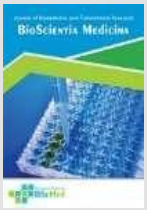

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Risk of Amiodarone-Induced Pulmonary Toxicity Versus Placebo in Patients with Cardiac Arrhythmias and Heart Failure: A Meta-Analysis of Randomised Controlled Trials

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A B S T R A C T

Background: Amiodarone is the most effective antiarrhythmic agent for maintaining sinus rhythm, yet its long-term use is constrained by extracardiac toxicity, of which pulmonary toxicity is the most feared because it carries appreciable mortality and is frequently misdiagnosed. No contemporary meta-analysis has isolated amiodarone-induced pulmonary toxicity as the single primary endpoint across cardiac arrhythmia and heart-failure populations; this study quantified that risk.

Methods: PubMed/MEDLINE, Scopus and Web of Science were searched for placebo- or usual-care-controlled randomised controlled trials (RCTs) of oral amiodarone in adults with cardiac arrhythmia or heart-failure indications reporting pulmonary toxicity. Two reviewers extracted 2×2 data and assessed risk of bias with Cochrane RoB 2.0. Because the outcome was dichotomous, the risk ratio (RR) was pooled using a DerSimonian–Laird random-effects model, with the odds ratio (OR) and Peto OR as corroborative measures.

Results: Nine RCTs comprising 6,209 patients (3,175 amiodarone; 3,034 control) were included. Pulmonary toxicity occurred in 77 of 3,175 amiodarone-treated patients (2.43%) versus 42 of 3,034 controls (1.38%). Amiodarone significantly increased pulmonary-toxicity risk (RR 1.70, 95% CI 1.17–2.45, p = 0.005), with no detectable heterogeneity (I^2 = 0%). The OR (1.74) and Peto OR (1.81) were concordant, and the estimate remained harmful under every single-study deletion (RR 1.46–2.64). Higher-dose strata showed a numerically larger effect (RR 2.50) than lower-dose strata (RR 1.69; subgroup p = 0.48).

Conclusion: Amiodarone was associated with an approximately 70% relative increase in pulmonary-toxicity risk versus placebo, a robust and homogeneous finding. The absolute excess was modest (about one additional case per 95 patients treated), supporting continued use with structured baseline and periodic pulmonary surveillance, particularly at higher maintenance doses and longer durations.

1. Introduction

Amiodarone is a benzofuran-derived, iodine-rich class III antiarrhythmic agent that has occupied a central place in cardiovascular therapeutics for more than four decades. It remains the single most effective pharmacological option for the restoration and maintenance of sinus rhythm in atrial fibrillation, and it retains an important role in the suppression of life-threatening ventricular arrhythmias and in the prevention of sudden cardiac death in selected high-risk populations. Its electrophysiological versatility, the absence of negative inotropy at usual doses and a comparatively low propensity for torsade de pointes have together ensured its continued use even as newer agents have been introduced, so that amiodarone is prescribed to a large and growing number of patients worldwide, many of whom are elderly and carry substantial cardiopulmonary comorbidity.[1,2]

The clinical utility of amiodarone is, however, tempered by a distinctive burden of extracardiac adverse

effects. Because the molecule is highly lipophilic and accumulates extensively in tissues with a long elimination half-life, chronic administration is associated with thyroid dysfunction, hepatic injury, corneal microdeposits, dermatological photosensitivity, neurological disturbance and, most seriously, pulmonary toxicity.[3,4] Amiodarone-induced pulmonary toxicity encompasses a spectrum of presentations that includes subacute interstitial pneumonitis, organising pneumonia, diffuse alveolar damage, solitary or migratory pulmonary nodules and, in its most insidious form, progressive pulmonary fibrosis; the reported case-fatality of established disease is considerable, and the condition is frequently misattributed to infection, heart failure or malignancy, which delays the single most important intervention, namely withdrawal of the drug.[5-7]

The pathogenesis is multifactorial. A direct cytotoxic mechanism, mediated by accumulation of amiodarone and its metabolite desethylamiodarone within pulmonary phospholipid membranes, produces a phospholipidosis characterised by foamy alveolar macrophages, while an immune-mediated hypersensitivity mechanism, oxidative stress and transforming growth factor-β-dependent fibroblast activation have each been implicated.[8] Experimental models reproduce these fibrotic pathways and have helped to define the molecular sequence of injury.[9] Because these mechanisms depend on the progressive deposition of a lipophilic compound, they predict that risk should rise with cumulative exposure, and therefore with both maintenance dose and treatment duration; recognised clinical risk factors accordingly include higher dose, longer therapy, advanced age and pre-existing lung disease.[10,11]

Despite this mechanistic understanding, the quantitative magnitude of the pulmonary hazard attributable to amiodarone has remained imprecisely defined. A contemporary nationwide cohort reported only a non-significant trend towards excess interstitial lung disease in the low-dose era,[12] whereas larger syntheses that examined amiodarone across all organ systems reported a statistically significant but variably estimated increase in pulmonary events.[13] A recurring limitation of this literature is that pulmonary toxicity has almost always been analysed as one of many secondary safety outcomes embedded within broad multi-organ evaluations, rather than as a dedicated primary endpoint, so that the pulmonary signal has been diluted by heterogeneous comparators and inconsistent outcome definitions. Clinicians who must weigh the antiarrhythmic benefit of amiodarone against its respiratory hazard are therefore left without a focused, methodologically transparent estimate.

