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Adverse Effects of Low Dose Amiodarone: A Meta-Analysis

VICKEN R. VORPERIAN, MD, FACC, THOMAS C. HAVIGHURST, MS, STEPHEN MILLER, MD, CRAIG T. JANUARY, MD, PhD, FACC

Madison, Wisconsin

Objectives. **We sought to assess the odds of experiencing adverse effects with low dose amiodarone therapy compared with placebo.**

Background. **An estimate of the likelihood of experiencing amiodarone-related adverse effects with exposure to low daily doses of the drug is lacking in the published reports, and little information is available on adverse effect event rates in control groups not receiving the drug.**

Methods. **Data from four published trials involving 1,465 patients were included in a meta-analysis design. The criteria for inclusion were 1) double-blind, placebo-controlled design; 2) absence of a crossover design between patient groups; 3) mean follow-up of at least 12 months; 4) maintenance amiodarone dose ≤400 mg/day; and 5) presence of an explicit description of adverse effects. Data were pooled after testing for homogeneity of treatment effects across trials, and summary odds ratios were calculated by the Peto-modified Mantel-Haenszel method for each adverse effect.**

Results. **The mean amiodarone dose per day ranged from 152 to 330 mg; 738 patients were randomized to receive amiodarone and 727 placebo. Exposure to amiodarone in this dose range, for a minimal duration of 12 months, resulted in odds similar to those of placebo for hepatic and gastrointestinal adverse effects, but in significantly higher odds than those of placebo ($p < 0.05$) for experiencing thyroid (odds ratio [OR] 4.2, 95% confidence interval [CI] 2.0 to 8.7), neurologic (OR 2.0, 95% CI 1.1 to 3.7), skin (OR 2.5, 95% CI 1.1 to 6.2), ocular (OR 3.4, 95% CI 1.2 to 9.6) and bradycardic (OR 2.2, 95% CI 1.1 to 4.3) adverse effects. A trend toward increased odds of pulmonary toxicity was noted (OR 2.0, 95% CI 0.9 to 5.3), but this did not reach statistical significance ($p = 0.07$). The unadjusted total incidence of drug discontinuation was 22.9% in the amiodarone group and 15.4% in the placebo group. The odds of discontinuing the drug in the amiodarone group was approximately 1.5 times that of the placebo group (OR 1.52, 95% CI 1.2 to 1.9) ($p = 0.003$).**

Conclusions. **Compared with placebo, there is a higher likelihood of experiencing several amiodarone-related adverse effects with exposure to low daily doses of the drug. Thus, although low dose amiodarone may be well tolerated, it is not free of adverse effects.**

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Low dose amiodarone has been advocated for use in the treatment of ventricular arrhythmias observed in congestive heart failure (1,2) and postmyocardial infarction (3–5), as well as in the treatment of symptomatic atrial fibrillation (6–12). The use of amiodarone in any clinical setting, however, has been associated with concerns about adverse effects and end-organ toxicity that might outweigh its potential beneficial antiarrhythmic effects. The adverse effects associated with amiodarone treatment have usually been related to dose and duration of therapy (13,14). When administered in high daily doses and for longer than 12 months, amiodarone is poorly tolerated and serious toxicity is frequently found (15). In contrast, European reports in the early 1980s have suggested that amiodarone is well tolerated, with few serious adverse effects, when it is administered in low maintenance doses (16–18). Nonetheless, an objective assessment of the likelihood of experiencing amiodarone-related adverse effects with exposure to low daily doses of the drug is lacking in the published data, and little information is available on adverse effect event rates in control groups not receiving the drug. Recent review articles (19–21) have commented on the toxicity of low dose amiodarone treatment by listing adverse effect rates reported in published drug efficacy trials. Most of these trials, however, lacked a randomized or blinded study design, and therefore did not report adverse effects in control groups (1,6–12,16,18,22–25).

We have performed, and recently described in preliminary form (26), a meta-analysis of randomized, placebo-controlled drug efficacy trials in which amiodarone was administered at relatively low maintenance doses and in which adverse effects were reported in both amiodarone and control groups. The purpose of our investigation was to estimate the odds of experiencing adverse effects with exposure to low dose amio-

From the Section of Cardiology, Department of Medicine and Department of Biostatistics, University of Wisconsin School of Medicine, Madison, Wisconsin. This study was supported in part by the Oscar Rennenbohm Foundation, Madison, Wisconsin.

