Itraconazole Prevents Invasive Fungal Infections in Neutropenic Patients Treated for Hematologic Malignancies: Evidence From a Meta-Analysis of 3,597 Patients

By Axel Glasmacher, Archibald Prentice, Marcus Gorschlüter, Steffen Engelhart, Corinna Hahn, Benjamin Djulbegovic, and Ingo G.H. Schmidt-Wolf

Purpose: **Efficacy of antifungal prophylaxis has not yet been convincingly proven in numerous trials of various antifungals. New evidence and the anti-*Aspergillus* efficacy of itraconazole prompted a new look at the data for the prevention of invasive fungal infections.**

Patients and Methods: **Randomized, controlled studies with itraconazole for antifungal prophylaxis in neutropenic patients with hematologic malignancies were identified from electronic databases and hand searching.**

Results: **Thirteen randomized trials included 3,597 patients who were assessable for invasive fungal infections. Itraconazole reduced the incidence of invasive fungal infection (mean relative risk reduction, 40% ± 13%; *P* = .002), the incidence of invasive yeast infections (mean, 53% ± 19%; *P* = .004) and the mortality from invasive fungal infections (mean, 35% ± 17%; *P* = .04) significantly. The incidence of invasive *Aspergillus* infections was only reduced in trials using the itraconazole cyclodextrine solution (mean, 48% ± 21%; *P* = .02) and not itraconazole capsules (mean, 75% ± 73% increase; *P* = .3). The overall mortality was not changed. Adverse effects were rare, hypokalemia was noted in three studies, and a higher rate of drug discontinuation was found in trials that compared itraconazole cyclodextrine solution to a control without cyclodextrine. The effect of prophylaxis was clearly associated with a higher bioavailable dose of itraconazole.**

Conclusion: **Antifungal prophylaxis with itraconazole effectively prevents proven invasive fungal infections and—shown for the first time for antifungal prophylaxis—reduces mortality from these infections and the rate of invasive *Aspergillus* infections in neutropenic patients with hematologic malignancies. Adequate doses of the oral cyclodextrine solution (at least 400 mg/d) or IV formulations (200 mg/d) of itraconazole are necessary for these effects.**

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INVASIVE FUNGAL infection is a leading cause of mortality and morbidity in neutropenic patients treated for hematologic malignancies. The risk of these infections depends, among other factors, on the underlying disease, and the treatment given and varies from 2% to 40%.[1] In Europe and North America the predominant causative fungi are *Aspergillus* and *Candida* species. The case fatality rate from invasive aspergillosis is 50% in patients with neutropenia alone and 86% in those who have had a stem-cell transplant.[2] Nonalbicans invasive candidal infections are now responsible for almost half of all nosocomial invasive candidal infections, with a case fatality rate of between 20% and 40%, depending on the species,[3] and in one transplant center, these species are responsible for more than 90% of all *Candida* infections.[4] Effective prophylaxis against these infections might reduce morbidity and mortality in such patients treated with curative intent.

Previous randomized trials and meta-analyses have shown reduction of the risk of invasive *Candida* infections using fluconazole but could not demonstrate successful prevention of invasive *Aspergillus* infections.[5,6] Most randomized controlled trials of antifungal prophylaxis have been underpowered to detect a significant difference in the incidence of proven invasive fungal infections and have not shown conclusive results. A focused meta-analysis of randomized controlled trials may overcome this difficulty.[7] Because itraconazole is the only azole tested in this setting so far that is equally active against most yeast and *Aspergillus* species, this meta-analysis is confined to itraconazole.

PATIENTS AND METHODS

Search Strategy

The Cochrane Central Register of Controlled Trials (http://www.update-software.com) and MEDLINE (PubMed version) were searched in February 2003 and updated in July 2003. Reference lists of all identified studies and related reviews were screened. The volume of abstracts of the annual meetings of the American Society of Hematology, the Interscience Conference on Antimicrobial Agents and Chemotherapy, the European Hematology Association, European Group for Blood and Marrow Transplantion, the German and Austrian Society of Hematology and Oncology, and the British Society for Hematology were screened from 1994 to 2003. The pharmaceu-

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tical manufacturer of itraconazole was contacted, and its representatives provided data on an unpublished trial in July 2003 (ITR-GER-23; Janssen-Cilag/Ortho-Biotech Ltd, Neuss, Germany).

Inclusion and Exclusion Criteria

For inclusion, trials had to be prospective and randomized with any preparation of itraconazole in one arm compared with control treatment (no treatment, placebo, oral polyenes or fluconazole) in patients with hematologic malignancies who were neutropenic (leukocytes $< 1 \times 10^9/\mu L$ or neutrophils $< 0.5 \times 10^9/\mu L$) following cytotoxic chemotherapy or hematopoietic stem cell transplantation.

Extraction Process

A structured form was used for an independent extraction by at least two reviewers. Disagreements were resolved by consensus. Reviewers were not blinded to authors or journals. The first authors of studies that were not fully published were contacted, and they kindly provided additional data.[8-10]

Definition of Outcomes

The incidence of proven invasive fungal infections was the predefined primary outcome. Predefined secondary outcomes were proven invasive yeast infections, proven invasive *Aspergillus* infections, the mortality from proven invasive fungal infections, and the mortality from any cause during the study period. Predefined adverse effects extracted were hypokalemia, liver toxicity, the rate of bacterial infections, and the rate of drug discontinuation.

Definition of Fungal Infections

Only proven invasive fungal infections were analyzed, and these were restricted to only those infections that fitted closely the consensus criteria proposed by the joint working party of the European Organization for Research and Treatment of Cancer and Mycoses Study Group in 2002.[11] Additionally, patients with typical findings in computed tomography scans and the isolation of the *Aspergillus* species from bronchoalveolar lavage were accepted from four trials[12-15] that did not differentiate *Aspergillus* infections proven by culture or histology from those that are probable, due to typical computed tomography findings and isolation from bronchoalveolar lavage. These infections would be classified as probable according to the EORTC/MSG criteria. Fungal infections of the nasal and paranasal sinuses or fungal esophagitis (two in the itraconazole arm[16] and four in the control arm[12,17,18]) were excluded a priori because they were considered to be localized infections.

Bioavailable Dose

We calculated, from reports in the literature[19-21] and from our own published[22] and unpublished observations, that the bioavailability of itraconazole capsules in neutropenic patients was 22% and 55% for itraconazole oral solution. The bioavailable daily dose (BDD) was taken as the dose multiplied by the bioavailability.