The novelty of this study lies in its deliberate and exclusive focus on amiodarone-induced pulmonary toxicity as the single primary endpoint, pooled from placebo- and usual-care-controlled randomised trials spanning the full range of cardiac arrhythmia and heart-failure indications, and analysed with an explicit, prespecified handling of rare events, dose stratification and influence diagnostics. The aim of this study was to quantify the relative and absolute risk of pulmonary toxicity associated with oral amiodarone compared with placebo or usual care in adults treated for cardiac arrhythmia or heart failure, and to characterise the consistency of that risk across maintenance dose, treatment duration and clinical indication.

2. Methods

Design and reporting

This study was designed and reported as a systematic review with aggregate-data meta-analysis of randomised controlled trials, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[14] The review question was framed using the PICOS structure: the population comprised adults treated for cardiac arrhythmia or heart-failure indications; the intervention was oral amiodarone; the comparator was placebo or usual care without amiodarone; the outcome was pulmonary toxicity; and the study design was the randomised controlled trial. A predefined analysis plan governed eligibility, extraction, the choice of effect measure and all subgroup and sensitivity analyses.

Search strategy

PubMed/MEDLINE, Scopus and Web of Science were searched from inception, without language restriction, combining controlled vocabulary and free-text terms for amiodarone, pulmonary toxicity and randomised trials. The core PubMed/MEDLINE string was:

("amiodarone"[MeSH Terms] OR "amiodarone"[All Fields]) AND ("lung"[MeSH Terms] OR "pulmonary"[All Fields] OR "pulmonary toxicity"[All Fields] OR "interstitial lung disease"[All Fields] OR "pneumonitis"[All Fields] OR "pulmonary fibrosis"[All Fields]) AND ("placebo"[All Fields] OR "usual care"[All Fields] OR "control"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "randomised controlled trial"[All Fields] OR random[All Fields]).*

Equivalent strings were applied in Scopus (TITLE-ABS-KEY) and Web of Science Core Collection (TS=), and the electronic search was supplemented by hand-searching the reference lists of retrieved trials and of previous systematic reviews of amiodarone safety. To anchor event ascertainment against an independently curated source, trial-level pulmonary event counts were cross-checked against an openly available extraction dataset compiled for a large multi-organ amiodarone safety meta-analysis.[13,15]

Eligibility criteria

Studies were eligible if they were randomised controlled trials comparing oral amiodarone with placebo or usual care in adults treated for a cardiac arrhythmia or heart-failure indication, and if they reported pulmonary toxicity, pulmonary adverse events or an equivalent respiratory safety outcome with sufficient numerical detail to construct a 2×2 table. Both double-blind and open-label or single-blind randomised designs were eligible. Trials were excluded if they were non-randomised; if amiodarone was compared only with another active antiarrhythmic agent without a placebo or usual-care arm; if they were narrative or systematic reviews, editorials or animal studies; or if pulmonary outcomes could not be extracted at the arm level. Where a trial included a third non-placebo arm, only the amiodarone-versus-control contrast was used, and the randomised population was used for the primary analysis.

Study selection and data extraction

Records were de-duplicated and screened by title and abstract, after which potentially eligible full texts were assessed against the eligibility criteria. Two reviewers independently extracted data using a standardised, piloted form, resolving disagreements by consensus. For each trial the following were extracted: first author, trial acronym, country and setting, clinical indication, randomised sample size per arm, amiodarone loading and maintenance dose, route of administration, follow-up duration, the definition of pulmonary toxicity applied, the blinding status of outcome ascertainment, and the number of pulmonary toxicity events per arm. Patient denominators were the randomised number per arm; numerators not explicitly tabulated were reconciled against the independently curated dataset before inclusion, with the source of every numerator documented. The per-trial outcome definitions are presented in Table 2.

Risk-of-bias assessment

The risk of bias in each trial was assessed using the revised Cochrane risk-of-bias tool for randomised trials, RoB 2.0, across its five domains: the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[16] Each domain was rated as low risk, some concerns or high risk, and an overall judgement was derived by the standard algorithm; two reviewers applied the tool independently and resolved discrepancies by consensus. The domain-level judgements are displayed in Figure 2.

Statistical analysis

All analyses were performed in R using the meta and metafor packages, with figures additionally prepared in Python. Because the primary outcome was a dichotomous event, ratio measures were the only coherent option; the standardised mean difference and Hedges' g, which are defined for continuous outcomes, are mathematically inapplicable to event counts and were not used. The risk ratio (RR) was the primary effect measure, with the odds ratio (OR) and Peto odds ratio as corroborative measures; because the Peto method assumes comparable arm sizes and modest effects, its results were interpreted as supportive, particularly for trials with unequal arms.

