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Systematic Review/Meta-analysis

Chronic Amiodarone Use and the Risk of Cancer: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Observational studies have identified inconsistent associations between chronic use of amiodarone and cancer-related outcomes. We performed a systematic review and meta-analysis to evaluate cancer risk among patients receiving amiodarone.

Methods: We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to May 1, 2020. We included randomized controlled trials (RCTs) with follow-up ≥2 years that compared amiodarone (any dose) to any comparator (placebo, active pharmacologic or interventional comparator, or usual care), and

RÉSUMÉ

Contexte : Des études d'observation ont révélé des associations incohérentes entre l'usage à long terme de l'amiodarone et les issues liées au cancer. Nous avons mené une revue systématique et une méta-analyse pour évaluer le risque de cancer chez les patients qui reçoivent l'amiodarone.

Méthodologie : Nous avons épluché les registres MEDLINE, Embase et Cochrane Central Register of Controlled Trials (CENTRAL) jusqu'au 1er mai 2020. Nous avons retenu les essais contrôlés randomisés (ECR) comportant une période de suivi d'au moins 2 ans qui visaient à

Amiodarone is the most commonly used antiarrhythmic medication for the chronic rhythm control of atrial fibrillation and prevention of ventricular arrhythmias.[1] Amiodarone's unique pharmacokinetic properties, namely its very long half-life and large volume of distribution, result in prolonged tissue exposure.[2] The most common adverse effects involve the lungs, liver, thyroid, and eyes, and require diligent monitoring.[3]

Previous studies have suggested a potential association between amiodarone use and cancer, particularly cancers of the thyroid, liver, lungs, and skin.[4-8] A meta-analysis of randomized controlled trials (RCTs) evaluating amiodarone for the prevention of sudden cardiac death demonstrated an increased risk of cancer-related death with amiodarone vs control.[9] However, this meta-analysis included only a subset of RCTs and was limited to trials with short follow-up. Two national observational studies that evaluated the association between chronic amiodarone use and cancer risk found conflicting results.[10,11] Given the ubiquitous use of amiodarone in cardiology, the association between amiodarone and cancer is concerning, yet no study has comprehensively analyzed the available experimental data on this risk.

The objective of this study was to perform a systematic review and meta-analysis of RCTs to evaluate the risk of cancer and cancer-related death with chronic amiodarone use.

Methods

Search and data sources

We conducted this systematic review and meta-analysis according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to May 1, 2020. The MEDLINE search query is available in Supplemental Appendix S1. Included studies were (i) RCTs reported in any language, (ii) comparing amiodarone at any dose for any indication to any other intervention (placebo, usual care, pharmacotherapy, or interventional or device therapy)

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Ethics Statement: No formal ethics approval was needed to conduct this systematic review and meta-analysis.

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reported ≥1 outcome of interest. We contacted authors of published chronic amiodarone trials for potentially unreported cancer outcomes. The primary outcome was cancer incidence. Secondary outcomes were cancer-related death and site-specific cancers. We determined risk ratios and 95% confidence intervals using a fixed-effect model, and statistical heterogeneity using I^2. We conducted prespecified subgroup and sensitivity analyses for amiodarone indication, amiodarone dose, duration of therapy, and trial-level risk of bias.

Results: From 1439 articles, we included 5 RCTs (n = 4357). Mean follow-up duration ranged from 21 to 37 months. We included previously unpublished cancer outcome data from 1 RCT. Our primary outcome was not reported in any RCT. There was no significant difference in cancer-related death between amiodarone (1.69%) and the comparator (1.75%) (risk ratio 0.96, 95% confidence interval 0.57-1.63; I^2 = 0%). There were no significant interactions from our subgroup or sensitivity analyses.

Conclusions: Chronic amiodarone use did not increase cancer-related deaths. Data from RCTs do not support an increased risk of cancer-related harms with amiodarone use, and these concerns should not deter use of amiodarone when indicated.

comparer l'amiodarone (toutes les doses) à un agent (placebo, agent de comparaison pharmacologique ou interventionnel actif, ou traitement standard) et qui ont rapporté au moins un résultat d'intérêt. Nous avons communiqué avec les auteurs de publications d'essais sur l'emploi à long terme de l'amiodarone dans le but de déceler des issues possibles de cancer non signalées. Le principal critère d'évaluation était la fréquence du cancer. Les critères d'évaluation secondaires étaient les décès liés au cancer et les cancers en fonction de leur localisation. Nous avons établi les rapports de risques et les intervalles de confiance à 95 % au moyen d'un modèle à effets fixes et d'une hétérogénéité statistique quantifiée à l'aide d'une I^2. Nous avons réalisé des analyses par sous-groupes et des analyses de sensibilité prédéfinies pour l'indication de l'amiodarone, la dose d'amiodarone, la durée du traitement et le risque de biais à l'échelle des essais.

