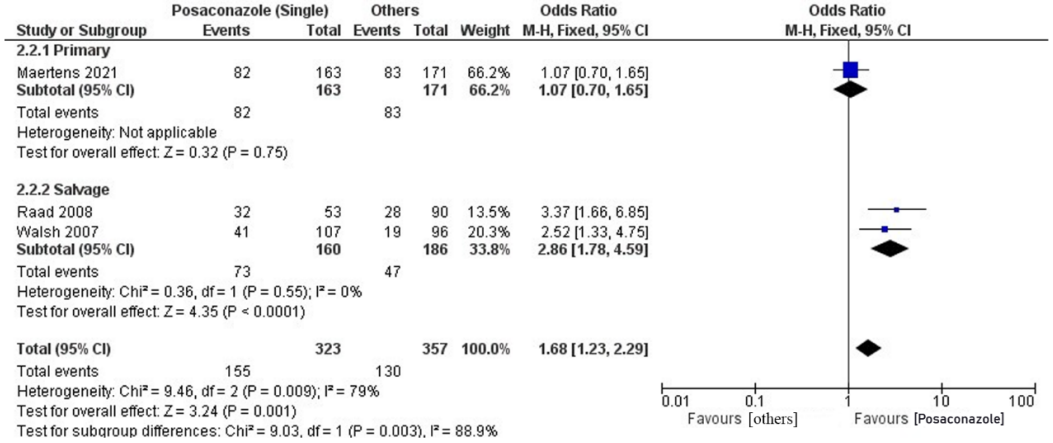
			leukemia, lymphoma, multiple myeloma, myelodysplastic syndrome, myeloproliferative syndrome, neutropenia	placebo (2- 4 weeks)				Adjusted treatment difference (response): 1·6% (-9·3 to 12·6) −10.4% (−21.6 to 1.2)
Maertens et al., 2016	Proven, probable, possible IA (EORTC/ MSG 2008)	208/ 308	Acute myeloid leukemia, acute lymphoblastic leukemia, lymphoma, myelodysplastic syndrome, chronic lymphocytic leukemia, aplastic anemia, chronic myeloid leukemia, multiple myeloma, allogeneic HSCT, chronic obstructive pulmonary disease, Hodgkins's disease, diabetes mellitus	Isavuconazole 200 mg TID IV (2 days) --> 200 mg QD IV/ PO --> placebo	Voriconazole 6 mg/kg BID IV (1 day) --> 4 mg/kg BID IV (1 day) --> 4 mg/kg BID IV/ 200 mg BID PO	Response, mortality	Mortality: 42 & 84 days	Adjusted treatment difference (mortality): –1·0% -7·8 to 5·7) -1·4% (-9·2 to 6·3) Adjusted treatment difference (response): 1·6% (-9·3 to 12·6)
Maertens et al., 2021	Proven, probable, possible IA (EORTC/ MSG 2008)	231/ 344	Prolonged neutropenia, allogeneic HSCT, treatment with other recognized T-cell immunosuppressant drugs, prolonged use of corticosteroid, inherited severe immunodeficiency	Posaconazole 300 mg BID IV/ PO (1 day) --> 300 mg QD IV/ PO	Voriconazole 6 mg/kg BID IV or 300 mg BID PO (1 day) --> 4 mg/kg BID IV or 200 mg BID PO	Response, mortality	Mortality: 42 & 84 days Response: 6 & 12 weeks	Adjusted treatment difference (mortality): −5·3% (−11·6 to 1·0) −2·5% (−9·9 to 4·9) Adjusted treatment difference (response): 0·6% (−11·2 to 10·1) −3·4% (−13·9 to 7·1)