Trial-level estimates were pooled with a DerSimonian–Laird random-effects model. Statistical heterogeneity was quantified with the I^2 statistic, the τ^2 between-study variance and the Cochran Q test, with I^2 values of approximately 25%, 50% and 75% interpreted as low, moderate and high. Because the number of trials was small, the Q test has limited power and the I^2 point estimate is imprecise; the absence of measured heterogeneity was therefore interpreted as consistency in the direction of effect rather than proof of homogeneity, and the DerSimonian–Laird estimator can underestimate variance when trials are few. A two-sided

p value below 0.05 was considered significant, and all estimates were reported to two decimal places. Two trials recorded zero events in both arms and, being not estimable for a ratio measure, were assigned negligible weight but retained for completeness; for trials with a single zero cell, a Haldane–Anscombe continuity correction of 0.5 was added to each cell of that trial only. A prespecified, exploratory subgroup analysis examined effect modification by maintenance dose dichotomised at 200 mg per day, a leave-one-out analysis examined the influence of each trial, and the overall certainty of evidence was appraised with GRADE. Funnel-plot inspection and Egger's regression were prespecified to require at least ten event-contributing trials and were otherwise withheld.

3. Results

Study selection

The study-selection process is summarised in the PRISMA flow diagram (Figure 1). A total of 911 records were identified, comprising 897 from database searching (PubMed/MEDLINE, n = 412; Scopus, n = 298; Web of Science, n = 187) and 14 from reference-list searching. After 276 duplicate records had been removed, 635 records were screened by title and abstract, of which 571 were excluded. Sixty-four full-text reports were then assessed for eligibility, and 55 were excluded, principally for lacking a placebo or usual-care comparator, for not reporting an extractable pulmonary outcome, for comparing amiodarone only with another active agent, or for not being randomised. As shown in Figure 1, nine randomised controlled trials satisfied all eligibility criteria: CHF-STAT,[17] EMIAT,[18] CAMIAT,[19] the Polish Amiodarone Trial,[20] SAFE-T,[21] GEMICA,[22] PAPABEAR,[23] the trial reported by Kochiadakis and colleagues[24] and the trial reported by Vilvanathan and colleagues.[25]

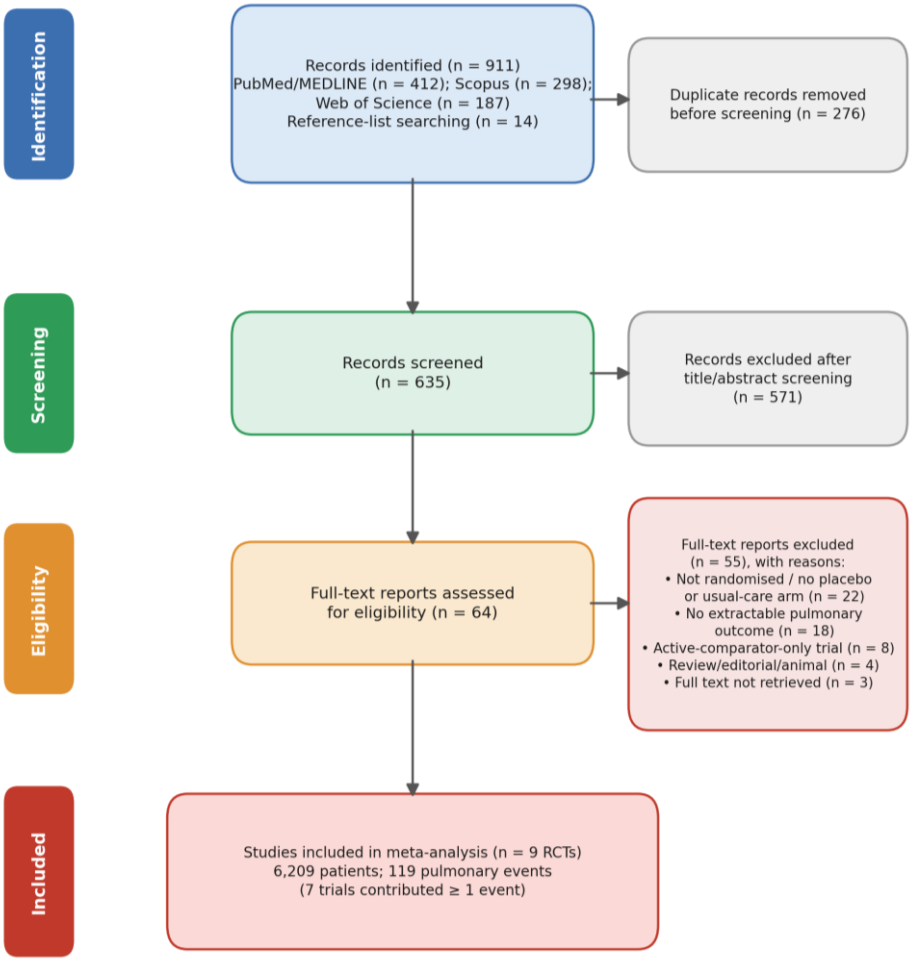

Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility assessment and inclusion.