Sensitivity Analysis

To assess the influence of possible biases (methodological, diagnosis- or treatment-related) on the meta-analysis, we performed a sensitivity analysis of various factors. These were attrition rate (intention-to-treat *v* per protocol), blinding of treatment, concealment of allocation, and repetitive inclusion (including one patient in several episodes of neutropenia) as well as certainty of diagnosis (proven *v* proven plus suspected), inclusion of patients after allogeneic stem cells transplantation only and treatment as a control arm (fluconazole or oral polyenes). A bias was suspected if the treatment effect differed clearly in the subgroups of this analysis.

Statistical Analysis

This meta-analysis was performed according to the guidelines of the Cochrane Collaboration[23] and the Quality of Reporting of Meta-Analysis statement[24] with two computer software applications, Comprehensive Meta Analysis Version 1.0.25 (Biostat, Englewood, NJ) and Review Manager 4.2.2 (The Cochrane Collaboration, Oxford, UK), with identical results. The statistical summary was expressed as the Peto odds ratio (risk calculated as the number of patients with a certain event divided by the number of patients without this event), which was analyzed with a fixed-effect model and reported with a 95% CI. Relative risk reductions are reported with their standard deviations (SDs). Heterogeneity between the trials was assessed by the Mantel-Haenszel χ^2 test for heterogeneity and no statistically significant heterogeneity ($P < .10$) was found in the analyses of any outcome. Funnel plots were graphically assessed and did not show significant asymmetry. The statistical significance of differences between subgroups was assessed by analysis of variance (calculated with Comprehensive Meta Analysis) and a χ^2 test for heterogeneity between subtotals (kindly calculated by Dr. R. Hills, Birmingham, UK) with identical results. A two-sided *P* value of less than .05 was considered statistically significant. To assess possible bias a sensitivity analysis was performed with the stratified subtotals.

Role of Funding Sources

Ortho-Biotech/Janssen-Cilag (Neuss, Germany) was asked to supply data of published and unpublished trials and provided partial funding for the study, but neither they nor any other manufacturer of antifungal agents had any role in the study design, data extraction, data interpretation, in the writing of the report or in the decision to submit the paper for publication.

RESULTS

Included Trials

Thirteen trials were identified which reported at least one outcome for 3,597 patients (1,812 treated with itraconazole and 1,785 controls). Table 1 shows the selection criteria, the proportion of patients with acute leukemia, and the median duration of neutropenia in each study. Methodological quality such as generation and concealment of allocation sequences, blinding and type of analysis is reported in Table 2. Five trials used itraconazole capsules, six itraconazole oral solution and two used the intravenous (IV) and oral solution (Table 3). In the control arm one trial compared itraconazole capsules to placebo only, one trial to no control treatment, five trials compared itraconazole to oral polyenes and six trials used fluconazole for comparison (Table 3). Some trials included several episodes of neutropenia in one patient; these trials were all included in the analysis.

Incidence of Invasive Fungal Infections

This outcome was reported in 13 trials. Proven invasive fungal infections occurred in 59 (3.3%) of 1,812 episodes with itraconazole prophylaxis and in 94 (5.3%) of 1,785 control episodes (odds ratio [OR], 0.60; 95%CI, 0.43 to 0.83; $P = .002$; Fig 1). In a subgroup analysis, a statistically significant effect was seen only in patients who received itraconazole solution (OR, 0.51; 95%CI, 0.35 to 0.75; $P = .0005$) and not in patients receiving capsules (OR, 0.92; 95% CI, 0.49 to 1.74; $P = .81$). This indicates a 40% ± 13% reduction of invasive fungal infections with any itraconazole prophylaxis and a 49% ± 14% reduction in episodes with the solution. The difference between the two subgroups (solution *v* capsule) was not significant ($P = .10$).

Incidence of Invasive Yeast Infections

This outcome was reported in twelve trials. Proven invasive yeast infections occurred in 19 (1.1%) of 1,668 episodes with

Table 1. Characteristics of Included Studies: Patient Selection

Study	Inclusion Criteria*	Itraconazole Arm					Control Arm				
		Acute Leukemia		Duration of Neutropenia† (Days)			Acute Leukemia		Duration of Neutropenia† (Days)		
		n/N	%	Mean	SD	Range	n/N	%	Mean	SD	Range
Vreugdenhil et al[12]	Untreated hematologic malignancy, intensive cytotoxic chemotherapy, age >15 years	37/46	80	28	NA	6-72	44/46	96	25	NA	8-68
Nucci et al[17]	Hematologic malignancy or autologous bone marrow transplantation, anticipated duration of neutropenia > 7 days, no evidence of fungal infection, no difficulty ingesting oral drugs, age > 4 years	83/104	80	12	NA	7-38	85/106	80	11	NA	7-30
Annaloro et al[25]	Allogeneic or autologous bone marrow transplantation, no evidence of infection, no history of infection or antimicrobial medication in 2 weeks, age > 11 years	NA	NA	23	NA	10-60	NA	NA	19	NA	10-70
Huijgens et al[18]	Hematologic malignancies, intensive cytotoxic chemotherapy or autologous stem cell transplantation; anticipated duration of neutropenia ≥ 10 days; no overt infection, age > 17 years	43/101	43	15	6.8	NA	35/101	35	15	6.6	NA
Harousseau et al[13]	Hematologic malignancy undergoing intensive therapy, autologous bone marrow transplantation, anticipated duration of neutropenia ≥ 14 days, no evidence of fungal infection, age > 14 years	199/281	71	18	NA	0-84	195/276	71	20	NA	0-88
Menichetti et al[16]	Hematological malignancy undergoing chemotherapy likely to induce neutropenia within 7 days, no history or clinical evidence of fungal infection, age > 14 years	149/201	74	13	NA	0-56	157/204	76	14	NA	0-56
Morgenstern et al[14]	Hematologic malignancy undergoing chemotherapy, anticipated neutropenia < 1,000/μl for ≥ 7 days, allogeneic or autologous stem cell transplantation, no hepatic or renal impairment, no profuse diarrhea or ileus, no history of proven fungal infection, age > 15 years	194/288	67	26	NA	NA	187/293	64	26	NA	NA
Boogaerts et al[15]	Leukemia, aplastic anemia, bone marrow transplantation or cytotoxic therapy with anticipated duration of neutropenia ≥ 10 days, no fungal infection at start of the study, age > 15 years	86/144	60	28	NA	NA	95/133	71	29	NA	NA
Winston et al[9]	Allogeneic stem cell transplantation, no fungal infection within 8 weeks prior to study, no severe liver disease, age > 12 years	22/71	31	19	NA	7-97	23/67	34	19	NA	9-42
Lass-Flörl et al[8]	Adult patients receiving myelosuppressive chemotherapy or high-dose chemotherapy with autologous peripheral stem cell transplantation, no prior azoles, no prior fungal infections	41/59	69	19	NA	NA	42/56	75	15	NA	NA
Marr et al[10]	Patients receiving allogeneic stem cell transplantation, no azoles or fungal infections at baseline	NA	NA	19	NA	10-35	NA	NA	19	NA	9-46
ITR-GER-23	Hematologic malignancy or autologous bone marrow transplantation with anticipated duration of neutropenia ≥ 10 days, no fungal infection at or before start of the study, age ≥ 18 years	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kaptan et al[26]	Acute leukemia with myelosuppressive chemotherapy with anticipated duration of neutropenia ≥ 7 days, no fungal infection, no previous antifungal chemotherapy < 15 days, no hepatic or renal dysfunction	31/31	NA	8-31	16	NA	24/24	NA	14	NA	9-29

Abbreviations: n, number of events; N, number of patients or episodes; SD, standard deviation; NA, not available (not reported).