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Address for correspondence: Dr. Vicken R. Vorperian, Section of Cardiology, Room H6/352 CSC, University of Wisconsin Hospitals and Clinics, 600 Highland Avenue, Madison, Wisconsin 53792. E-mail: vrv@medicine.wisc.edu.

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Table 1. Characteristics of Studies

		Trial Duration		Dose				Amiodarone			Placebo			
Study (ref no.)	Year	Total Duration (mo)	Mean F/U (mo)	Load/ Day (mg)	Load Period (days)	Maint/ Day (mg)	Mean/ Day (mg)	No. of Pts	Age (yr)	Gender (male)	No. of Pts	Age (yr)	Gender (male)	Cardiac Status
Nicklas et al. (42)	1991	33	12	400	28	200	215*	49	56	84%	52	59	86%	CHF
Singh et al. (43)	1995	54	45†	800	14	300–400	330*	336	65	99%	338	66	99%	CHF
Cairns et al. (5)	1991	24	20	800	21	100–400	152–179‡	48	64	73%	29	66	79%	Post-MI
Ceremuzynski et al. (3)	1991	47	12	800	7	100–400	278–326‡	305	59	71%	308	59	68%	Post-MI

*Calculated value, where mean dose/day = cumulative dose (mg)/mean follow-up (days), and cumulative dose = total loading dose (mg) + total maintenance dose (mg); and where total loading dose = (loading dose/day) × (number of loading days) and total maintenance dose = (maintenance dose/day) × (mean follow-up excluding loading days). †Median follow-up time. ‡Reported value. CHF = congestive heart failure; F/U = follow-up; Maint = maintenance; MI = myocardial infarction; Pts = patients; ref = reference.

darone compared with placebo for a minimal duration of 12 months.

Methods

Acquisition of data. A MEDLINE data base search of the published medical reports in all languages through April 1996 was conducted to identify all studies that have reported adverse effects with oral amiodarone administration, irrespective of indications for amiodarone therapy or efficacy of treatment. Manual searches of references and review articles complemented the computerized search, and only full-length published trials were considered. The criteria for inclusion in this meta-analysis were: 1) double-blind, placebo-controlled design; 2) absence of a crossover design between patient groups; 3) mean follow-up of at least 12 months; 4) maintenance amiodarone dose ≤400 mg/day; and 5) presence of an explicit description of adverse effects.

The search of the published data revealed 300 amiodarone studies in which adverse effects were reported, and of these 35 used oral maintenance doses ≤400 mg/day. Data in tables, text and figures were independently extracted by two of the authors. Trials in which adverse effects were not systematically looked for and reported in the control group because of nonrandomized study design (7–12,16,23–25) or absence of a placebo-control group (1,4,27–29) were excluded from the analysis, as were trials with a crossover design between control and amiodarone groups (30–32). In addition, if a mean or a median follow-up period was not reported (33) or was shorter than 12 months (2,31,34–36), the trial was excluded from the analysis.

Statistical analysis. Data regarding adverse effects were grouped by organ system. Unadjusted pooled incidence rates of adverse effects for each organ system were calculated. To estimate the likelihood of adverse effects of treatment with low dose amiodarone compared with placebo, odds ratios (ORs) and associated 95% confidence intervals (95% CIs) were calculated for each study; a weighted average of the ORs from each study (pooled OR) for each adverse effect and the probability that the pooled OR was equal to 1 were calculated using the Peto-modified Mantel-Haenszel method (37). This method produces a weighted average of the ORs, where weights are given by the inverse of the intrastudy variance. Comparison of adverse effects in a treatment group was made exclusively with the placebo group in the same trial. No comparison was made between trials and no assumption was made that any differences in adverse effect rates for a given organ system were of the same magnitude across trials. To avoid the possibility of potential bias in the Peto-modified method for pooling study results (38), the results were confirmed by calculating summary ORs, as described by Mantel and Haenszel (39). The homogeneity of treatment effect on the calculated ORs of an adverse effect across trials was assessed using a chi-square test for heterogeneity (37,40). In the presence of heterogeneity, the results were confirmed by calculation of summary ORs by the Miettinen method (41), which does not assume homogeneity among studies. The most conservative of the three estimators calculated by this method was selected. Statistical significance was set at $p < 0.05$.