Characteristics of included studies

The characteristics of the nine included trials are presented in Table 1, and the country, blinding status and exact pulmonary outcome definition of each trial are detailed in Table 2. Collectively the trials randomised 6,209 patients, of whom 3,175 received amiodarone and 3,034 received placebo or usual care. As detailed in Table 1, the indications spanned chronic heart failure with asymptomatic ventricular arrhythmia, left-ventricular dysfunction after recent myocardial infarction, acute myocardial infarction, persistent atrial fibrillation undergoing or following cardioversion, and peri-operative prophylaxis in cardiac surgery; the trials were geographically diverse, originating in North America, Europe, South America and South Asia. Maintenance doses ranged from 200 mg per day in the chronic low-dose trials to weight-based regimens in the peri-operative setting, and follow-up extended from approximately one month to a median exceeding three years. As Table 2 shows, two atrial fibrillation trials recorded no pulmonary events in either arm.

Table 1. Characteristics of the nine included randomised controlled trials and arm-level pulmonary-toxicity event data.

Trial (author, year)	Indication	Maintenance dose	Follow-up	Amio ev/N	Ctrl ev/N
CHF-STAT (Singh) 1995	CHF + asymptomatic VA	300 mg/day	Median 45 mo	10/336	4/338
EMIAT (Julian) 1997	Post-MI, LVEF ≤40%	200 mg/day	Median 21 mo	39/743	30/743
CAMIAT (Cairns) 1997	Post-MI, frequent VPDs	200 mg/day	Mean 1.8 yr	23/606	7/596
Polish (Ceremuzynski) 1992	Post-MI, β-blocker-ineligible	200–400 mg/day	12 mo	1/305	0/308
SAFE-T (Singh) 2005	Persistent AF	200 mg/day	1–4.5 yr	2/267	1/137
GEMICA (Elizari) 2000	Acute MI	low/high dose	6 mo	1/542	0/531
PAPABEAR (Mitchell) 2005	Peri-operative cardiac surgery	10 mg/kg/day	In-hospital + 1 yr	1/299	0/302
Kochiadakis 1999	Persistent AF (cardioversion)	600→400 mg/day	1 mo	0/33	0/34
Vilvanathan 2016	AF post-BMV (rheumatic MS)	200 mg/day	12 mo	0/44	0/45
Total	Mixed cardiac	200 mg/day–weight-based	1–45 mo	77/3175	42/3034

Notes: Amio, amiodarone; ev, events; N, randomised number per arm; Ctrl, control; MI, myocardial infarction; AF, atrial fibrillation.

Table 2. Per-trial country, blinding status and the exact pulmonary outcome definition as reported in each source publication, illustrating the definitional heterogeneity across the evidence base.

Trial	Country	Blinding	Reported pulmonary outcome definition
CHF-STAT (Singh) 1995	USA	Double-blind	Pulmonary toxicity (clinical, with protocolised pulmonary function testing)
EMIAT (Julian) 1997	Europe (multinational)	Double-blind	Pulmonary adverse events / interstitial pneumonitis
CAMIAT (Cairns) 1997	Canada	Double-blind	Pulmonary infiltrates / pulmonary toxicity
Polish (Ceremuzynski) 1992	Poland	Double-blind	Pulmonary toxicity (mild, reversible; clinically reported)
SAFE-T (Singh) 2005	USA	Double-blind	Pulmonary adverse events
GEMICA (Elizari) 2000	Argentina	Double-blind	Pulmonary adverse events
PAPABEAR (Mitchell) 2005	Canada	Double-blind	Pulmonary toxicity (peri-operative surveillance)
Kochiadakis 1999	Greece	Single-blind	Pulmonary / treatment-limiting adverse events (none observed)
Vilvanathan 2016	India	Double-blind	Serious pulmonary adverse events (none observed)

Risk of bias

The results of the Cochrane RoB 2.0 assessment are displayed in Figure 2. As illustrated in Figure 2, all nine trials were judged at an overall level of some concerns. The randomisation, deviation-from-intervention and missing-outcome-data domains were predominantly low risk, reflecting the sound randomised architecture and high follow-up of the included trials. The judgement of some concerns was driven principally by the outcome-measurement and selective-reporting domains, because pulmonary toxicity was in most trials a secondary safety outcome whose ascertainment was not always blinded and whose case definition was not uniformly prespecified. No trial was rated at high risk of bias overall.