*Age limits either as previously defined or lowest age of included patients.

†Leukocytes < 1,000/μL or neutrophils < 500/μL if not stated otherwise.

itraconazole prophylaxis and in 40 (2.4%) of 1,652 control episodes (OR, 0.47; 95% CI, 0.28 to 0.79; $P = .004$; Fig 2). In a subgroup analysis, a statistically significant effect was seen only in patients who received itraconazole solution (OR, 0.40; 95% CI, 0.21 to 0.76; $P = .005$) and not in patients receiving capsules (OR, 0.63; 95% CI, 0.26 to 1.55; $P = .32$). This indicates a 53% ± 19% reduction of invasive yeast infections with itraconazole prophylaxis in all studies and a 60% ± 21% reduction in episodes with itraconazole solution only. The difference between the two preparation subgroups was not significant ($P = .40$). The effectiveness of itraconazole prophylaxis could also be found in a separate analysis of the rate of proven *C. albicans* (OR, 0.43; 95% CI, 0.16 to 1.11) and nonalbicans *Candida* species (OR, 0.47, 95% CI, 0.25 to 0.89) infections.

Incidence of Invasive Aspergillus *Infections*

This outcome was reported in twelve trials. Proven invasive *Aspergillus* infections occurred in 27 (1.6%) of 1,668 episodes with itraconazole prophylaxis and in 39 (2.4%) of 1,652 control episodes (OR, 0.67; 95% CI, 0.41 to 1.10; $P = .12$; Fig 3). In a subgroup analysis, a statistically significant effect was seen in patients who received itraconazole solution (OR, 0.52; 95% CI, 0.30 to 0.90; $P = .02$) and not in patients receiving capsules (OR, 1.75; 95% CI, 0.61 to 5.07; $P = .30$). Thus there was no significant reduction of invasive *Aspergillus* infection episodes

Table 2. Characteristics of Included Studies: Methodological Assessment

Study	Generation of Allocation Sequences	Concealment of Allocation Sequences	Double-Blinding	Analysis
Vreugdenhil et al[12]	Not reported	Not reported	Yes (identical placebo)	Per protocol (three patients withdrawn in each arm)
Nucci et al[17]	Not reported	Yes	Yes (identical placebo)	Modified intention-to-treat*
Annaloro et al[25]	Not reported	Not reported	No (not reported)	Intention-to-treat (no exclusions reported)
Huijgens et al[18]	Not reported	Not reported	Yes (identical capsules)	Per protocol† (five and six patients excluded)
Harousseau et al[13]	Computer-generated	Yes	Yes (double placebo)	Intention-to-treat (no exclusions reported)
Menichetti et al[16]	Not reported	Yes	Yes (identical placebo)	Intention-to-treat (no exclusions from analysis)
Morgenstern et al[14]	Computer-generated	Not reported	No	Per protocol
Boogaerts et al[15]	Not reported	Not reported	No	Intention-to-treat (no exclusions from analysis)
Winston et al[9]	Not reported	Yes	No	Per protocol (one patient excluded in each arm)
Lass-Flörl et al[8]	Not reported	Not reported	No	Per protocol
Marr et al[10]	Computer-generated	Yes	No	Per protocol
ITR-GER-23	Computer-generated	Yes	No	Intention-to-treat
Kaptan et al[26]	Not reported	Not reported	No	Per protocol

*Eleven patients were excluded from analysis by the investigators for violations of inclusion criteria.

†The authors stated that the analysis was done intention-to-treat; however, because of the large number of excluded patients, the study was regarded as analyzed per protocol in this review.

with itraconazole prophylaxis overall but a 48% ± 21% reduction in episodes with itraconazole solution only ($P = .02$). The difference of the two preparation subgroups approached statistical significance ($P = .0537$).

Mortality From Proven Invasive Fungal Infections

This outcome was reported in thirteen trials. Mortality from proven invasive fungal infections occurred in 40 (2.2%) of 1,812 episodes with itraconazole prophylaxis and in 59 (3.3%) of 1,785 control episodes (OR, 0.65; 95% CI, 0.43 to 0.98; $P = .04$). This corresponds to a 35% ± 17% reduction in all trials and a 42% ± 18% reduction in the itraconazole solution trials only. The case fatality rate for invasive fungal infections was 40 (68%) of 59 patients in the itraconazole arm and 59 (63%) of 94 patients in the control arm and not statistically different ($P = .60$). In a subgroup analysis a significant effect on mortality was seen only in patients who received itraconazole solution (OR, 0.58; 95%CI, 0.36 to 0.91; $P = .02$) and not in patients receiving capsules (OR, 1.01; 95% CI, 0.43 to 2.39; $P = .98$). The difference between the two preparation subgroups was not statistically significant ($P = .30$).

Mortality From All Causes

Data for this outcome could be extracted from all trials. Death from any cause (including the underlying disease) occurred during the period of prophylaxis in 207 (11.4%) of 1,812

Table 3. Characteristics of Included Studies: Antifungal Prophylaxis in Intervention and Control Arm