Results

Characteristics of trials analyzed. Four double-blind, placebo-controlled trials (3,5,42,43) meeting the selection criteria for inclusion in this meta-analysis were identified. Characteristics of the four placebo-controlled trials are shown in Table 1. The trials included a total of 1,465 patients: 738 were randomized to amiodarone and 727 to placebo. The minimal mean follow-up period was 12 months in all trials, and the total trial duration extended from 24 to 45 months. The loading dose of amiodarone did not exceed 800 mg/day in any trial, and the loading period varied from 7 to 28 days. The maintenance dose of amiodarone per day did not exceed 400 mg in any trial; it was 200 mg in one trial (42) and was reduced to ≤300 mg during the course of the other three trials (3,5,43). The mean daily amiodarone dose for the duration of the studies varied

Table 2. Definitions of Adverse Effects and Drug Discontinuation

	Criteria Common to All Included Trials	Additional Criteria in Individual Trials
Adverse effect		
Hepatic	Two- to threefold elevations in hepatic transaminases (AST, ALT) (3,5,42,43)	Persistent elevations in alkaline phosphatase and lactic dehydrogenase (5)
Gastrointestinal	Nausea, vomiting, diarrhea and constipation (3,5,42,43)	
Pulmonary	Respiratory symptoms and new chest X-ray film findings (3,5,42,43)	>30% reduction in diffusion capacity (5,43)
Thyroid	Clinical hypothyroidism or hyperthyroidism (3,5,42,43)	Changes in thyroid functions (TSH, T_4 and T_3) that required medical therapy (3,45)
Neurologic	Tremor, ataxia/gait disturbance and numbness/tingling (3,5,42,43)	Insomnia (5)
Skin	Photosensitive and nonphotosensitive rash and bluish discoloration (slate gray) (3,5,42,43)	
Eye	Visual complaints (3,5,42,43)	Blurred or nocturnal halo vision (5), severe corneal microdeposits on slit-lamp examination (3)
Bradycardia/conduction disturbance	Symptomatic bradycardia and third-degree AV block (3,5,42,43)	Asymptomatic rest heart rate <50 beats/min or development of first- or second-degree AV block (3)
Drug discontinuation	Intolerable adverse effects or any patient's decision to voluntarily discontinue trial—excludes death, noncompliance or loss of follow-up (3,5,42,43)	Asymptomatic bradycardic or conduction disturbance or asymptomatic thyroid function abnormality (3)

ALT = alanine transaminase; AST = aspartate transaminase; AV = atrioventricular; TSH = thyroid-stimulating hormone; T_3 = tri-iodothyronine; T_4 = thyroxine.

from 152 to 330 mg/day. The majority of the patients were men in their fifth or sixth decade of life, and all had underlying heart disease.

The definitions of the adverse effects and of drug discontinuation, as they appeared in the four trials, are shown in Table 2. Definition criteria common to all the trials, as well as additional criteria unique to individual trials, are listed. The potential of additional definition criteria in individual trials to differentially affect the ORs of adverse effects across trials was examined by performing a chi-square test of heterogeneity (see later).

Adverse effects. The combined ORs, associated 95% CIs and unadjusted pooled incidence of clinically significant adverse effects by organ system are summarized in Table 3. A visual presentation of individual and combined ORs with 95% CIs is presented for each organ system in Figure 1.