Résultats : À partir de 1 439 articles, nous avons retenu 5 études contrôlées à répartition aléatoire (n = 4 357). La durée de suivi moyenne variait de 21 à 37 mois. Nous avons inclus des données d'un ECR portant sur l'issue de cancer qui n'avaient pas été publiées auparavant. Notre principal critère d'évaluation n'a fait l'objet d'aucun rapport dans les ECR. En ce qui concerne les décès liés au cancer, aucune différence n'a été observée entre l'amiodarone (1,69 %) et l'agent de comparaison (1,75 %) (rapport des risques de 0,96; intervalle de confiance à 95 % de 0,57 à 1,63; I^2 = 0 %). Aucune interaction notable n'est ressortie de nos analyses par sous-groupe ou de nos analyses de sensibilité.

Conclusions : L'administration à long terme d'amiodarone n'a pas augmenté le taux de décès liés au cancer. Selon les données des ECR, l'emploi de l'amiodarone n'est pas associé à une augmentation du risque de cancer, et les craintes à cet égard ne devraient pas dissuader d'utiliser l'amiodarone lorsqu'elle est indiquée.

with (iii) follow-up of at least 2 years (iv) that reported at least one of the outcomes of interest described below.

We incorporated several searches to identify grey literature, including a reverse-citation search using Web of Science, and a manual search of bibliographies of included studies and relevant reviews. Furthermore, when the published reports of otherwise relevant trials did not describe our outcomes of interest, we contacted the original corresponding authors to request data on these outcomes. If we could not contact corresponding authors, we attempted to contact the first or last authors and coauthors from other studies. We sent the last correspondence on May 30, 2020.

Outcomes

The primary outcome of interest was cancer incidence, defined as new onset of malignancy in any body system, as originally defined and reported in the studies. Secondary outcomes included cancer-related death and incidence of site-specific cancers.

Data extraction and quality assessment

One reviewer (LS) screened the titles, abstracts, and full-text articles of the identified records for inclusion, documented the reasons for exclusion, and then extracted data from included studies using a prespecified form. A second reviewer (RT) replicated study screening and cross-referenced data extraction. We resolved discrepancies via consensus.

We assessed individual study risk of bias using the Cochrane Risk of Bias tool.[13] We evaluated certainty of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[14]

Statistical analysis

We used a Mantel-Haenszel fixed-effect model analysis to calculate the risk ratio and 95% confidence interval for each outcome of interest. We evaluated statistical heterogeneity using the I^2 statistic and χ^2 test. We used the threshold of $I^2 > 50\%$ or χ^2 test P-value <0.10 to indicate significant statistical heterogeneity. We conducted prespecified subgroup and sensitivity analyses for each outcome based on study population (atrial fibrillation or ventricular arrhythmias), daily amiodarone dose (≤ 200 mg daily, > 200 mg daily, or mixed regimen), trial duration (below or above the median study duration), and study risk of bias (low risk of bias in all domains vs high/unclear risk of bias in any domain).

Results

Characteristics of included studies

Of 1440 identified records, we included 5 RCTs (n = 4357) that met the inclusion criteria and reported at least 1 outcome of interest (Fig. 1).[15-19] Across trials, the mean age was 66 years, and 16% were female (Table 1). In the only trial[17] that reported smoking history, 79% were prior