Study	Incidence*		Intervention Arm: Itraconazole	Control Arm
	n/N	%		
Vreugdenhil et al[12]	11/167	6.6	Capsules 400 mg/day PO plus amphotericin B 4,000 mg/day PO	Amphotericin B 4,000 mg/day PO
Nucci et al[17]	13/210	6.2	Capsules 200 mg/day PO	Placebo only
Annaloro et al[25]	5/59	8.5	Capsules 400 mg/day PO plus nystatin 4.5 MU/day	Fluconazole 300 mg/day PO plus nystatin 4.5 MU/day PO
Huijgens et al[18]	8/213	3.8	Capsules 200 mg/day PO plus intranasal amphotericin B 6 mg/day	Fluconazole capsules 100 mg/day PO plus intranasal amphotericin B 6 mg/day
Harousseau et al[13]	21/557	3.8	Oral solution 5 mg/kg body weight/day PO	Amphotericin B 2,000 mg/day PO
Menichetti et al[16]	12/405	3.0	Oral solution 5 mg/kg body weight/day PO plus nystatin 2.0 MU/day PO	Nystatin 2.0 MU/day PO
Morgenstern et al[14]	7/581	1.2	Oral solution 5 mg/kg body weight/day PO	Fluconazole 100 mg/day PO
Boogaerts et al[15]	14/277	5.1	Oral solution 200 mg/day PO	Amphotericin B 1,500 mg/day PO plus nystatin 8.0 MU/day PO
Winston et al[9]	23/138	16.7	Intravenous solution 400 mg day 1-2, 200 mg day 3-14, oral solution 400 mg day 15-100 (back to IV if necessary)	Fluconazole: IV solution 400 mg day 1-14, oral 400 mg day 15-100 (back to IV if necessary)
Lass-Flörl et al[8]	4/115	3.5	Oral solution 10 mg/kg body weight/day PO	Amphotericin B 3,000 mg/day PO
Marr et al[10]	19/295	6.4	Oral solution 7.5 mg/kg body weight/day PO or 200 mg/day IV	Fluconazole 400 mg/day PO or IV
ITR-GER-23	9/494	1.8	Oral solution 5 mg/kg body weight/day PO	Fluconazole 400 mg/day PO
Kaptan et al[26]	4/97	4.1	Capsules 400 mg/day PO	No treatment

Abbreviations: n, number of events; N, number of patients or episodes; PO, orally; IV, intravenous.

*Incidence of proven invasive fungal infections in the complete study population.

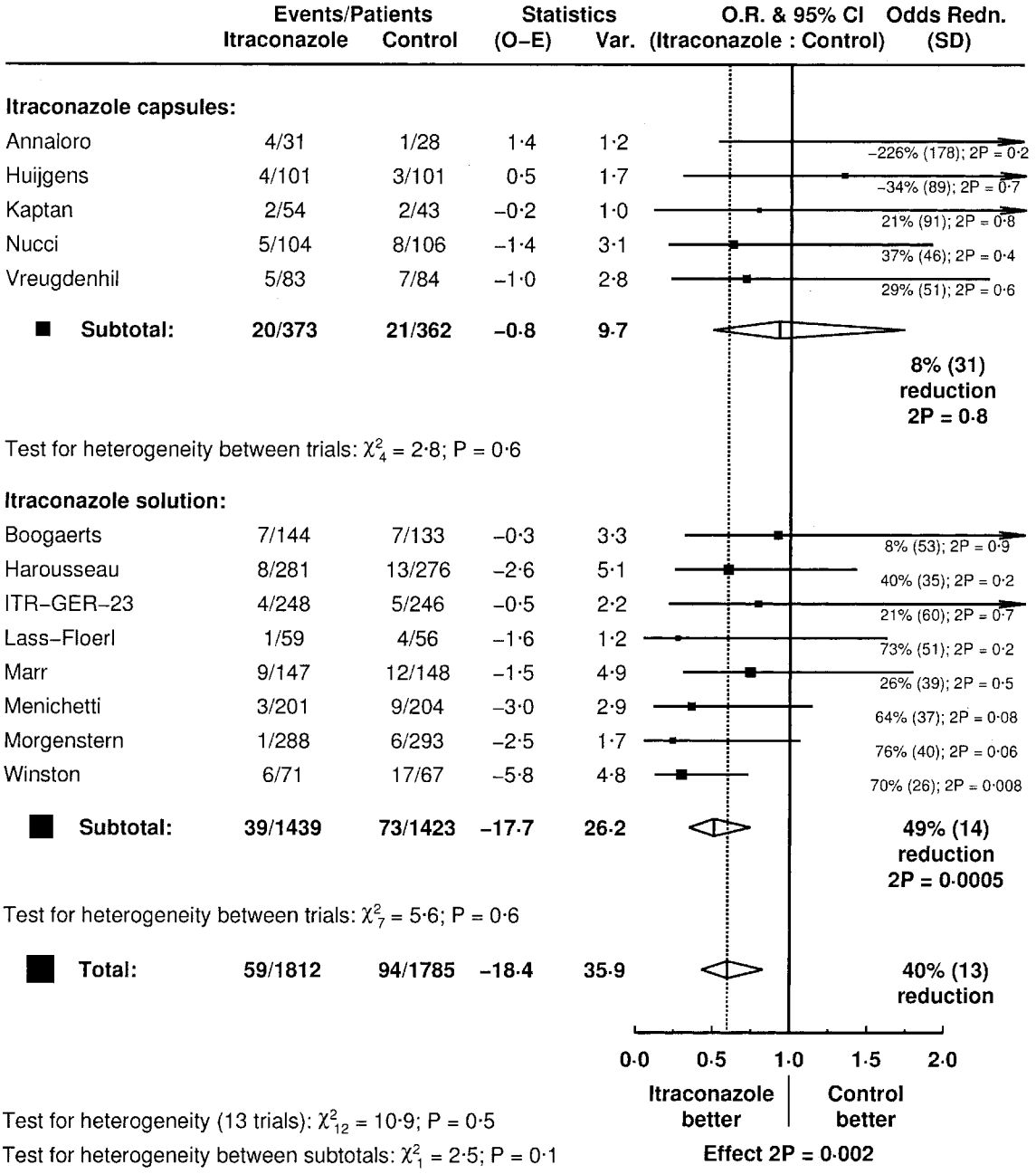

Fig 1. Incidence of proven invasive fungal infections. OR, odds ratio; O-E, observed minus expected events; Var., variance of O-E; Odds Redn., odds reduction; SD, standard deviation.

episodes with itraconazole prophylaxis and in 206 (11.5%) of 1,785 control episodes (OR, 0.98; 95% CI, 0.79 to 1.22; $P = .88$) with no difference between itraconazole solution and capsules.

