Meta-Analysis Comparing the Relative Risk of Adverse Events for Amiodarone Versus Placebo

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Amiodarone has been associated with adverse events that may restrict its use. We performed a meta-analysis of placebo-controlled trials to assess the relative risk of adverse events of amiodarone compared with placebo. In total, 43 randomized trials were included. A total of 11,395 patients were included (5,792 patients randomized to amiodarone and 5,603 patients randomized to placebo). The incident rate of adverse events per 10,000 person-years was higher in the amiodarone group compared with placebo for pulmonary (129 vs 74; relative risk (RR) 1.77, p = 0.002), thyroid (201 vs 42; RR 4.44, p <0.001), hepatic (54 vs 25; RR 2.27, p = 0.01), cardiac (771 vs 450; RR 1.94, p <0.001), neurological (140 vs 76; RR 1.93, p <0.001), and skin (81 vs 23; RR 1.99, p = 0.04) adverse events. Low-dose amiodarone was not associated with statistically significant increase in pulmonary adverse events but was still associated with thyroid and liver adverse events. In conclusion, the likelihood of experiencing adverse events related to amiodarone was higher than that of placebo. The overall rate of adverse events however, was low, and severe adverse events were rare. **(Am J Cardiol 2019;124:1889−1893)**

Despite amiodarone's superior efficacy in controlling atrial[1,2] and ventricular[3] arrhythmias compared with other antiarrhythmic drugs, the most recent guidelines[4,5] recommend its use only when other agents have failed or are contraindicated, due to concerns about potential toxicities. Nonetheless, amiodarone-related adverse events have largely been reported using unblinded observational study designs that lack control groups and case reports.[6,7] The purpose of this study is to provide an updated meta-analysis of amiodarone-related adverse events when its use is compared with placebo in randomized controlled trials.

Methods

We searched PubMed, Google Scholar, the Cochrane Central Register for randomized controlled trials, and ClinicalTrials.gov for studies that evaluated amiodarone use irrespective of indication or efficacy of amiodarone therapy. Two authors (MM and MR) independently reviewed all articles for inclusion and independently extracted required information. Criteria for inclusion were (1) randomized controlled trial, (2) documentation of adverse events and drug discontinuation related to adverse events, and (3) presence of placebo arm. The primary outcomes were pulmonary, hepatic, thyroid, ocular, cardiac, skin, neuro, and drug discontinuation related to adverse events.

RevMan version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration; Copenhagen, Denmark) was used to perform the primary analysis. Relative risk (RR) was calculated for all studies using Mantel-Haenszel random effects model with 95% confidence interval (CI). A 2-sided p value of <0.05 was considered to be statistically significant.

Results

Our search identified 10,348 studies, of which 43 full texts met inclusion criteria, Figure 1. A total of 11,395 patients were included (5,792 patients randomized to amiodarone and 5,603 patients randomized to placebo). The mean (range) of follow-up time was 24.5 (12 to 54 months) in studies with follow-up ≥12 months and 1.3 months (1 week to 6 months) for studies with follow-up <12 months. Amiodarone maintenance dose ranged from 200 to 600 mg daily.

The incident rate per 10,000 person-years of pulmonary adverse events was higher in patients receiving amiodarone compared with placebo (129 vs 74; RR 1.77; 95% CI [1.24 to 2.52], p = 0.002, 1^2 0%; Figure 2). Most (98%) amiodarone-related pulmonary adverse events occurred in studies with follow-up ≥12 months. Surprisingly, confirmed cases of pulmonary fibrosis occurred at similar rates in the amiodarone and placebo groups, 12 and 11 per 10,000 person-years, respectively. All cases of pulmonary fibrosis appeared in trials where patients received a maintenance dose of 300 mg per day or more of amiodarone.