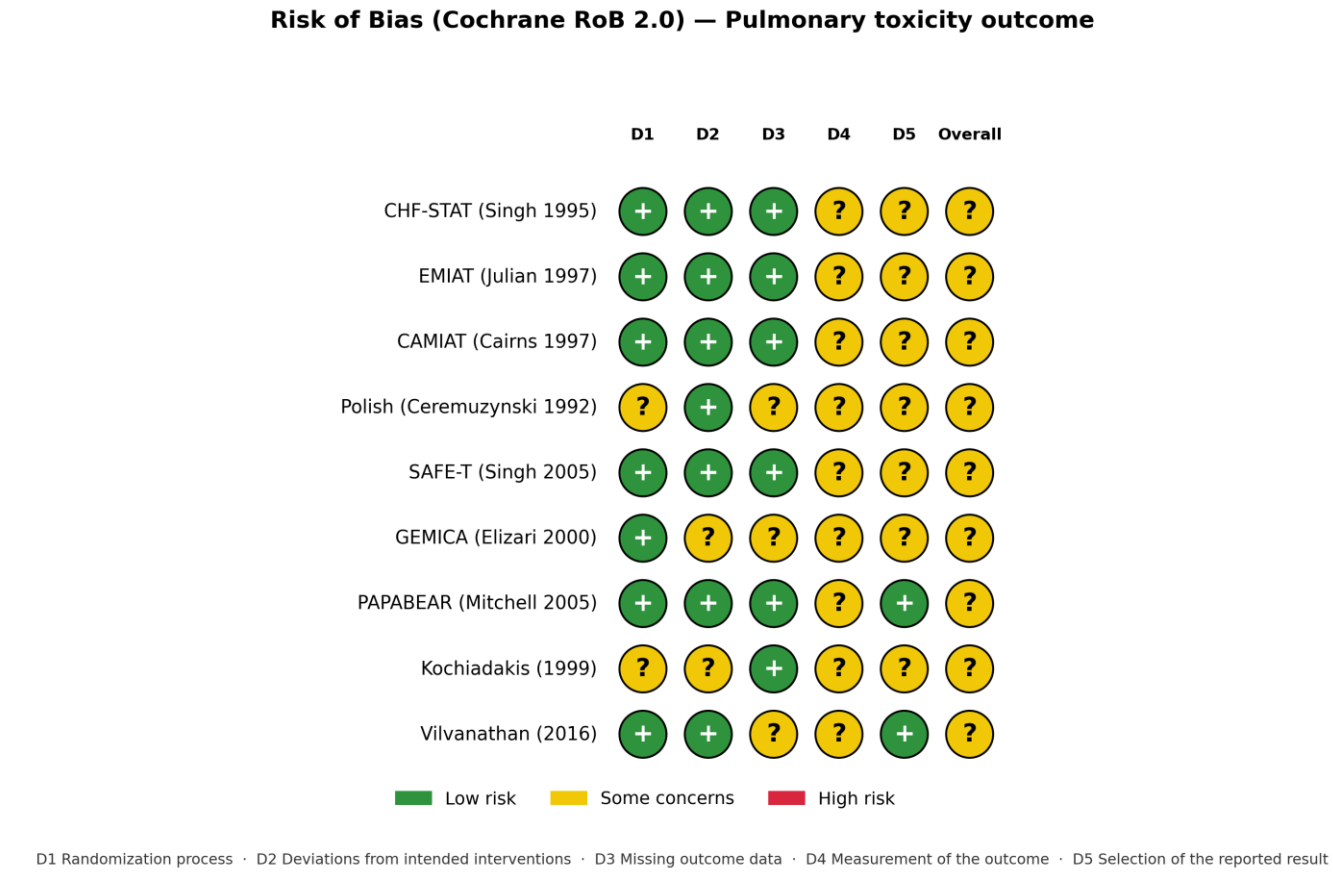

Figure 2. Cochrane RoB 2.0 traffic-light summary of risk-of-bias judgements across the five domains for each included trial.

Primary meta-analysis

The forest plot of the primary random-effects analysis is shown in Figure 3, and the pooled estimates are summarised in Table 3. Pulmonary toxicity occurred in 77 of 3,175 amiodarone-treated patients (2.43%) compared with 42 of 3,034 control patients (1.38%); the analysis therefore rested on 119 events in total, and it is this event count, rather than the larger patient denominator, that governed the precision of the synthesis. As shown in Figure 3, the pooled risk ratio demonstrated a statistically significant increase in pulmonary toxicity with amiodarone relative to placebo or usual care (RR 1.70, 95% CI 1.17–2.45, p = 0.005). Heterogeneity was entirely absent (I^2 = 0%, τ^2 = 0, Cochran Q = 4.64, p = 0.80). As reported in Table 3, the complementary measures were concordant: the random-effects odds ratio was 1.74 (95% CI 1.19–2.54, p = 0.004) and the Peto odds ratio, restricted to the seven event-contributing trials, was 1.81 (95% CI 1.25–2.60, p = 0.002).