Hepatic and gastrointestinal adverse effects occurred with equal likelihood in patients randomized to low-dose amiodarone compared to placebo treatment. The combined odds ratios across all studies for these two adverse effects were near unity (Fig. 1, a and b). The unadjusted pooled incidences of adverse effects for the amiodarone and placebo groups were

Table 3. Adverse Effects

	Amiodarone Group (n = 738) [no. (%)]	Placebo Group (n = 727) [no. (%)]	OR (95% CI)	p Value	Heterogeneity	
					Chi-Square Statistic	p Value
Adverse effect						
Hepatic	9 (1.2)	6 (0.8)	1.198 (0.435–3.298)	0.726	0.650	0.885
GI	31 (4.2)	24 (3.3)	1.124 (0.647–1.949)	0.678	1.692	0.635
Pulmonary	14 (1.9)	5 (0.7)	2.217 (0.929–5.288)	0.073	0.233	0.972
Thyroid	27 (3.7)	3 (0.4)	4.228 (2.044–8.745)	0.001	1.745	0.627
Neurologic	34 (4.6)	14 (1.9)	2.004 (1.085–3.697)	0.026	1.564	0.668
Skin	17 (2.3)	5 (0.7)	2.479 (1.050–6.173)	0.050	4.053	0.256
Eye	11 (1.5)	1 (0.1)	3.425 (1.217–9.639)	0.020	1.527	0.676
Bradycardia	24 (3.3)	10 (1.4)	2.177 (1.111–4.267)	0.024	1.634	0.652
Drug discontinued	169 (22.9)	112 (15.4)	1.602 (1.228–2.088)	0.000	9.906	0.019
			1.522 (1.216–1.906)*	0.003	†	†

*Miettinen estimator OR_{S1}. †Application of the Miettinen estimator does not require homogeneity assumptions (41). CI = confidence interval; GI = gastrointestinal; OR = odds ratio.