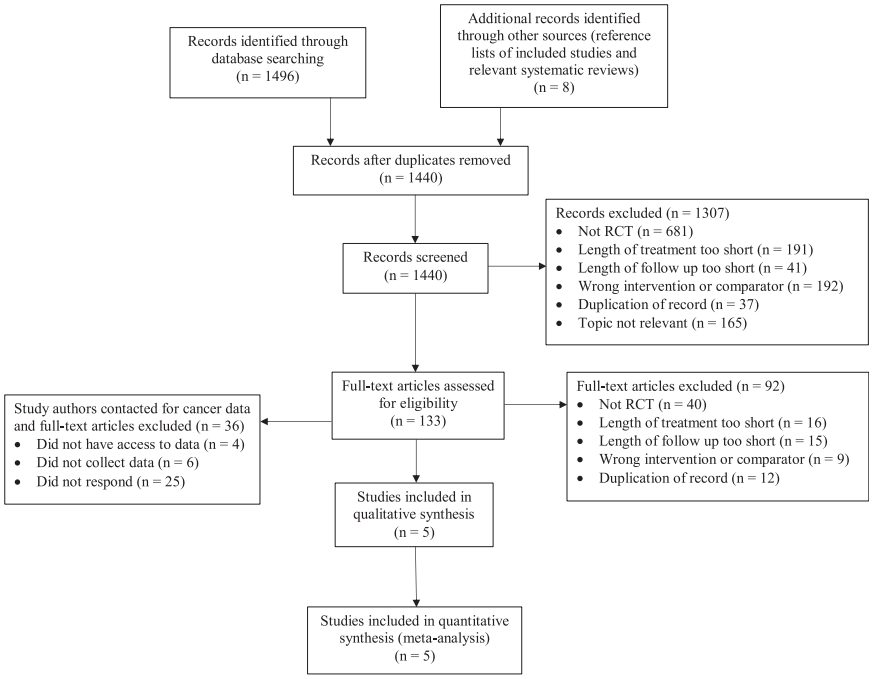

Figure 1. Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram. RCT, randomized controlled trial.

smokers. One trial evaluated patients with atrial fibrillation,[15] and the other 4 trials evaluated patients at risk for ventricular arrhythmias.[16-19] Three trials compared amiodarone to placebo[16,17,19]; 1 trial compared amiodarone to pharmacologic rate control (beta-blocker ± digitalis) [15]; and 1 trial compared amiodarone to ventricular tachycardia catheter ablation.[18] The amiodarone maintenance dose was ≤ 200 mg daily in 4 trials[15,16,17,19] and varied in 1 trial.[18] The median length of follow-up was 22 months (range: 21-37 months).

Unpublished data

We contacted the corresponding authors of 37 otherwise relevant published RCTs that did not report on cancer outcomes. The authors of 10 studies responded, and the author of 1 trial[19] provided unpublished cancer data, which we included in the analyses. Four authors who responded reported that they did not have access to the relevant data if it existed,[20-23] and 6 authors responded that they did not collect data on cancer outcomes.[24-29]

Risk of bias and certainty of evidence

Only 1 trial was at a low risk of bias in all domains (Fig. 2).[17] In contrast, other trials had a high or unclear risk of bias arising primarily due to unclear or no allocation concealment or blinding of patients and outcome assessors,[15,16,18] and 1 trial was not analyzed according to intention-to-treat principles.[19] Overall, we did not judge the risk of bias to be sufficient to downgrade certainty of evidence for this domain. We could not grade the certainty of evidence for our primary outcome of cancer incidence, or for our secondary outcome of site-specific cancer incidence, as these outcomes were not reported in any published RCTs. We graded the certainty of evidence for cancer-related death outcome as moderate, downgraded one category, due to imprecision.[14]

Effect of amiodarone on cancer outcomes

Incident cancer, our primary outcome of interest, and site-specific cancer, were not collected or reported in any of the 5 included trials. Data on cancer-related deaths were available from the 5 included studies. There was no significant increase in cancer-related death in patients treated with amiodarone vs the comparator (risk ratio 0.96, 95% confidence interval 0.57-1.63; $I^2 = 0\%$; Fig. 3).

Subgroup and sensitivity analyses

There was no significant interaction by indication in the subgroup analysis comparing amiodarone indicated for atrial fibrillation or ventricular arrhythmias ($P = 0.15$ for interaction; Supplemental Figure S1). Sensitivity analyses did not demonstrate an interaction with cancer-related death based on amiodarone dose ($P = 0.92$ for interaction), trial duration below or above the median ($P = 0.30$ for interaction), or trial risk of bias ($P = 0.48$ for interaction; Supplemental Figures S2-S4).

Discussion

In this comprehensive systematic review and meta-analysis evaluating the risk of cancer outcomes with use of amiodarone over a median of 22 months, we did not find a significant increased risk of cancer-related death with amiodarone compared with placebo, other pharmacotherapy, or catheter ablation. These results were consistent among patients receiving amiodarone for atrial fibrillation or ventricular arrhythmias, and regardless of dose, duration, or trial-level risk of bias. Overall, we found that few published RCTs of