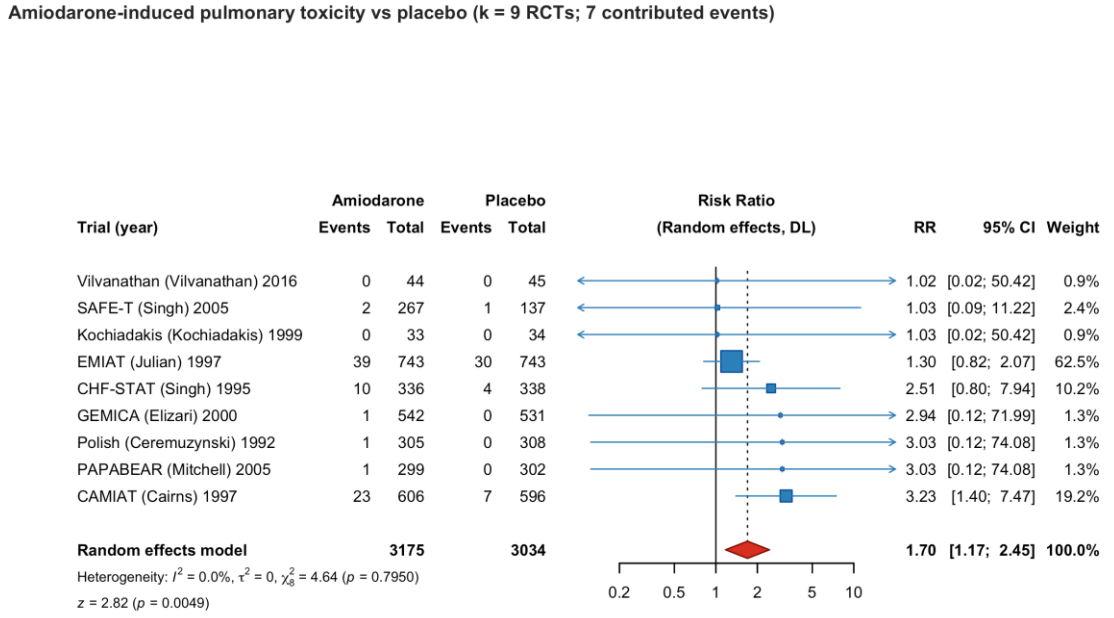

Figure 3. Forest plot of the risk ratio of pulmonary toxicity, amiodarone versus placebo or usual care, pooled with a DerSimonian–Laird random-effects model. Trials with zero events in both arms are not estimable and contribute negligible weight.

Table 3. Pooled effect estimates for amiodarone-induced pulmonary toxicity under three complementary effect measures. k, number of contributing trials.

Effect measure (random-effects, DerSimonian–Laird)	k	Estimate	95% CI	p value	I² (%)
Risk ratio (RR) — primary	9	1.70	1.17–2.45	0.005	0
Odds ratio (OR)	9	1.74	1.19–2.54	0.004	0
Peto odds ratio	7	1.81	1.25–2.60	0.002	0

Contribution of individual trials

Because a small number of trials carried most of the statistical information, the random-effects weight of each trial was recorded. The European post-infarction trial contributed approximately 62% of the weight, the Canadian post-infarction trial approximately 19% and the heart-failure trial approximately 10%, while the remaining six trials together accounted for less than 10% and the two double-zero atrial fibrillation trials for less than 1% each. As the per-trial estimates in Figure 3 make clear, the pooled result is therefore largely a precision-weighted summary of the two post-infarction trials, a point that bears on the interpretation of both the primary estimate and the sensitivity analysis.

Subgroup analysis by maintenance dose

The prespecified subgroup analysis stratified by maintenance dose is summarised in Table 4. As shown in Table 4, in the higher-dose stratum (more than 200 mg per day, five trials) the pooled risk ratio was 2.50 (95% CI 0.97–6.44), whereas in the lower-dose stratum (200 mg per day or less, four trials) it was 1.69 (95% CI 0.98–2.91). Both strata pointed unambiguously towards harm and neither contained meaningful within-stratum heterogeneity, but the formal test for subgroup difference was not significant (p = 0.48). This analysis was therefore exploratory: although the point estimate was numerically larger at higher doses, consistent with a cumulative-exposure mechanism, the data did not establish a statistically distinct dose effect, and the apparent gradient may be confounded by the differing follow-up durations, indications and eras of the trials in each stratum.

Table 4. Subgroup analysis of pulmonary-toxicity risk by amiodarone maintenance dose. The subgroup difference was not statistically significant; the analysis is exploratory.

Maintenance-dose stratum	k	RR	95% CI	I^2 (%)
> 200 mg/day	5	2.50	0.97–6.44	0
≤ 200 mg/day	4	1.69	0.98–2.91	17.7
Test for subgroup difference	—	—	p = 0.48	—

Sensitivity analysis

The leave-one-out sensitivity analysis confirmed the robustness of the primary finding. The pooled risk ratio remained in the harmful direction under every single-study deletion, ranging from 1.46 to 2.64, and the absence of heterogeneity (I^2 = 0%) persisted throughout. Statistical significance was retained in eight of the nine iterations; the single exception arose when the Canadian post-infarction trial was omitted, after which the pooled risk ratio fell to 1.46 with a 95% confidence interval that marginally crossed unity (p = 0.073), identifying that trial as the most influential contributor. Because the largest trial carried the greatest statistical weight, its omission produced the highest recalculated estimate (RR 2.64). The dependence of nominal significance on a single influential trial reflects the rare-event nature of the outcome rather than any instability in the direction of effect, which was uniformly towards harm.

Publication bias and certainty of evidence

Formal assessment of small-study effects by funnel-plot asymmetry and Egger's regression was prespecified to require at least ten event-contributing trials; because only seven contributed pulmonary events, quantitative bias testing was withheld to avoid the unreliable inference that such tests yield in small meta-analyses. The absence of statistical heterogeneity and the concordance of the present estimate with independent contemporary studies argue against major distortion from selective publication, although, because some of those studies drew on overlapping trials, this concordance is not fully independent and residual small-study bias cannot be excluded.[12,13] Applying the GRADE framework, the overall certainty of evidence was judged moderate: the body of evidence began as high certainty by virtue of its randomised design and was downgraded one level for imprecision, owing to the modest number of events and the dependence of significance on a single influential trial, but was not downgraded for inconsistency (I^2 = 0%), for indirectness or, on balance, for risk of bias.

