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CLINICAL RESEARCH
Arrhythmias

Amiodarone and pulmonary toxicity in atrial fibrillation: a nationwide Israeli study

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Abstract

Background and Aims Amiodarone-related interstitial lung disease (ILD) is the most severe adverse effect of amiodarone treatment. Most data on amiodarone-related ILD are derived from periods when amiodarone was given at higher doses than currently used.

Methods A nationwide population-based study was conducted among patients with incident atrial fibrillation (AF) between 1 December 1999 and 31 December 31 2021. Amiodarone-exposed patients were matched 1:1 with controls unexposed to amiodarone based on age, sex, ethnicity, and AF diagnosis duration. The final patient cohort included only matched pairs where amiodarone therapy was consistent throughout follow-up. Directed acyclic graphs and inverse probability treatment weighting (IPTW) modelling were used. Patients with either prior ILD or primary lung cancer (PLC) were excluded. The primary outcome was the incidence of any ILD. Secondary endpoints were death and PLC.

Results The final cohort included 6039 amiodarone-exposed patients who were matched with unexposed controls. The median age was 73.3 years, and 51.6% were women. After a mean follow-up of 4.2 years, ILD occurred in 242 (2.0%) patients. After IPTW, amiodarone exposure was not significantly associated with ILD [hazard ratio (HR): 1.45, 95% confidence interval (CI): 0.97, 2.44, $P = 0.09$]. There was a trivial higher relative risk of ILD among amiodarone-exposed patients between Years 2 and 8 of follow-up [maximal risk ratio (RR): 1.019]. Primary lung cancer occurred in 97 (0.8%) patients. After IPTW, amiodarone was not associated with PLC (HR: 1.18, 95% CI: 0.76, 2.08, $P = 0.53$). All-cause death occurred in 2185 (18.1%) patients. After IPTW, amiodarone was associated with reduced mortality risk (HR: 0.65, 95% CI: 0.60, 0.72, $P < 0.001$). The results were consistent across a variety of sensitivity analyses.

Conclusion In a contemporary AF population, low-dose amiodarone was associated with a trend towards increased risk of ILD (15%-45%) but a clinically negligible change in absolute risk (maximum of 1.8%), no increased risk of PLC, and a lower risk of all-cause mortality.

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Structured Graphical Abstract

Key Question

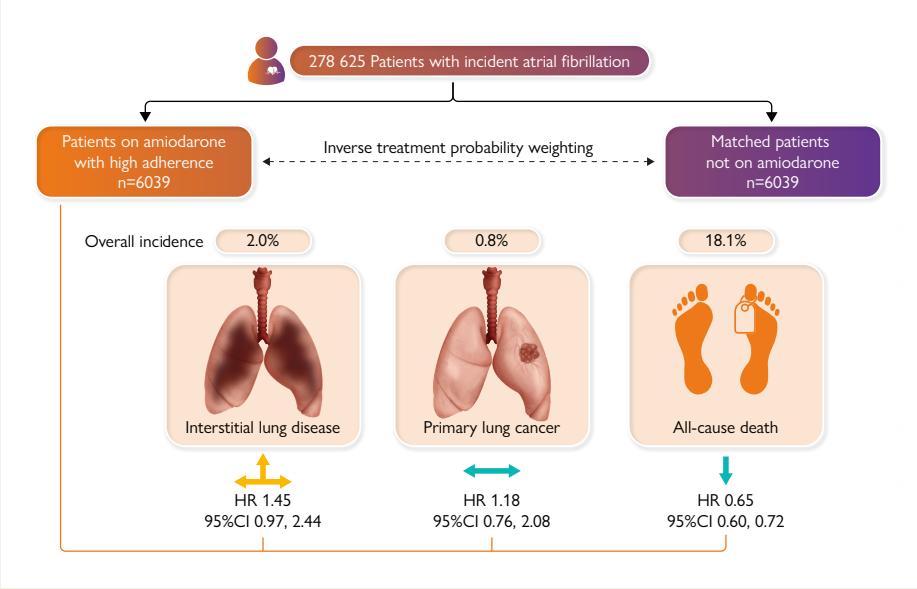
What is the association between constant exposure to low-dose amiodarone and risk of interstitial lung disease (ILD), primary lung cancer (PLC), or all-cause mortality among contemporary atrial fibrillation (AF) patients?

Key Finding

In a nationwide population study, constant exposure to low-dose amiodarone was associated with a clinically negligible, increased risk of ILD, no increased risk of PLC, and a lower risk of all-cause mortality. These results were consistent across various sensitivity analyses.