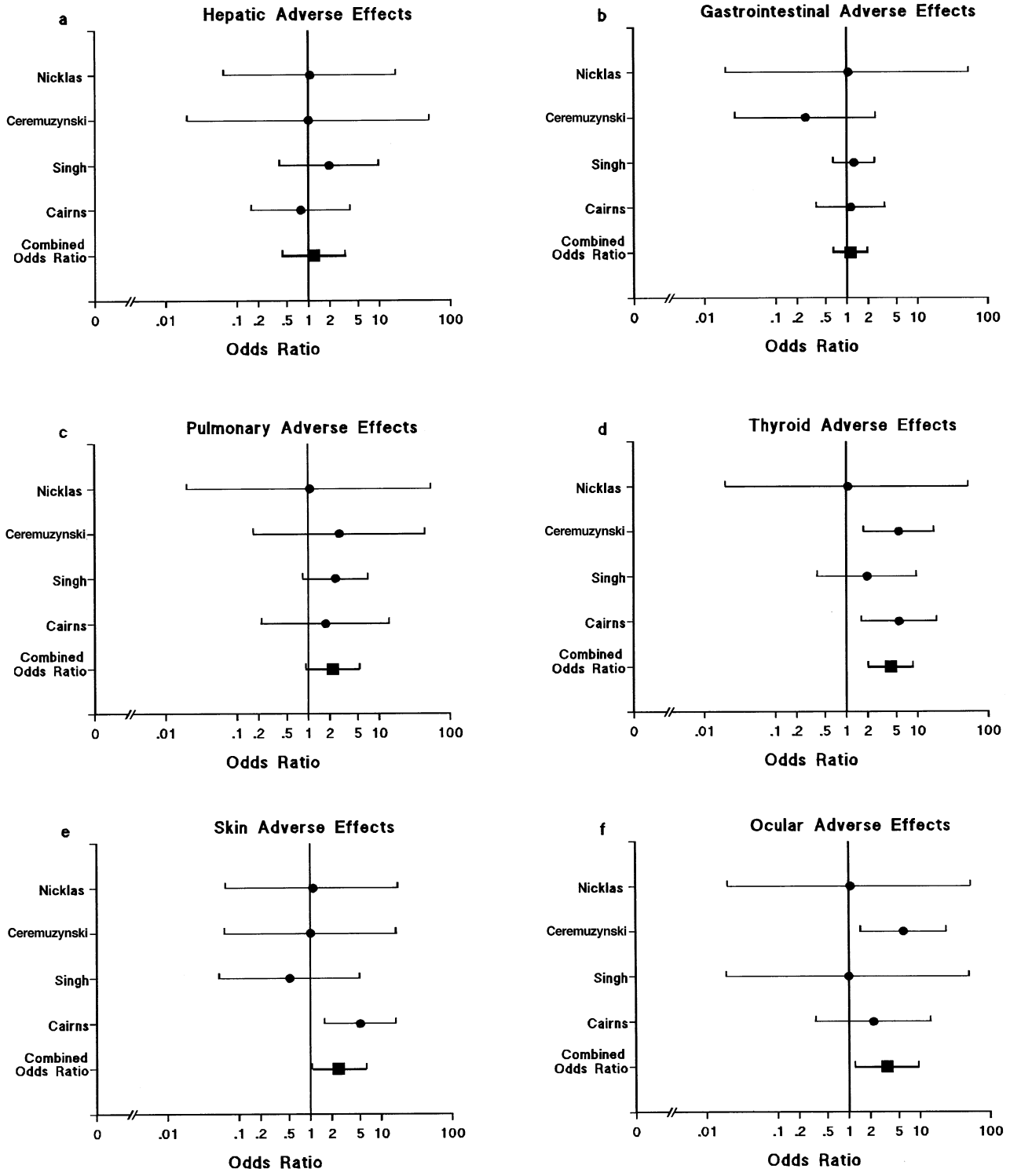

Figure 1. Odds ratio (OR) for adverse effects is shown on a logarithmic scale on the **x axis;** individual trials (identified by the first author) and the combined OR are shown on the **y axis. Horizontal lines** depict the 95% confidence interval. The individual ORs are depicted by **solid circles,** and the combined OR by **solid squares. Vertical lines** depict OR of 1 (equal chance of toxicity of amiodarone vs. placebo). Odds ratios falling to the right imply increased amiodarone toxicity, and those to the left, increased placebo toxicity.

1.2% and 0.8% for hepatic and 4.2% and 3.3% for gastrointestinal sources, respectively.

For pulmonary adverse effects in patients randomized to low dose amiodarone compared with placebo, the calculated combined OR was 2.2 (95% CI 0.9 to 5.3) ($p = 0.073$). This value did not reach statistical significance (Fig. 1c); however, it suggested a trend toward an increase in the odds of pulmonary