Adverse Effects

Only a few studies reported a difference in adverse effects. Severe drug-related adverse effects were reported in one study where itraconazole was administered concomitantly with high-dose cyclophosphamide.[10] A higher rate of hepatic toxicity occurred. This was not seen after the start of the itraconazole prophylaxis was delayed until the cyclophosphamide conditioning was completed. To maintain comparability with the other trials, the per-protocol analysis ("on drug") of this trial was used for the evaluation of invasive fungal infections. Hypokalemia was associated with itraconazole solution twice as often in three trials (including the ITR-GER-23 trial) that reported this outcome (OR, 1.93; 95% CI, 1.41 to 2.65; $P < .0001$).[13,14] The rate of drug discontinuation was reported in twelve trials. The rate of discontinuation was comparable between the arms of the trials that used itraconazole capsules (OR, 0.90, 95% CI, 0.34 to 2.37; $P = .83$)[12,17,18,25] or cyclodextrine as placebo (OR, 1.09; 95% CI, 0.81 to 1.48; $P = .56$).[13,16] In trials that compared itracon-

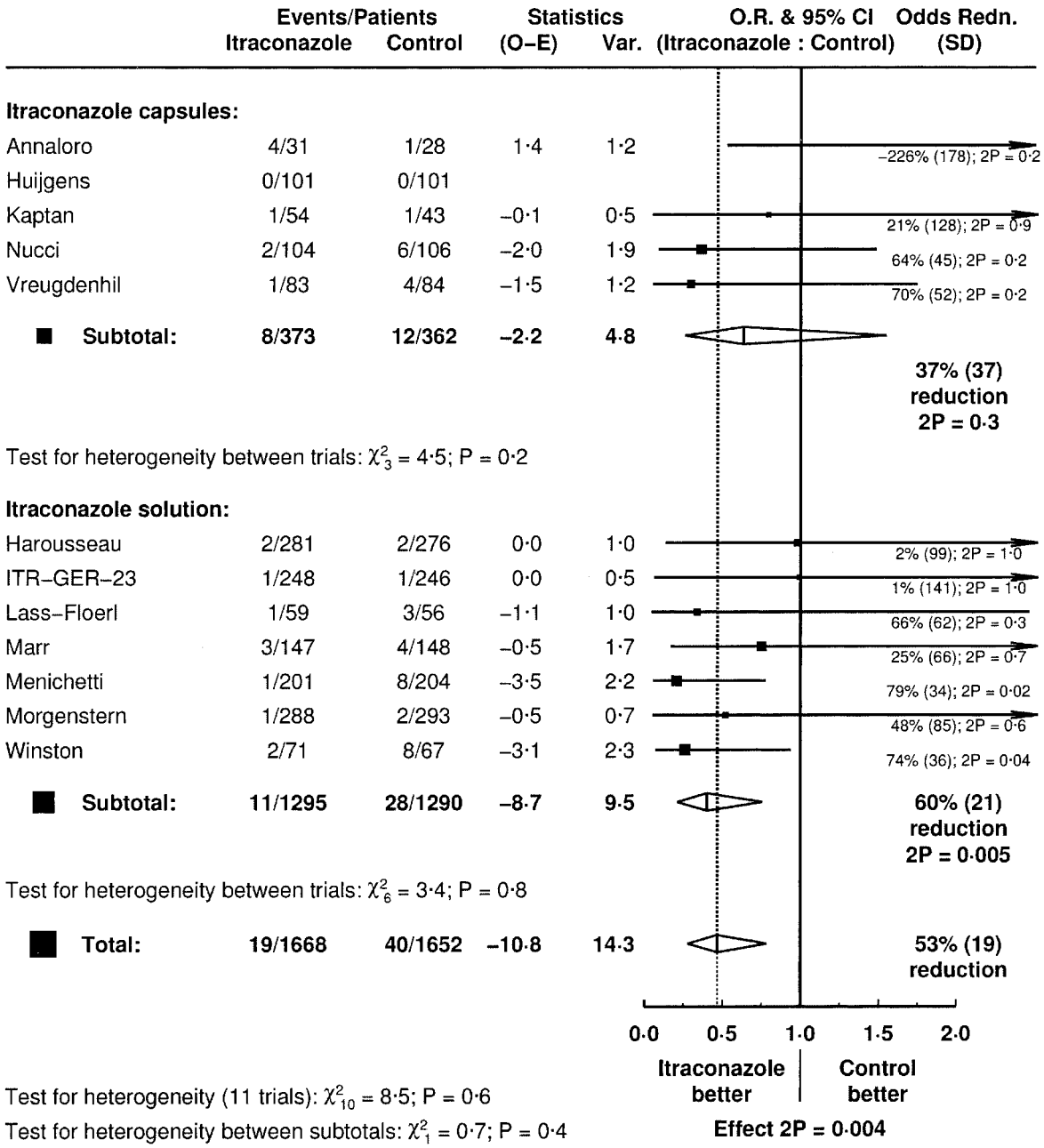

Fig 2. Incidence of proven invasive yeast infections. OR, odds ratio; O-E, observed minus expected events; Var., variance of O-E; Odds Redn., odds reduction; SD, standard deviation.

azole oral solution with fluconazole (four trials[9,10,14] and the unpublished ITR-GER-23) or oral amphotericin B (one trial[15]) the discontinuation rate was twice as high in the itraconazole arm (OR, 1.95, 95% CI, 1.57 to 2.44; $P < .0001$). The reason most often reported for drug discontinuation in the itraconazole solution arms was nausea.

Dose-Response Relationship

For all trials, the BDD was calculated as described above and the incidence of invasive fungal infections was compared in one group with a BDD of less than 110 mg/d[12,15,17,18,25,26] (OR, 0.92; 95% CI, 0.54 to 1.59; $P = .77$) with another group with a BDD above 200 mg/d (including the ITR-GER-23 trial)[8-10,13,14,16] (OR, 0.47; 95% CI, 0.31 to 0.70; $P = .0001$). The difference between these two subgroups was statistically significant for the incidence of invasive fungal infections ($P = .0495$, Fig 4) and nearly so for the incidence of invasive *Aspergillus* infections ($P = .0537$, data not shown).

Sensitivity Analysis

This analysis was performed to detect bias in the pooling of studies with different methodological quality and different