Table 1. Characteristics of included studies

Characteristic	AF-CHF 2008	CAMIAT 1997	EMIAT 1997	VANISH 2016	Hamer et al. 1989
n	1376	1202	1486	259	34
Time frame	2001-2007	1990-1995	1990-1995	2009-2014	1985-1987
Length of follow-up, mo	Mean: 37	Mean: 21	Median: 21	Mean: 28	Median: 23
Geographic location	North America, South America, Europe	North America	Europe	North America, Europe, Australia	Australia (single centre)
Amiodarone indication	AF rhythm control	VT/VF prevention	VT/VF prevention	VT/VF prevention	VT/VF prevention
Key inclusion criteria	ECG-confirmed paroxysmal/persistent AF plus HF with LVEF $\leq$ 35% and: NYHA II-IV or HF hospitalization in previous 6 months, or LVEF $\leq$ 25%	Prior MI	LVEF $\leq$ 40%	Prior MI, ICD, VT, failed class I or III AAD therapy	HF NYHA IV at enrolment, LVEF $\leq$ 27%, medical therapy optimized, no history of symptomatic VT/VF
Mean age, y	66	64	60	70	70
Female, %	22	18	16	7	NR
Baseline amiodarone use, %	NR	NR	0	66	NR
Prior smoking, %	NR	79	NR	NR	NR
Diabetes, %	22	15	17	32	NR
Heart failure, %	100	21	100	100	100
Intervention	Rhythm control (drug of choice was amiodarone; used in 73%* of intervention group)	Amiodarone	Amiodarone	Amiodarone $\pm$ mexiletine	Amiodarone
Amiodarone dose	200 mg/d	10 mg/kg per d for 2 wk, 300-400 mg for 3.5 mo, 200-300 mg for 4 mo, then 200 mg for 5-7 d/wk for 16 mo	800 mg/d for 14 d, 400 mg/d for 14 wk, then 200 mg/d	1. If VT/VF with non-amiodarone AAD: 400 mg BID for 2 wk, 400 mg for 4 wk, then 200 mg. 2. If VT/VF with amiodarone $<$ 300 mg/d: 400 mg BID for 2 wk, 400 mg/d for 1 wk, then 300 mg/d 3. If VT/VF with amiodarone $\geq$ 300 mg/d: $\geq$ 300 mg/d plus mexiletine	200 mg every 8 h for 2 wk, then 200 mg/d
Comparator (proportion taking amiodarone, %)	Rate control with beta blocker $\pm$ digitalis (7†)	Placebo (0)	Placebo (0)	Catheter ablation + previous AAD (64)	Placebo (0)

AAD, anti-arrhythmic drug; AF, atrial fibrillation; AF-CHF, Atrial Fibrillation and Congestive Heart Failure; BID, twice daily; CAMIAT, Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; ECG, electrocardiogram; EMIAT, European Myocardial Infarct Amiodarone Trial; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NYHA, New York Heart Association; VANISH, **V**entricular Tachycardia **A**blation vs E**n**hanced Drug Therapy **I**n **S**tructural **H**eart Disease VT/VF, ventricular tachycardia/ventricular fibrillation.

*At 36 months.

†At 12 months.

amiodarone systematically collected any cancer-related data, and no included RCTs evaluated the incidence of cancer.

Concerns regarding an association between amiodarone and cancer outcomes have been based largely on case reports, observational studies, and a subset of RCTs. A previous meta-analysis[9] of RCTs designed to evaluate the effect of amiodarone on sudden cardiac death found a statistically borderline increased risk of cancer-related death with amiodarone. However, this review was restricted to patients at high risk of sudden cardiac death, and the observed risk was driven mainly by trials with 6 to 12 months of follow-up. An alternate explanation for these findings is that amiodarone reduced the short-term risk of sudden cardiac death without impacting all-cause mortality, creating shifts among competing causes of death for patients treated with amiodarone.

Data on the association between amiodarone and cancer incidence come from 2 conflicting cohort studies. The first study used the Taiwan National Health Insurance Research database to evaluate the association between amiodarone dose and incident cancer among patients treated with amiodarone for at least 1 month.[10] This study found an association between higher doses of amiodarone and cancer in men, but no association among women. However, these analyses did not account for important sources of confounding, including smoking history. Furthermore, the highest risk was in patients who received amiodarone for less than a year, suggesting that this association may be explained by surveillance bias from increased monitoring required during amiodarone use. The second study used the Danish National Patient Registry to evaluate the association between amiodarone dose and risk of incident cancer among patients with atrial