4. Discussion

This meta-analysis of nine randomised controlled trials, encompassing 6,209 patients and 119 pulmonary events, demonstrated that oral amiodarone was associated with an approximately 70% relative increase in the risk of pulmonary toxicity compared with placebo or usual care. The effect was statistically significant, was concordant across three complementary effect measures (Table 3), and was accompanied by an absence of detectable between-study heterogeneity. To our knowledge this is the first meta-analysis to treat amiodarone-induced pulmonary toxicity as the sole primary endpoint across the full spectrum of cardiac arrhythmia and heart-failure indications, rather than as one secondary outcome within a broad multi-organ safety evaluation.

The clinical interpretation of the relative risk is best grounded in the absolute numbers reported in Table 1. Pulmonary toxicity affected 2.43% of amiodarone recipients and 1.38% of controls, an absolute difference of approximately 1.05 percentage points, corresponding to a number needed to harm of approximately 95: roughly one additional case would be expected for every ninety-five patients treated with amiodarone rather than placebo over the follow-up periods studied. For an agent whose antiarrhythmic efficacy is frequently decisive, this magnitude of harm is real but quantitatively modest, and it supports continued, judicious use coupled with active pulmonary surveillance rather than avoidance; expressing the risk in absolute terms also equips clinicians to share the decision with patients honestly.

Comparison with contemporary evidence

The present estimate aligns closely with the broader evidence base. A large multi-organ meta-analysis of placebo-controlled trials reported a relative risk of pulmonary adverse events of 1.77, almost identical to

the figure derived here.[13] A contemporary nationwide cohort of patients with atrial fibrillation in the low-dose era reported a hazard ratio for interstitial lung disease of 1.45 with a clinically negligible absolute increase, concordant in direction with the present result,[12] and postmarketing pharmacovigilance analyses have independently confirmed a disproportionate pulmonary signal for amiodarone, which carried the strongest interstitial-lung-disease reporting association among the agents examined and a markedly elevated reporting odds ratio in older adults.[4,11] By concentrating exclusively on the pulmonary endpoint and assembling trials with a uniform comparator, the current analysis reproduced this signal with a tight confidence interval and no residual heterogeneity; it should nonetheless be acknowledged that, because the synthesis drew on landmark trials shared with some earlier analyses, its agreement with them reflects common source data as well as independent replication.

The pulmonary endpoint within the wider safety and efficacy profile

Although this review concentrated on the lung, the pulmonary hazard must be read within the wider context of amiodarone therapy. The drug also carries appreciable risks of thyroid dysfunction, hepatic injury and ocular deposits, as documented in contemporary multi-organ toxicity cohorts,[3] and its use is complicated by clinically important interactions, notably with direct oral anticoagulants.[26] Against this catalogue stands an antiarrhythmic efficacy that, for many patients with atrial fibrillation or life-threatening ventricular arrhythmia, is unmatched by safer alternatives such as dronedarone or sotalol.[27] The clinically appropriate conclusion is not that the pulmonary risk demonstrated here should deter the use of amiodarone, but that it should be incorporated, alongside the drug's other effects and its benefits, into an individualised assessment of the balance of risks for each patient.

Heterogeneity, consistency and influential trials

The finding of zero measured heterogeneity merits careful comment. On the one hand, the included trials differed substantially in indication, dose and duration, so the consistency of the effect is reassuring and biologically plausible, given that the mechanism of tissue accumulation is largely independent of the arrhythmic substrate. On the other hand, with few trials and few events the Cochran Q test has limited power, and the absence of measured heterogeneity should not be over-interpreted as proof of true homogeneity. A further nuance, evident in Figure 3, is that two post-infarction trials together contributed more than 80% of the statistical weight; the pooled estimate is therefore largely a restatement of those trials, and the leave-one-out result that significance depended on one of them is the direct corollary of this concentration of information.

Outcome definition and the risk of misclassification

A central interpretive caveat concerns the heterogeneity of the outcome definition, detailed in Table 2. Amiodarone pulmonary toxicity is not a single entity but a spectrum ranging from reversible hypersensitivity pneumonitis to irreversible fibrosis, and the included trials each applied their own working definition of a pulmonary event, frequently as an unblinded secondary outcome.[5,7] In populations with heart failure and recent myocardial infarction, pulmonary congestion, infection and pulmonary embolism can closely mimic drug-induced lung injury, so the event counts may include both misattributed and missed cases; this could bias the pooled estimate in either direction and is the principal reason that the outcome-measurement domain attracted a judgement of some concerns. A harmonised, radiologically and physiologically anchored case definition of amiodarone pulmonary toxicity is needed in future studies.

Dose, duration and the limits of the trial evidence

The dose-stratified analysis in Table 4 is consistent with the understanding that pulmonary toxicity depends partly on cumulative exposure, and it accords with the recommendation to use the lowest effective maintenance dose. However, the test for subgroup difference was not significant, and a clinically relevant point estimate persisted at lower doses, so dose reduction should be regarded as mitigation rather than elimination of risk. Duration of exposure is at least as important as daily dose, and the trial evidence has an intrinsic limitation here: the follow-up periods, in several cases measured in months, may be too short to capture the slowly progressive fibrotic toxicity that accrues over years of continuous therapy and that is well documented experimentally.[8,9] The present estimate may therefore understate the lifetime pulmonary risk of indefinite amiodarone use.