Raad et al., 2008	Proven, probable IA (EORTC/MSG 2002)	55/ 88	Acute leukemia, chronic leukemia, lymphoma, myeloma, allogeneic HSCT, autologous HSCT, graft-versus-host disease, neutropenia, steroid use, ICU, mechanical ventilation	Posaconazole 200 mg QID PO/ enteral route (inpatient) --> 400 mg BID PO (outpatient) up to 6 months	HD-LPD AmB ≥7.5 mg/kg QD IV or ≥ HD-LPD AmB 7.5 mg/kg QD IV + caspofungin 70 mg QD IV (1 day) --> 50–100 mg QD IV	Response, mortality	12 weeks	Posaconazole vs HD-LPD/AmB OR: 9,5 (2.8–32.5) Posaconazole vs HD-LPD/AmB +caspofungin OR: 4 (1.1–14.5)
Singh et al., 2006	Proven, probable IA (EORTC/MSG 2002)	36/ 51	Organ transplant recipients	Voriconazole 6 mg/kg BID IV (1 day) --> 4 mg/kg BID IV + caspofungin 70 mg QD IV (1 day) --> 50 mg QD IV	LAmB 5-7.4 mg/kg QD IV	Response, survival	90 days	HR: 0.58 (0.30 –1.1)
Walsh et al., 2007	Proven, probable IA (EORTC/MSG 2002)	NA	Hematological malignancy, nonhematological malignancy, autologous HSCT, allogeneic HSCT, solid organ transplantation, acquired immunodeficiency, diabetes mellitus, HIV/ AIDS, congenital immunodeficiency	Posaconazole 200 mg QID PO/ enteral route (inpatient) --> 400 mg BID PO (outpatient)	AmB or itraconazole or AmB + itraconazole	Response, survival	Survival: 30 days Response: 372 days	OR: 4.06 (1.50–11.04)
Marr et al., 2004	Proven, probable IA EORTC/MSG 2002	29/ 18	Allogeneic HSCT, autologous HSCT	Voriconazole 6 mg/kg BID IV (1 day) -->4 mg/kg BID IV + caspofungin 70mg QD IV (1 day) --> 50 mg QD IV	Voriconazole 6 mg/kg BID IV (1 day) --> 4 mg/kg BID IV	Survival	3 months	HR: 0.28 (0.28–0.92)

A. Odds Ratio of Favorable Overall Response of Posaconazole vs Others

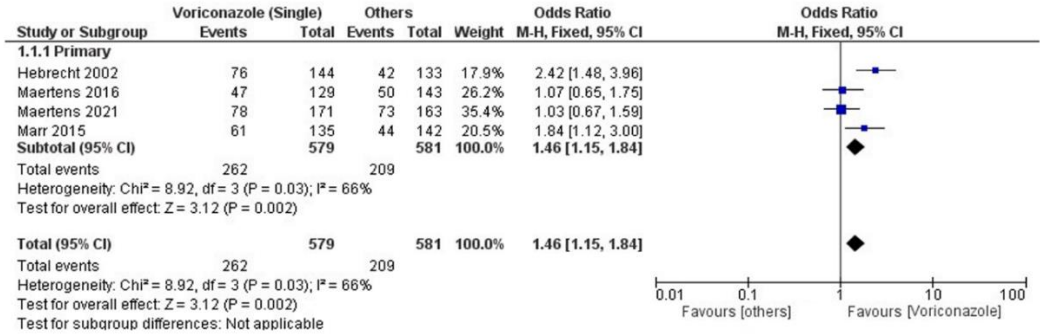


B. Odds Ratio of Survival of Posaconazole vs Others

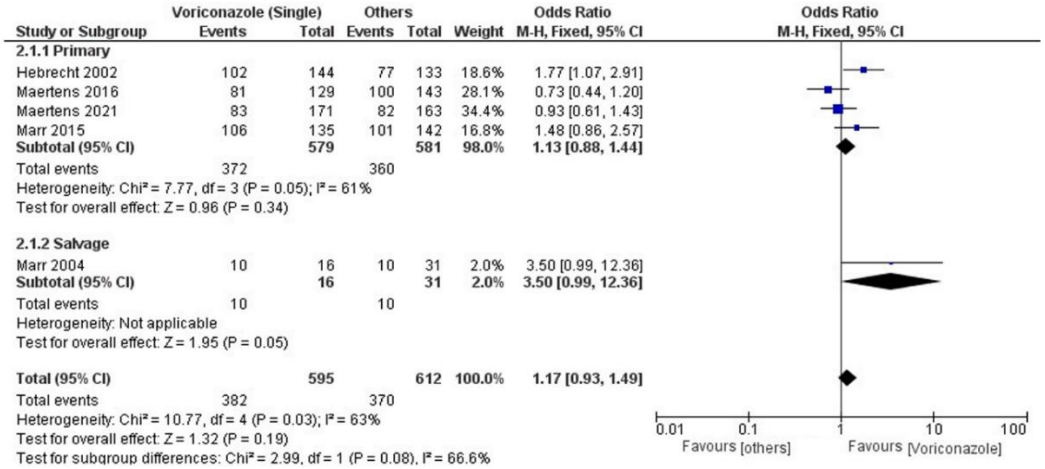


Supplementary Figure 1. Extended Forest plot analysis of posaconazole favorable response and survival benefits across different studies compared to other drugs. The studies involved preferred posaconazole as a salvage treatment compared to control variables.