Take Home Message

In a contemporary AF population, low-dose amiodarone is associated with a lower risk of all-cause mortality in the absence of a substantial increase of ILD and PLC risk.



In a historical database from a large health maintenance organization, atrial fibrillation (AF) patients who were exposed to continuous amiodarone treatment had no to marginally higher risk for interstitial lung disease (ILD), similar risk for primary lung cancer (PLC), and lower risk of all-cause death compared with patients not exposed to amiodarone. The results were replicated in several sensitivity analyses including intention-to-treat and as-treated target emulation trial. CI, confidence interval; HR, hazard ratio.

Keywords Amiodarone • Interstitial lung disease • Primary lung cancer • All-cause mortality • Atrial fibrillation

Introduction

Amiodarone is the most effective pharmacotherapy to achieve and maintain rhythm control in atrial fibrillation (AF), surpassed in effectiveness by catheter ablation.[1–3] The importance of early rhythm control in patients with AF has been reinforced by the EAST-AFNET 4 study results showing improved prognosis.[4]

Despite its effective antiarrhythmic properties, prolonged amiodarone treatment has been attributed to several significant side effects, limiting its widespread use. Amiodarone-related interstitial lung disease (ILD) is an uncommon, severe, and potentially fatal adverse effect of amiodarone treatment.[5] Amiodarone-related ILD was first described a decade after the introduction of amiodarone, and most data regarding this side effect are derived from a period when amiodarone was administered in high doses (≥400 mg/day) for prolonged periods.[6] A study from the same era suggested that daily doses lower than 305 mg pose a dramatically lower risk of ILD.[7] This observation was supported by a meta-analysis of randomized studies that failed to show a significant increase in ILD rates among patients treated with amiodarone doses of <330 mg/day.[8] Also, in a sizeable population-scale study, amiodarone treatment was associated with an increased risk of cancer, with a numerical increase in primary lung cancer (PLC) events.[9] These data led to an awareness of amiodarone-related pulmonary adverse effects and a recommendation to actively follow patients treated with amiodarone for early detection of this condition both clinically and radiographically.[10,11]

Currently, amiodarone is typically administered in low doses (200 mg/day). Data regarding the occurrence of amiodarone-related ILD when low doses of amiodarone are used are scarce. Existing data suggest that the incidence of ILD among amiodarone-treated patients is between 2% and 10%.[12–14] Nevertheless, whether low-dose amiodarone is associated with excess risk of ILD or PLC remains debated.

This study aimed to assess the association between consistent low-dose amiodarone pharmacotherapy and the occurrence of ILD, PLC, and all-cause mortality in a nationwide large contemporary population of AF patients.

Methods

A retrospective nationwide cohort study using Clalit Health Services (CHS) electronic medical records database was conducted. Clalit Health Services is Israel's largest healthcare maintenance organization, with