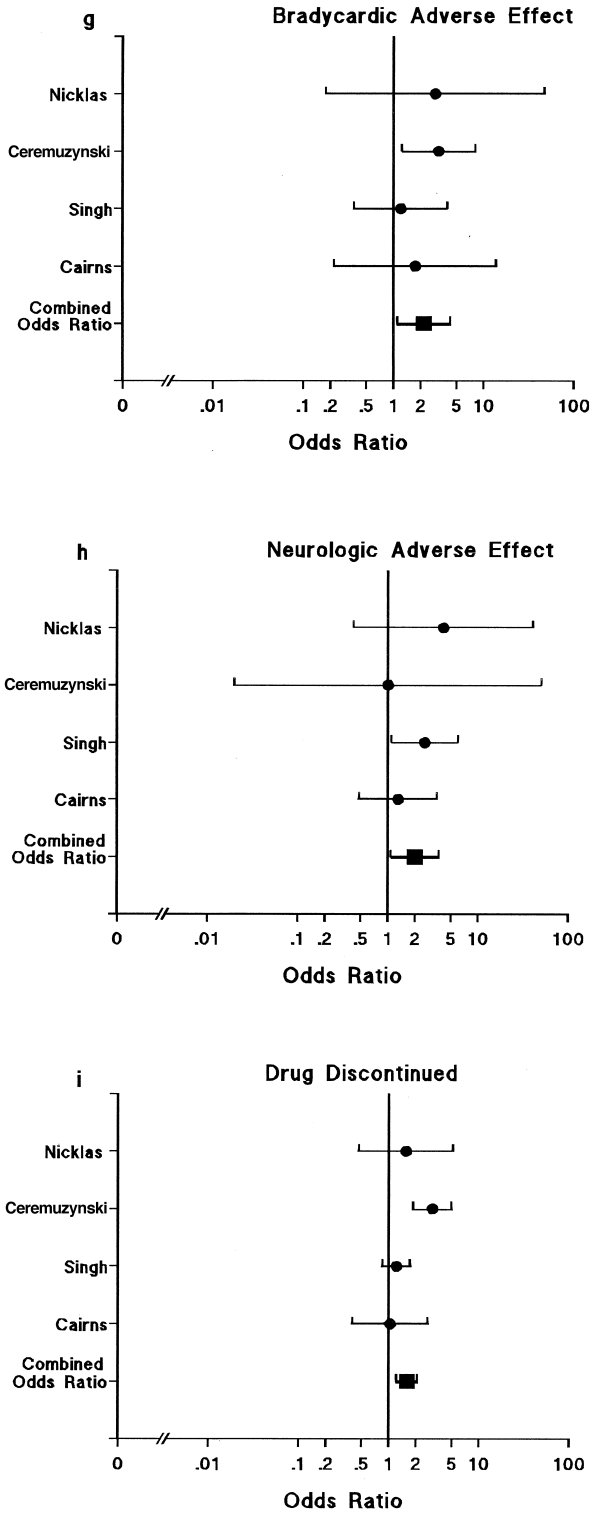

Figure 1. (continued).

toxicity with low dose amiodarone exposure. The unadjusted pooled incidence of pulmonary adverse effect was 1.9% in the amiodarone group and 0.7% in the placebo group.

The odds of experiencing thyroid, neurologic, skin, ocular and bradycardic adverse effects was significantly increased with low dose amiodarone exposure compared with placebo ($p < 0.05$ for each adverse effect). For these adverse effects, the combined mean ORs ranged from 4.2 (thyroid) to 2.0 (neurologic) and the 95% CIs were to the right of the unity line (Fig. 1, d to h). The unadjusted pooled incidence of each of these adverse effects was <5% in the amiodarone group and <2% in the placebo group.

For each adverse effect, the chi-square of heterogeneity was small and statistically insignificant, confirming the absence of a heterogeneity effect on calculated ORs due to interstudy variations in patient group type, trial duration, amiodarone dosage and variable presence of additional adverse effect definition criteria across trials (Table 3); hence, no adjustments to the combined ORs were required.

Drug discontinuation. The odds of drug discontinuation was increased with treatment with low dose amiodarone compared with placebo (Fig. 1i). A significant heterogeneity in the ORs of drug discontinuation was detected across the four trials (chi-square statistic 9.9, $p = 0.019$) (Table 3). Therefore, the combined OR estimate of 1.6 was recalculated by the Miettinen method, which does not require a homogeneity assumption. This yielded a more conservative estimate of the combined OR that demonstrated a statistically significant 1.5-fold increase ($p = 0.003$) in the likelihood of drug discontinuation in patients randomized to low dose amiodarone compared with those randomized to placebo (Table 3). The unadjusted pooled incidence of drug discontinuation was 22.9% in the amiodarone group and 15.4% in the placebo group.

Discussion

In this meta-analysis, we have shown that exposure to amiodarone at relatively low maintenance doses for a minimal duration of 12 months resulted in odds similar to those of placebo of hepatic and gastrointestinal adverse effects, but in significantly higher odds than those of placebo of experiencing thyroid, neurologic, skin, ocular and bradycardic adverse effects. In addition, the odds of discontinuing low dose amiodarone therapy were significantly higher than those of discontinuing placebo. We also observed a trend toward increased odds of pulmonary adverse effects, although this did not reach statistical significance.

Study rationale. Objective assessment of the likelihood of an adverse effect with exposure to a drug is only possible when information on adverse event rates in those exposed to the drug and in those exposed to placebo is available for comparison. A double-blind, placebo-control study design allows for such a comparison of event rates because data on adverse effects are obtainable in both treatment and control groups. Moreover, because of the blinded, randomized design, a selection bias in assignment to treatment or placebo groups is avoided. In this report, a meta-analysis design increased the statistical power of adverse effect likelihood estimates derived from individual double-blind, placebo-controlled, low dose amiodarone drug efficacy trials (44). Pooling of information

from individual trials was considered appropriate because of similarity of trial design and interstudy homogeneity of treatment effect on calculated ORs, despite potential methodologic differences in study duration, amiodarone dosage, patient group and adverse effect definition (37,40). When significant heterogeneity was detected, such as interstudy differences in the odds of drug discontinuation, a stringent statistical estimate of the combined OR, which did not require homogeneity, was calculated (41).