A. Odds Ratio of Favourable Overall Response of Voriconazole vs Others

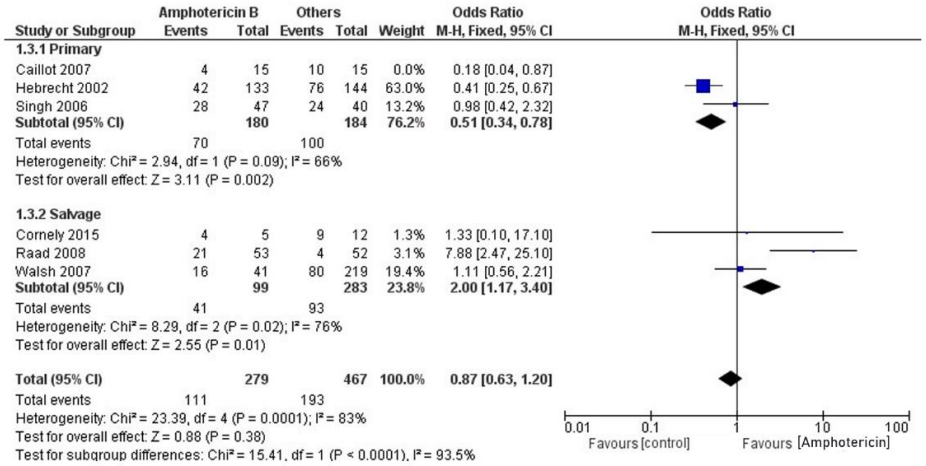


B. Odds Ratio of Survival of Voriconazole vs Others

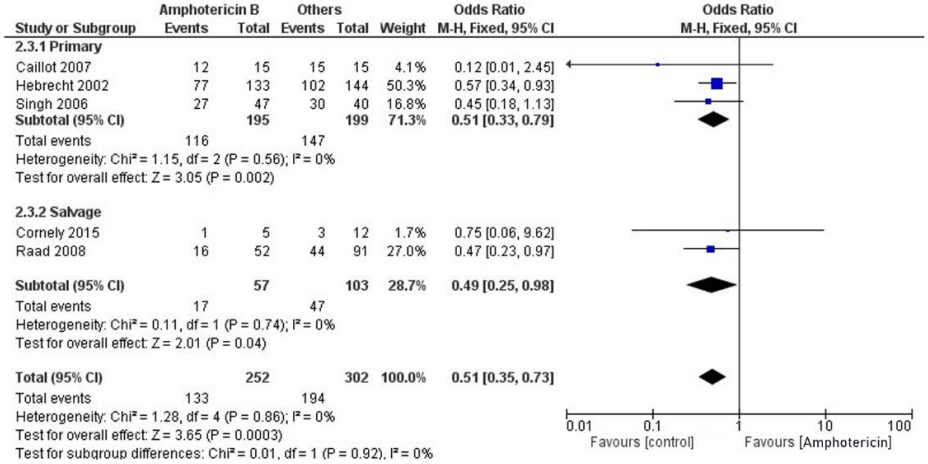


Supplementary Figure 2. Odds Ratio breakdown of voriconazole's effects on favorable response rates and survival outcomes compared to other drugs in various clinical settings. Voriconazole still excels as a primary or salvage treatment for invasive aspergillosis.

A. Odds Ratio of Overall Favorable Response of Amphotericin B vs Others



B. Odds Ratio of Survival of Amphotericin B vs Others



Supplementary Figure 3. Odds Ratio of amphotericin B's impact on response and survival. Note the low heterogeneity of the studies in the survival plot. It supports the low efficacy of amphotericin B for response and survival compared to other drugs.