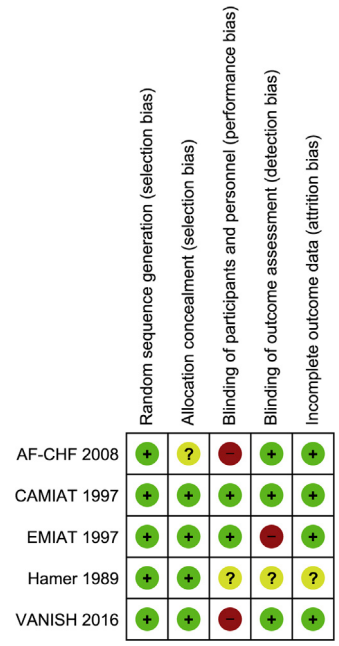

Figure 2. Risk of bias of included trials. AF-CHF, Atrial Fibrillation and Congestive Heart Failure; CAMIAT, Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; EMIAT, European Myocardial Infarct Amiodarone Trial; VANISH, **V**entricular Tachycardia **A**blation vs E**n**hanced Drug Therapy **I**n **S**tructural **H**eart Disease.

fibrillation treated with amiodarone.[11] The Danish study found no association between higher doses of amiodarone and risk of all-cause or site-specific (liver, lung, or skin) cancer. Moreover, this study found no difference in the incidence of cancer between patients with atrial fibrillation treated with amiodarone compared with those treated with digoxin. Taken together with the results of our meta-analysis, these data do not support a causal relationship between amiodarone use and cancer outcomes. Therefore, this concern should not deter the use of amiodarone when indicated. Future prospective studies using prospective surveillance for the incidence of overall and site-specific cancers may provide further information on the longer-term safety of chronic amiodarone use.

Limitations

Although this systematic review and meta-analysis is the most exhaustive assessment of data on cancer outcomes with chronic amiodarone use in randomized trials, it does have some limitations inherent to the included studies. First, we could not evaluate the impact of amiodarone on cancer incidence despite a search of published and unpublished data on this outcome, as no included RCTs collected data on this outcome. Therefore, our study conclusions are limited to data on fatal cancers. Second, only 5 included trials provided sufficient data on cause of death to evaluate cancer-related death. Third, although the experimental nature of the data included is not impacted by confounding and can elucidate a cause-and-effect relationship, the results of this analysis are likely impacted by selection bias and detection bias. Finally, it is possible that the included studies may have missed an association between amiodarone and cancer-related events with an extended latency period. Notably, however, there was no signal of increased cancer-related deaths with amiodarone use in the Atrial Fibrillation—Congestive Heart Failure (AF-CHF) trial despite a median and longest follow-up of up to 37 and 74 months, respectively.

Conclusions

Chronic amiodarone did not increase cancer-related deaths. There are no available data from RCTs on the incidence of cancer with chronic amiodarone use. Data from RCTs do not support an increased risk of cancer-related harms with amiodarone, and these concerns should not deter use of amiodarone when indicated. Future prospective surveillance studies may provide further information on the incidence of cancer with longer-term amiodarone use.

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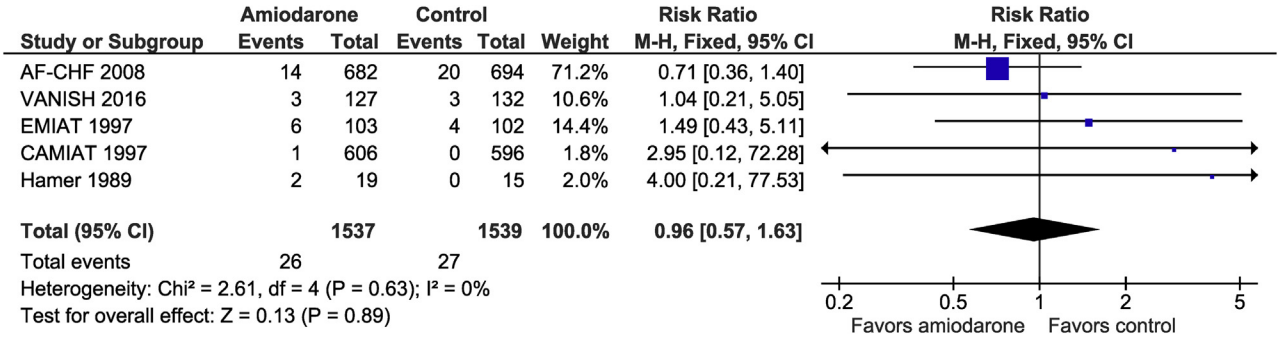

Figure 3. Meta-analysis of cancer-related death. AF-CHF, Atrial Fibrillation and Congestive Heart Failure; CAMIAT, Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; CI, confidence interval; df, degrees of freedom; EMIAT, European Myocardial Infarct Amiodarone Trial; M-H, Mantel-Haenszel; VANISH, **V**entricular Tachycardia **A**blation vs E**n**hanced Drug Therapy **I**n **S**tructural **H**eart Disease.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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