Adverse effects. The likelihood of experiencing gastrointestinal and hepatic adverse effects were not increased significantly by exposure to low dose amiodarone. In previous reports, gastrointestinal symptoms have occurred with high amiodarone doses, and elevations in hepatic enzymes have been correlated with plasma concentrations of amiodarone and its desethyl metabolite (17). The reported incidences of these adverse effects in nonrandomized or uncontrolled low dose amiodarone trials range from 0% for significant elevations in hepatic enzymes to 20% for gastrointestinal symptoms (18,20–22). Our findings, however, suggest that the likelihood of experiencing gastrointestinal and hepatic adverse effects with amiodarone cannot be directly related to the incidence of these adverse effects. Gastrointestinal adverse effects occurred more frequently than other adverse effects, whereas hepatic adverse effects were less frequent (Table 3), yet the weighted ORs of both of these adverse effects were similar (near unity) because of comparable event rates in amiodarone and placebo groups (Fig. 1, a and b).

Compared with placebo treatment, exposure to low dose amiodarone increased the odds of experiencing pulmonary adverse effects by twofold; however, this did not achieve statistical significance. The unadjusted pooled incidence of this adverse effect was low (1.9%), with no resultant fatalities in any of the trials included in this meta-analysis, suggesting reduced severity of this serious adverse effect. An estimate of the odds of pulmonary toxicity in patients treated with low dose amiodarone compared with placebo has not been previously reported in the published data. Although it is generally accepted that amiodarone-induced pulmonary toxicity is a dose-related phenomenon (45,46), there are reports of fatal (23) and nonfatal (12) pulmonary fibrosis in patients exposed to low average daily maintenance doses of amiodarone in uncontrolled trials. It is plausible that if the patient group were larger in the current meta-analysis, the increased odds of pulmonary toxicity with amiodarone versus placebo exposure would have achieved statistical significance.

Exposure to amiodarone at low doses was associated with a fourfold increase in the odds of experiencing clinically evident hyperthyroidism or hypothyroidism or chemical thyroid function abnormalities necessitating treatment (Fig. 1d). The unadjusted pooled incidence of this adverse effect was 3.7% in the amiodarone group and 0.4% in the placebo group (Table 3). Previous uncontrolled studies have suggested that thyroid toxicity can be avoided by lowering the maintenance dosage (20,47). The results of this meta-analysis suggest that a significant increase in the odds of experiencing this adverse effect persists even with the use of low dose amiodarone. These findings are more consistent with earlier European reports by Harris et al. (17), in which thyroid adverse effects could not be related to the daily amiodarone dose.

Neurologic, dermatologic and ocular adverse effects were reported at event rates that were higher in the amiodarone group than in the placebo group; thus, there also was an increase in the odds of experiencing these adverse effects with low dose amiodarone (Fig. 1, e, f and h). The unadjusted pooled incidences of these side effects (Table 3) were similar to those event rates reported in uncontrolled drug trials (19,20).

The odds of experiencing bradycardic adverse effects with amiodarone were significantly higher than with placebo, and the trend toward increased bradycardic adverse effects in the amiodarone group was a consistent finding among all four trials in this meta-analysis (Fig. 1g). Although it is generally regarded as a benign side effect, amiodarone-related bradycardia was implicated in one fatality (42). The severity of this adverse effect may be related to the patient group studied. Elderly patients with structural heart disease may be more predisposed to the bradycardic adverse effect of amiodarone, even when this drug is administered in low mean daily doses.

Although proarrhythmic effects (torsade de pointes) have previously been reported with amiodarone (48), none was reported in patients receiving low dose amiodarone in any of the four trials included in this meta-analysis. It is interesting that three proarrhythmic adverse effects were noted in patients receiving placebo (5).