The incident rate per 10,000 person-years of thyroid adverse events was higher in the amiodarone group compared with placebo (201 vs 42; RR 4.44; 95% CI [2.87 to 6.89], p <0.001, 1^2 0%; Figure 2). The RR of developing

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See page 1893 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.09.008

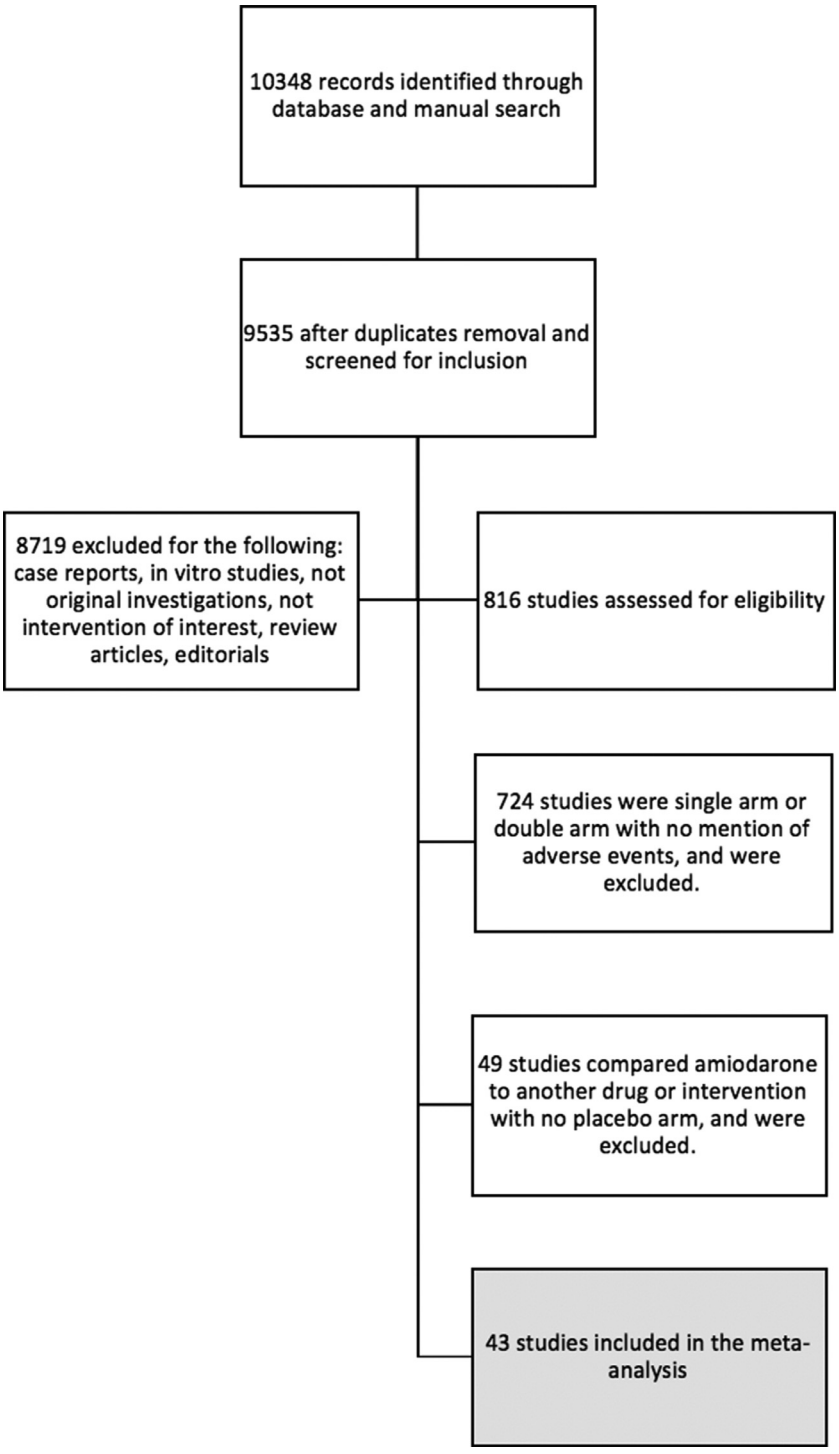

Figure 1. PRISMA diagram showing search strategy results.

thyroid adverse events was higher in studies with follow-up ≥12 months (RR 5.32; 95% CI [2.99 to 9.44], p <0.001, I^2 0%) compared with studies with follow-up <12 months (RR 3.17; 95% CI [1.40 to 7.16], p = 0.005, I^2 16%). In the amiodarone group, clinical (defined as symptomatic or requiring treatment) hypothyroidism developed more frequently than clinical hyperthyroidism, 47 versus 33 per 10,000 person-years, respectively.