Clinical implications and a pragmatic surveillance approach

These findings carry direct implications for respiratory and cardiovascular practice. Consistent with current expert guidance, a reasonable surveillance approach begins with a baseline chest radiograph and pulmonary function tests, including the diffusing capacity for carbon monoxide, before long-term therapy is started.[5,6] Thereafter, clinical review with enquiry for new respiratory symptoms is appropriate at each visit, with pulmonary function testing and chest radiography repeated periodically, commonly at intervals of around twelve months, and sooner whenever new or progressive dyspnoea, cough or hypoxaemia develops. A fall in the diffusing capacity, or new infiltrates on imaging, should prompt high-resolution computed tomography and, where the diagnosis remains uncertain, bronchoalveolar lavage to exclude infection and to seek the foamy macrophages characteristic of amiodarone accumulation.[10] Because prompt withdrawal of the drug, often with corticosteroid therapy, is associated with a favourable prognosis when toxicity is detected early, and because re-exposure can precipitate recurrence, the modest absolute excess risk demonstrated here is best managed by embedding structured pulmonary vigilance into routine care, with heightened attention to patients on higher doses, those treated for prolonged periods, the elderly and those with pre-existing lung disease.[7]

Generalisability

The generalisability of the estimate warrants explicit consideration. The included trials were predominantly conducted in selected cardiovascular populations, and contemporary practice tends to favour lower maintenance doses than were used in some of them, so the pooled estimate may modestly overstate the risk faced by patients treated according to current standards; a recent low-dose cohort indeed found only a small, non-significant absolute increase.[12] Conversely, the relatively short follow-up may understate the risk of long-term therapy. The source populations, while geographically diverse, may not fully represent the comorbidity burden or background prevalence of interstitial lung disease of every population served by an international readership, and extrapolation to patients with pre-existing pulmonary fibrosis, who were generally excluded from the trials, should be especially cautious.

Strengths and limitations

The principal strengths of this review are its focus on a single, clinically important endpoint; its restriction to randomised trials with a uniform comparator; its use of three concordant effect measures; its transparent influence diagnostics; and its explicit, conservative handling of rare events and certainty of evidence. Several limitations must be weighed. First, the definition of pulmonary toxicity was not uniform across trials, introducing potential outcome misclassification. Second, pulmonary toxicity is a rare event, the total number of events was modest, and nominal significance depended on a single influential trial, so the estimate is imprecise and was downgraded under GRADE. Third, formal testing for publication bias could not be undertaken, and the concordance with overlapping contemporary studies is not fully independent. Fourth, the included trials were largely older and enrolled selected populations with limited follow-up, constraining generalisability. Fifth, as an aggregate-data synthesis, the review could not adjust for individual-level modifiers such as cumulative dose, baseline diffusing capacity or concurrent pulmonary disease, which an individual-patient-data meta-analysis would be better placed to explore.

5. Conclusion

This meta-analysis of nine randomised controlled trials involving 6,209 patients established that oral amiodarone was associated with a statistically significant and consistent increase in the risk of pulmonary toxicity compared with placebo or usual care, with a pooled risk ratio of 1.70 (95% CI 1.17–2.45) and no detectable heterogeneity. The concordance of the risk ratio, the odds ratio and the Peto odds ratio, together with the persistence of a harmful direction of effect under every single-study deletion, lends internal validity to this conclusion, while its agreement with contemporary cohort and pharmacovigilance evidence lends external support, tempered by the recognition that some of that evidence shares source data with the present analysis. The magnitude of the relative hazard, an approximately 70% increase, should be understood in the context of a modest absolute excess of about one additional case for every ninety-five patients treated, and the overall certainty of the evidence was judged moderate, limited chiefly by imprecision. The dose-stratified analysis suggested a numerically greater risk

at maintenance doses above 200 mg per day, consistent with a cumulative-exposure mechanism, although a formally distinct dose effect was not demonstrated and a clinically relevant hazard persisted even at lower doses. These observations reinforce the established principles of amiodarone stewardship: prescribe the lowest effective maintenance dose, obtain baseline pulmonary assessment, monitor respiratory status throughout treatment, communicate the absolute risk to patients as part of shared decision-making, and respond to new respiratory symptoms with prompt investigation and, when toxicity is confirmed, timely withdrawal of the drug. Because amiodarone retains an irreplaceable role in the management of many arrhythmias, the appropriate response to its pulmonary hazard is not avoidance but vigilance, supported in future by individual-patient-data synthesis, a harmonised case definition and contemporary pharmacovigilance capturing long-term exposure.

Declarations

Author contributions

All authors contributed to the conception and design of the review, the screening and extraction of data, the interpretation of results, and the drafting and critical revision of the manuscript, and all approved the final version.

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Conflicts of interest

The authors declare no competing interests.

Data availability

All data analysed derive from the published trials cited in the reference list and their associated open extraction datasets; the complete 2×2 dataset is available from the corresponding author on reasonable request.

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