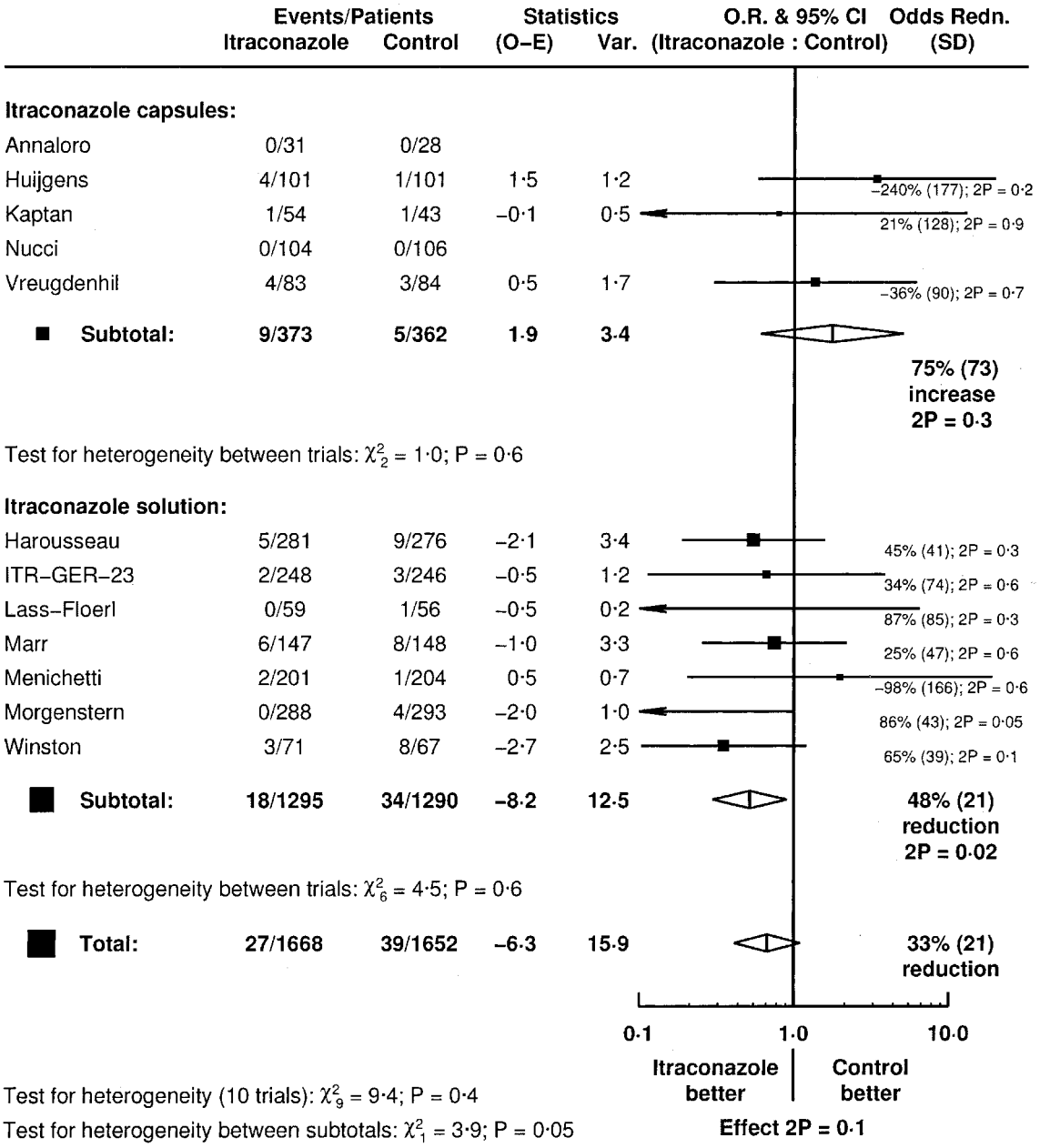

Fig 3. Incidence of proven invasive *Aspergillus* infections. OR, odds ratio; O-E, observed minus expected events; Var., variance of O-E; Odds Redn., odds reduction; SD, standard deviation.

treatments in the control arm. Figure 5 summarizes the results of these analyses and shows no important deviations. The incidence of proven and suspected (as defined by the investigators) fungal infections was also included and compared with the incidence of proven infections only (OR, 0.65; 95% CI, 0.52 to 0.80; $P < .0001$ for proven and suspected infections). Itraconazole was as superior in randomized controlled trials against fluconazole in the control arms as it was in randomized controlled trials against nonsystemic antifungal drugs in the control arm (fluconazole in control arm: OR, 0.60, 95% CI, 0.37 to 0.97; $P = .04$; oral polyenes in control arm: OR, 0.60, 95% CI, 0.38 to 0.95; $P = .03$). Also the effect of itraconazole prophylaxis was superior in the two trials that included patients only after allogeneic stem cell transplantation.[9,10]

DISCUSSION

This meta-analysis demonstrates that antifungal prophylaxis with itraconazole reduces invasive fungal infections, invasive yeast infections, and death from these infections in neutropenic patients with hematologic malignancies and myelosuppressive chemotherapy significantly. These benefits are derived mainly from trials using the oral or IV cyclodextrine solution of the drug. Subgroup analysis also showed that with the solution, itraconazole significantly reduced invasive *Aspergillus* infections, which has not been shown before with any other antimycotic drug. Furthermore, there seems to be an important dose-response relationship. None of these effects could have been clearly shown in previous single randomized trials.