The overall incident rate per 10,000 person-years of liver adverse events was rare but still higher in the amiodarone group compared with placebo (54 vs 25; RR 2.27; 95% CI [1.20 to 4.29], p = 0.01, I^2 0%; Figure 2). The RR of hepatic adverse events in studies with follow-up <12 months was not statistically different between amiodarone and placebo (RR 1.31; 95% CI [0.16 to 10.97], p = 0.80, I^2 18%). No cases of liver failure or cirrhosis were reported.

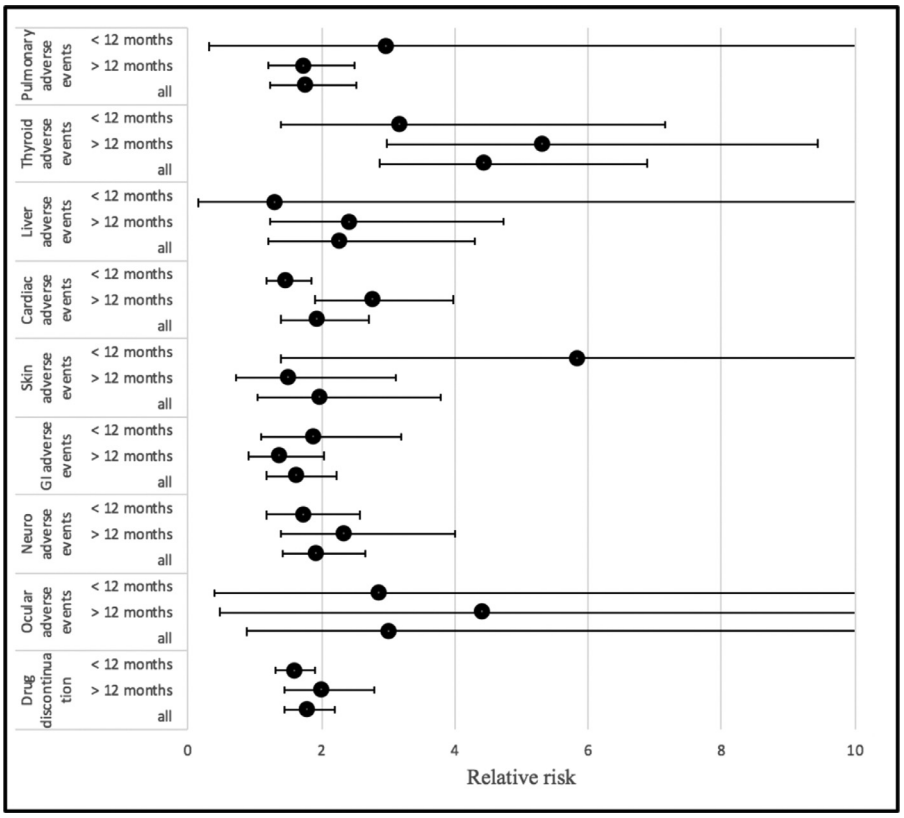

Figure 2. Relative risk for adverse events over time.

Cardiac adverse events were the most common reported adverse events in both the amiodarone and placebo groups. The incident rate per 10,000 person-years of cardiac adverse events was higher in the amiodarone group compared with placebo (771 vs 450; RR 1.94; 95% CI [1.39 to 2.71], p <0.001, I^2 23%; Figure 2). The RR of developing cardiac adverse events was higher in studies with follow-up ≥12 months (RR 2.76; 95% CI [1.91 to 3.98], p <0.001, I^2 0%) compared with studies with follow-up <12 months (RR 1.47; 95% CI [1.17 to 1.85], p <0.001, I^2 0%). The most common amiodarone-related cardiac adverse events reported were bradyarrhythmias and hypotension with an incident rate of 468 and 172 per 10,000 person-years, respectively. Hypotension was only reported in studies with follow-up <12 months. The incident rate of QTc prolongation that necessitated amiodarone discontinuation was 36 per 10,000 person-years. Nonetheless, no cases of torsades de pointes were reported.