Drug discontinuation. Significant interstudy differences in the ORs of drug discontinuation were noted. This heterogeneity could be explained by the trial of Ceremuzynski et al. (3), in which the OR of drug discontinuation was displaced to the right compared with that in other trials (Fig. 1i) and in which the 95% CIs did not overlap with those of another trial (43). This may reflect the influence of interstudy differences in drug discontinuation criteria. Asymptomatic bradycardia, first-degree heart block as well as asymptomatic thyroid function abnormalities fulfilled criteria for discontinuing treatment in the Ceremuzynski trial (3), but not in other trials (Table 2) (5,42,43). A lower threshold of discontinuing the drug in a given trial could account for an OR that is significantly different from that in other trials. However, when the combined OR of drug discontinuation was recalculated using a method that did not assume homogeneity among studies (41), the increased likelihood of drug discontinuation, which was 1.5 times that of placebo, remained highly significant (Table 3, last row). The unadjusted pooled incidence of drug discontinuation was 22.9% in patients randomized to low dose amiodarone compared with 15.4% in patients randomized to placebo. Incidences of drug withdrawal reported in other uncontrolled trials (19,20), where amiodarone was administered at low doses, vary widely from 3% (6) to 29% (12). A comparison of drug discontinuation curves for the amiodarone and placebo groups, as a function of trial duration, might have been even more informative; however, primary data in individual trials

included in this meta-analysis were not presented in a time-to-drug withdrawal format.

Study limitations. The patients in the trials we analyzed tended to be older and had congestive heart failure or were postmyocardial infarction; also, women were underrepresented. Side effects of amiodarone also may be different in other patient groups—for example, in younger patients or in patients with atrial fibrillation. Thus, extrapolation of our findings to other clinical settings requires care.

The data provided in the individual trials included in this meta-analysis do not permit the identification of the timing of the appearance of adverse effects in relation to the mean daily drug dose and trial duration. Although this limitation did not interfere with calculation of ORs, such data would have been useful to calculate weighted incidence rates for each adverse effect at specific time intervals after initiation of amiodarone therapy.

Clinical implications. The findings of this meta-analysis indicate that antiarrhythmic drug therapy with low dose amiodarone should not be considered innocuous or free of adverse effects. At the mean daily doses used in the trials we analyzed, amiodarone exposure was associated with an increased likelihood of adverse events compared with placebo in several organ systems, including thyroid, skin, ocular and neurologic. In addition, there was an increased likelihood of bradycardia and drug discontinuation in patients treated with amiodarone. Our results show that pulmonary toxicity, a potentially serious side effect of amiodarone, was not statistically more likely in the drug treatment group. However, there was a trend toward an increase in pulmonary toxicity in patients receiving amiodarone in the patient groups we analyzed. Our findings also show that hepatic and gastrointestinal toxicities are unchanged in patients receiving low dose amiodarone compared with placebo. The likelihood of occurrence of these adverse effects should be taken into account when administering this antiarrhythmic agent in low doses, and appropriate clinical and laboratory tests should be conducted, as necessary, to monitor patients for drug toxicity.

It is of interest to compare our findings with the recently published placebo-controlled, low dose, European Myocardial Infarction Amiodarone Trial (EMIAT) (49) and the Canadian Myocardial Infarction Amiodarone Trial (CAMIAT) (50), both of which were not available when this meta-analysis was performed. Increased adverse effects and drug withdrawal were reported with amiodarone in both of these trials, and in general the organ systems affected were the same as the ones in our meta-analysis. Regarding pulmonary toxicity, the CAMIAT data showed a statistically significant increase with amiodarone treatment, whereas this did not achieve statistical significance in our analysis. Comparison of our findings with adverse effects data from EMIAT is more difficult because statistical interpretation was not provided.

Finally, what drug dose constitutes low dose amiodarone? In recent years, there has been a continuing trend toward administering lower daily doses of amiodarone; thus, the definition of "low dose" is difficult to specify and is likely to change. Furthermore, in different human diseases, this definition may not be the same. Until a sufficient number of large, placebo-controlled, blinded trials enrolling patients assigned to different drug doses for long periods of time are performed, and data are analyzed for both drug efficacy and adverse effects, an exact definition of "low dose" amiodarone is likely to elude us.

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