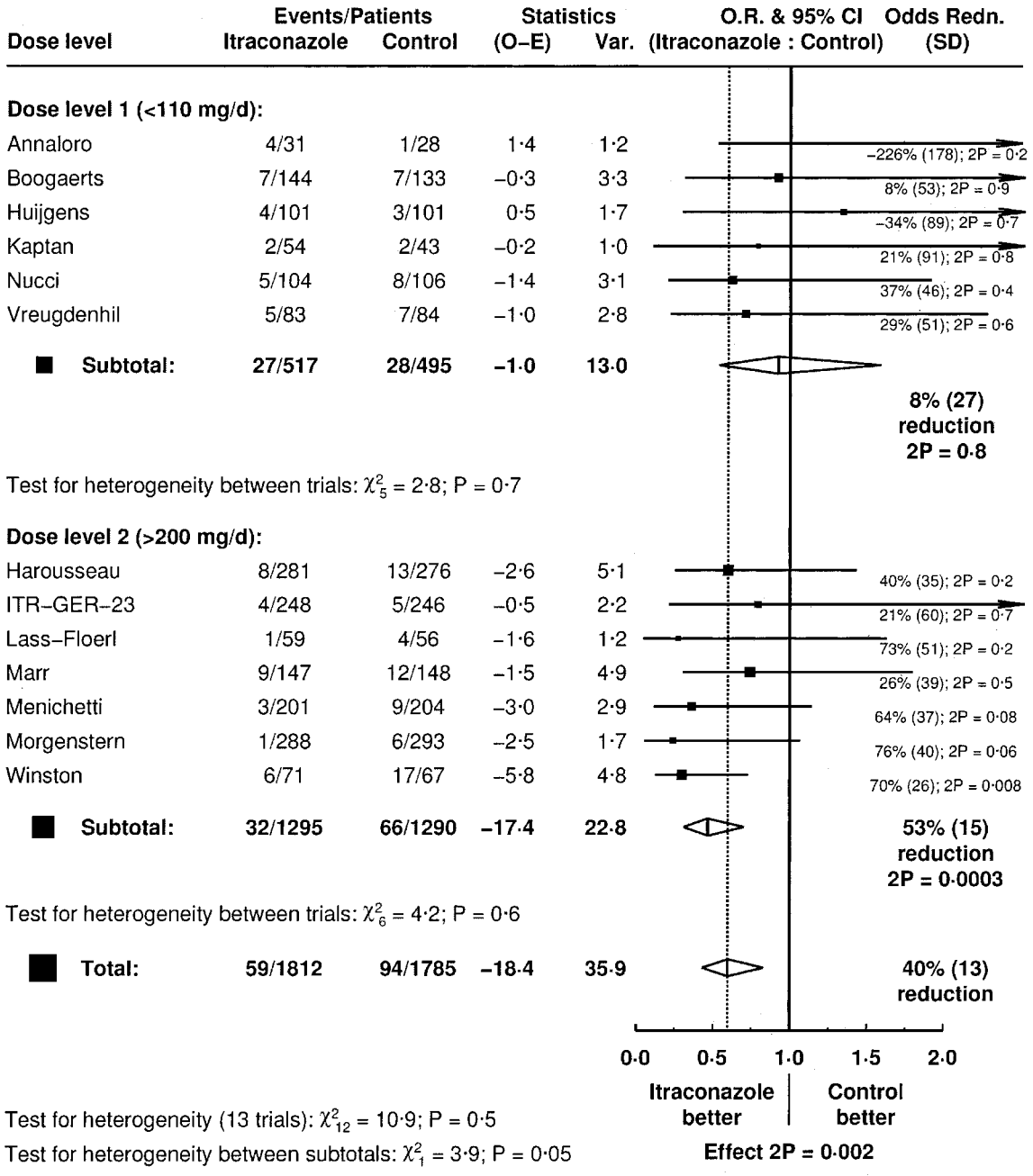

Fig 4. Dose-response analysis (outcome: incidence of proven invasive fungal infections). OR, odds ratio; O-E, observed minus expected events; Var., variance of O-E; Odds Redn., odds reduction; SD, standard deviation.

Our findings concur overall with a recent systematic review which suggested that antifungal prophylaxis with various drugs reduced invasive fungal infections and death from these infections in neutropenic patients who had been given myelosuppressive therapy.[6] However, that study differed from ours in several respects. First, it included trials of patients who had nonhematologic malignancies and therefore different and probably lower risks of developing invasive fungal infections. Second, it pooled the results of studies of drugs with very different spectra of antifungal activity and bioavailability. Third, several important studies with itraconazole were not included (only five were included). Therefore, no clear therapeutic recommendation was derived from that study, and the findings required confirmation in a more specific and focused meta-analysis.

A previous meta-analysis by Gotzsche and Johansen[27,28] was seriously flawed in assuming an equivalent range of antifungal activity and bio-availability across very different drugs and by different modes of delivery (eg, pooling oral polyenes with azoles). It was also incomplete as only three of thirteen relevant randomized controlled trials of itraconazole were included.

In this meta-analysis of itraconazole, clear reductions are demonstrated not only in the rate of invasive fungal infections

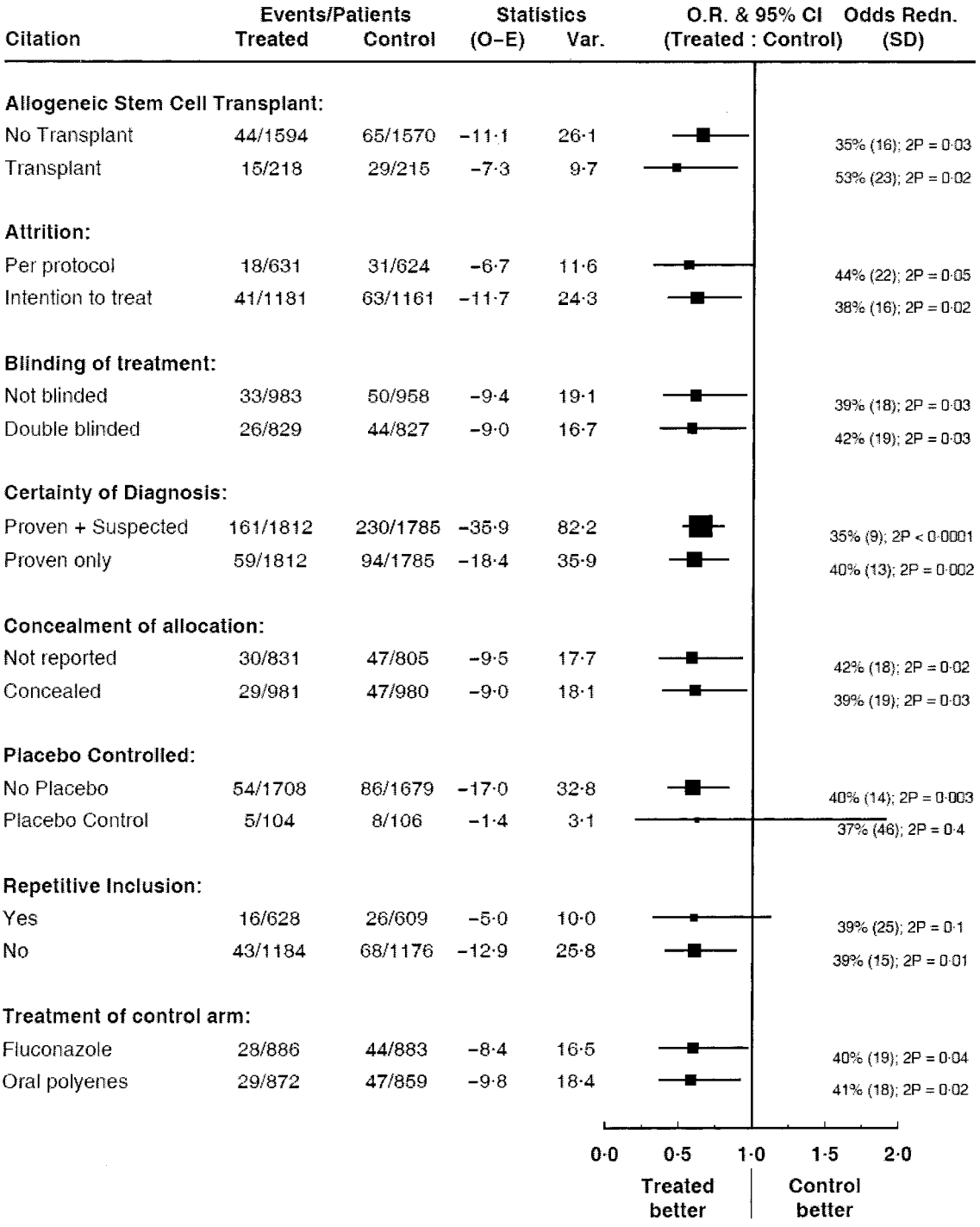

Fig 5. Sensitivity analysis (outcome: incidence of proven invasive fungal infections). OR, odds ratio; O-E, observed minus expected events; Var., variance of O-E; Odds Redn., odds reduction; SD, standard deviation.

and deaths from invasive fungal infections but also in the incidence rate of a broad spectrum of invasive yeast infections. In contrast, one previous meta-analysis of sixteen randomized controlled trials with fluconazole provided evidence of effective prevention of invasive yeast infections due to *Candida albicans* but failed to demonstrate a significant reduction in invasive infections due to all yeasts or *Aspergillus* species, and this effect of fluconazole was seen only in randomized controlled trials with an incidence of more than 15% invasive yeast infections in the control group.[5] Several trials in this meta-analysis compared itraconazole with fluconazole (Table 3). In these trials, the efficacy of itraconazole was as superior to fluconazole as in trials with other comparators, especially oral polyenes (Fig 5).