The incident rate per 10,000 person-years of skin adverse events was significantly higher in the amiodarone group compared with placebo (81 vs 23; RR 1.99; 95% CI [1.04 to 3.78], p = 0.04, I^2 0%; Figure 2). This was driven by photosensitivity and skin rash. Unexpectedly, the classical blue/gray skin discoloration appeared at similar rate in the amiodarone and placebo groups, 4 versus 6 events per 10,000 person-years, respectively.

The incident rate per 10,000 person-years of gastrointestinal (GI) adverse events occurred more significantly in the amiodarone group (336 vs 212; RR 1.63; 95% CI [1.18 to 2.24], p = 0.003, I^2 14%; Figure 2). The RR of amiodarone-related GI adverse events was higher in studies with follow-up <12 months, Figure 2. The RR of incident rates for GI adverse events in studies with follow-up ≥12 months was not statistically significant between the amiodarone and the placebo groups (105 vs 86; RR 1.36; 95% CI [0.91 to 2.04], p = 0.14, I^2 0%).

The incident rate per 100,000 person-years of neurological adverse events was higher in the amiodarone group compared with placebo (140 vs 76; RR 1.93; 95% CI [1.41 to 2.65], p <0.001, 1^2 0%; Figure 2).

The incident rate per 10,000 person-years of ocular adverse events was higher in the amiodarone group compared with placebo, however, this did not reach statistical significance (37 vs 10; RR 3.01; 95% CI [0.87 to 10.36], p = 0.08, I^2 30%; Figure 2).

The incident rate per 10,000 person-years of drug discontinuation secondary to side effects was significantly higher in the amiodarone group compared with placebo (1,614 vs 896; RR 1.79; 95% CI [1.45 to 2.19], p <0.001, I^2 43%; Figure 2). When limiting the analysis to studies with follow-up ≥12 months, there was moderate heterogeneity and the difference was still significant (1,230 vs 650; RR 2.01; 95% CI [1.46 to 2.78], p <0.001, I^2 66%).

For studies with follow-up ≥12 months, when limiting the analysis to studies that had a maintenance dose of 200 mg per day of amiodarone, the incident rate per 10,000 person-years of pulmonary adverse events was similar between amiodarone and placebo (213 vs 174; RR 1.30; 95% CI [0.81 to 2.08], p = 0.27). Bradyarrhythmias incident rate per 10,000 person-years was still significantly higher in

the amiodarone group (125 vs 6; RR 6.58; 95% CI [2.15 to 20.11], p = 0.001, I^2 0%). Similarly, the RR of liver and thyroid adverse events remained to be statistically significant higher in the amiodarone group compared with placebo, Figure 3.

Discussion

In this meta-analysis, amiodarone use was associated with statistically significant higher RR of developing pulmonary, cardiac, thyroid, hepatic, skin, neurological, and ocular adverse events and higher rates of drug discontinuation when compared with placebo.

The likelihood of experiencing pulmonary adverse events was significantly higher in the amiodarone group compared with placebo. Nonetheless, pulmonary fibrosis occurred at similar incident rates in the amiodarone and placebo groups. Furthermore, when limiting the analysis to studies that used an amiodarone dose of 200 mg per day, the likelihood of pulmonary adverse events was not statistically different between the amiodarone and the placebo groups. This suggests a dose-dependent mechanism which is consistent with previous reports.[8] The RR of hepatic and GI adverse events were higher in the amiodarone group. However, no serious liver or GI adverse events were noted, and no cases of liver failure or liver cirrhosis were reported. Amiodarone-related GI adverse events were more frequent in studies with follow-up <12 months, suggesting a potential loading dose phenomenon. The RR of cardiac adverse events was higher in the amiodarone group and this increased overtime. Bradyarrhythmias occurred at significantly higher incident rates in the amiodarone group compared with placebo. Of note, hypotension events were only described in studies with <12 months of follow-up, suggesting a potential loading dose effect. Neurological, ocular, and skin adverse events were higher in the amiodarone group and occurred at similar rates compared with previous reports.