This systematic review is the first to demonstrate effective prevention of invasive aspergillosis in the treatment of patients with hematologic malignancy. In these patients, this infection has a high mortality rate.[2] This meta-analysis also provides the first evidence that these benefits are derived mainly from those trials using the cyclodextrine solution of the drug with at least 400 mg/d PO or 200 m g/d IV.

This dose-response relationship of itraconazole has not yet been systematically studied in humans, but other studies clearly support our findings.[29-35] It is likely that at least 200 mg/d itraconazole should be systemically available for effective prophylaxis (ie, at least 400 mg/d oral solution) and a loading dose may achieve steady-state more quickly.[22] The bioavailability of itraconazole has been shown to be variable, largely poor for the capsules,[36] and clearly better with the solution.[22,37,38] Previous retrospective human and animal studies suggested that minimum blood levels of itraconazole were needed to reduce the risk of invasive fungal infections, particularly with *Aspergillus*.[29,33,35,39] The highly significant dose-response relationship reported in this meta-analysis confirms the findings of these previous studies and the importance of bioavailability to proof of efficacy and emphasizes the need to establish pharmacokinetic profiles in advance of randomized controlled trials and in the patient population for whom the drug is intended.

Our data indicate the importance of bioavailability. Hence, measuring the serum concentration of itraconazole may be important. One recommendation from our previous work is that the itraconazole serum concentration should be monitored by high-performance liquid choromatography and be above 500 ng/mL.[33,35] The use of the IV preparation of itraconazole (followed by the oral solution) is recommended in patients with allogeneic stem cell transplantation and other high-risk patients who cannot take the oral solution. From the data of this meta-analysis the use of itraconazole capsules should be avoided for this indication.

We have restricted our analysis to proven invasive fungal infections to provide the greatest possible specificity of the results. The inclusion of suspected invasive fungal infections would have resulted in less reliable conclusions about the efficacy of antifungal prophylaxis with itraconazole, because of the wide variation of the definition of "suspected" infections among the trials, although our sensitivity analysis showed that the results remain unchanged when suspected fungal infections are included.

This restriction to proven infections makes it more difficult to calculate representative numbers-needed-to-treat (NNTs) for antifungal prophylaxis with itraconazole. These numbers need to be applied cautiously, because the NNT is highly dependent on the absolute incidence of the event rate in any cohort. For example, given that a 53% reduction of the incidence of invasive fungal infection has been shown in the higher dose group (Fig 5), the NNT of a center with a 15% incidence of invasive fungal infections would be low, at approximately 13 (1:12.6), whereas it would rise to 38 (1:37.7) in a center with an incidence of 5%. Reports in the literature have indicated that invasive fungal infections cost between US $22,197[40] and US $31,200[41] per episode, whereas 20 days of prophylaxis with itraconazole oral solution (400 mg/d PO) would cost approximately US $683 (German pharmacy prices). Therefore, in a center with a 15% incidence of invasive fungal infections and a 68% case-fatality rate, the use of itraconazole oral solution would result in a cost of US $8,538 for one avoided invasive fungal infection and a cost of US $15,958 for one avoided death from invasive fungal infection.

It has been suggested that overall mortality is a more important end point than any other and that determining invasive fungal infections as the cause of death may be difficult.[27,28] This meta-analysis did not show any significant benefit of prophylaxis for this end point. But again, it is very probable that our meta-analysis underestimates the influence of invasive fungal infections on the mortality of neutropenic patients. Two studies, one of which[14] is included in this meta-analysis, have reported prolonged protective effects of antifungal prophylaxis that may have been missed in this analysis.[42] It is also evident that any invasive fungal infection will delay further antineoplastic treatment (including stem cell transplantation) and thereby reduce the chances of cure for the patient.

In conclusion, this meta-analysis demonstrates that antifungal prophylaxis with itraconazole, if adequately dosed, can significantly reduce the incidence of and the mortality from invasive fungal infections in neutropenic patients with hematologic malignancies. For the first time, it is shown that invasive *Aspergillus* infections can also be prevented in these patients.

In the view of these data, patients with acute leukemia who receive myelosuppressive cytotoxic chemotherapy and patients who have undergone allogeneic stem cell transplantation should receive an antifungal prophylaxis with itraconazole. The potentially serious neurotoxic interaction of itraconazole with vincristine in patients treated for acute lymphoblastic leukemia has to be avoided. Prophylaxis should be given for the duration of neutropenia in leukemia patients as it was in the trials in this meta-analysis, but it is more difficult to determine its optimal duration in patients after allogeneic stem cell transplantation. Previous studies have described a biphasic distribution of the incidence of invasive *Aspergillus* infections with a second peak at approximately 100 days after transplantation.[43,44] In the trials of Winston et al[9] and Marr et al,[10] prophylaxis was consequently continued for up to 100 days after transplantation.

ACKNOWLEDGMENT AND APPENDIX

The acknowledgment and appendix are included in the full-text version of this article, available on-line at www.jco.org. They are not included in the PDF (via Adobe® Acrobat Reader®) version.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Axel Glasmacher, MSD Sharp and Dohme, Ortho-Biotech, Schering-Plough; Archibald Prentice, Gilead, MSD Sharp and Dohme, Ortho-Biotech, Pfizer, Schering-Plough. Performed contract work within the last 2 years: Axel Glasmacher, MSD Sharp and Dohme, Ortho-Biotech, Pfizer; Archibald Prentice, Ortho-Biotech. Received more than $2,000 a year from a company for either of the last 2 years: Axel Glasmacher, MSD Sharp and Dohme, Ortho-Biotech, Schering-Plough; Archibald Prentice, Gilead, MSD Sharp and Dohme, Ortho-Biotech, Pfizer, Schering-Plough.

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