This meta-analysis is the most comprehensive review of amiodarone adverse effects using data from randomized controlled trials. The strengths of this analysis are its inclusion of more contemporary studies and the use of only randomized controlled trials. The latter point is important because objective assessment of adverse events from a drug is best assessed when information on adverse events is available for patients receiving the drug and those receiving placebo. Data derived from claims and registries lack control groups and should not be used as a gold standard for determining adverse event rates of a drug.

The observation that low-dose (200 mg per day) amiodarone lowers the RR of developing serious pulmonary but not liver or thyroid adverse events suggests that amiodarone may not follow the same rule as some other drugs—toxicity is dose dependent. This finding challenges the notion of idiosyncratic amiodarone toxicity and may warrant future pragmatic studies of the use of amiodarone drug levels for improving safety and efficacy. Cumulative drug dose is only a good surrogate for exposure until steady state is achieved.[9,10]

The authors recognize several limitations in regards to this study. The patients analyzed in this study were relatively old (average age 62 years), and the side effects might be different for younger patients. Most studies excluded patients who had underlying lung, thyroid, and liver conditions, and the rate of amiodarone adverse events in these patients is unknown. Amiodarone can increase the risk of bleeding especially due its interaction with Warfarin. Nonetheless, the bleeding complications were not explicitly reported in most trials. Lastly, the authors recognize that there may be adverse events that were not captured by these trials due to short follow-up.

In conclusion, the likelihood of experiencing adverse events related to amiodarone was higher than that of

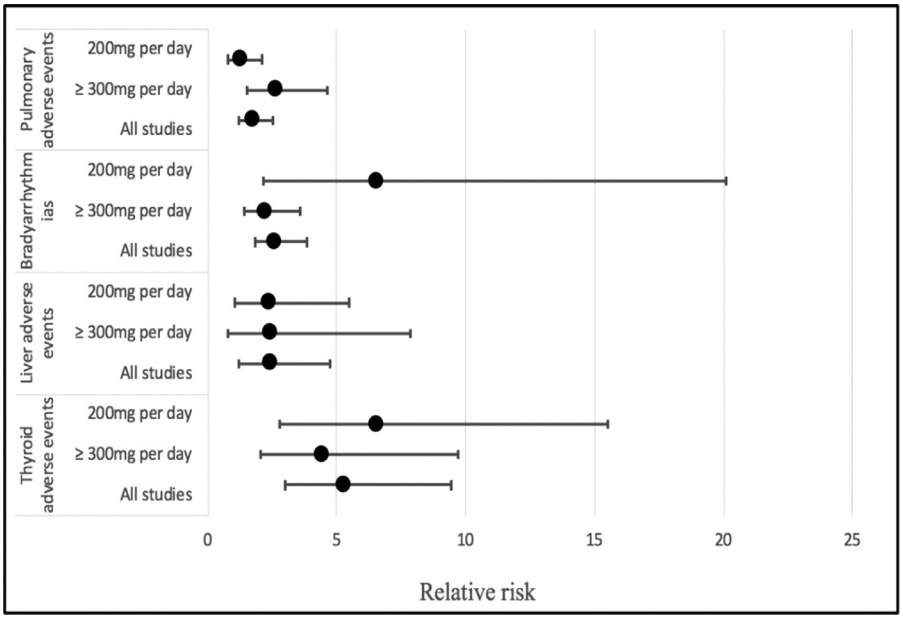

Figure 3. Relative risk of adverse events for different amiodarone doses.

placebo. However, the overall rate of adverse events was low and severe adverse events were rare when amiodarone was used with proper monitoring.

Disclosures

The authors have no conflicts of interest to disclose.

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