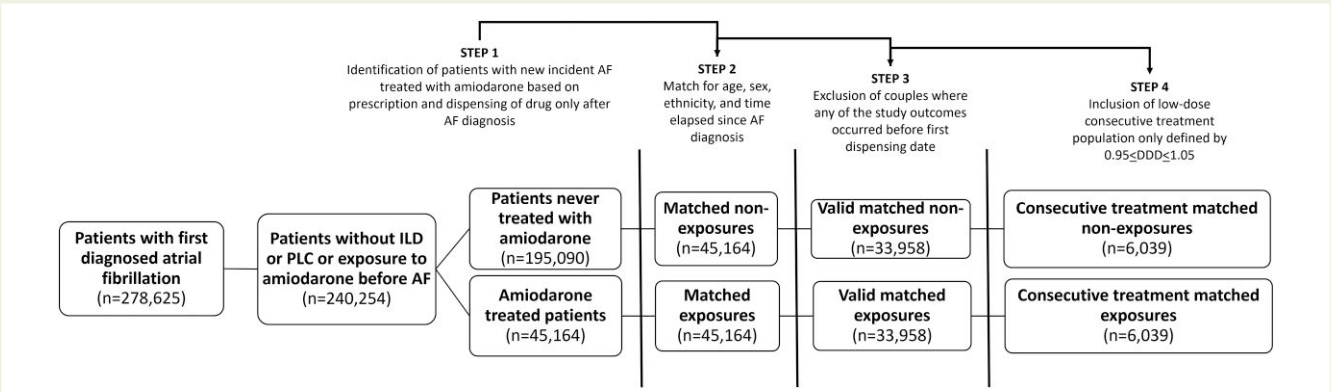


Figure 1 Flow chart of the study

more than 4.2 million insured citizens, and has an extremely low annual turnover of <1%.[15] Clalit Health Services has an integrated comprehensive electronic health record (EHR) system since 2000, storing all patient data from primary, ambulatory, and in-hospital care. Clalit Health Services EHRs are continuously updated with real-time input from administrative, medical, and pharmaceutical systems. This unique, continuously monitored, validated database environment provides high reliability, consistency, and accuracy of exposure and follow-up data. This study was approved by the Institutional Committee on Human Research of Soroka University Medical Center, Beersheva, Israel.

Study design and oversight

The target trial for this study would assign adult patients with AF, no prior exposure to amiodarone, and no history of ILD or PLC to either low-dose amiodarone therapy or no-intervention/placebo groups and require consistent and prolonged adherence to therapy during the study. The study population was constructed in a four-stage process (*Figure 1*).

Step 1: preliminary cohort

In the first step, the target trial population comprised all adult (age > 18) CHS members diagnosed with AF between 1 December 1999 and 31 December 2021. The end of the follow-up was set for 31 December 2022. Atrial fibrillation cases were identified based on the International Classification of Diseases-9th Revision (ICD-9) codes 427.3, 427.31, or 427.32. Cases of atrial flutter (427.32) were not differentiated from AF, given the frequent overlap between flutter and AF, the lack of electrocardiographic validation of the diagnoses, and the similarities in treatment. Patients with prior ILD or PLC and those prescribed amiodarone for any reason prior to AF diagnosis were excluded.

Step 2: identification of exposed patients and control selection

The definition of exposure in the study relied on a double-verification procedure that required documentation of prescription and dispensing of amiodarone after AF diagnosis for the exposed patients. Simultaneously, the controls were selected from those who never had records of prescription or pharmacy dispensing of amiodarone after their AF diagnosis. The first documentation of amiodarone dispensing determined the index event and date of exposure. Amiodarone-exposed patients were matched with amiodarone-unexposed patients based on age, sex, ethnicity, and time elapsed since AF diagnosis. Each control was given the exact follow-up start date as their matched cases, relating to the first amiodarone dispensing date.

Step 3: exclusion of patients with documented outcomes before drug dispensing

Following the matching of patient couples according to the first amiodarone exposure matched date, patients who had a documented ILD or PLC diagnosis prior to their first amiodarone or control-equivalent dispensing date were excluded from the cohort.

Step 4: identification of uninterrupted 'on-treatment' population

Since the trial outcome represented an adverse effect related to exposure to amiodarone that, by definition, had to be recognized during treatment, the final study population included only patients who had documented consecutive exposure to the drug. To ensure maximal specificity to true continuous and consistent 'on-treatment' population, the final study cohort exposure arm included only patients who adhered to amiodarone therapy throughout their follow-up term. Also, patients not treated with low-dose amiodarone (i.e. more than 200 mg q.d.) most of the time were excluded. The amiodarone dose and adherence were calculated based on a defined daily dose (DDD) where a value of 1 was equal to 200 mg q.d. during the follow-up period. Adherence to low-dose treatment was defined as 0.95 < DDD < 1.05 (equivalent to a calculated daily dose of 190–210 mg during follow-up, minimizing dispensing interruption or persistent dispensing of higher doses). Given the primary cohort's definition that resulted in a relatively advanced mean population age (over 70 years) and to avoid misclassification of non–drug-related and natural death beyond the expected population's lifespan, a maximal follow-up term of 10 years was set. To address a potential misclassification bias, where the end of amiodarone dispensing was caused by mortality and not vice versa, the last follow-up time was defined at 42 days (6 weeks) following the last recorded date of amiodarone dispensing of the amiodarone-treated patients (see Supplementary data online, Supplement S1). To ensure an equal time frame for developing any outcomes, the amiodarone-unexposed controls were followed from the exact first amiodarone dispensing date of the amiodarone-exposed patients and up to 42 days following the last recorded date of amiodarone dispensing of their matched exposures.

Target trial emulation sensitivity analysis

This study primary analysis comprised exposed patients on consistent amiodarone therapy and controls never exposed to therapy. This analytical approach was required to ensure optimal balance between sufficient sample size and sufficient follow-up term. Hence, a sensitivity analysis based on target trial emulation was carried out.[16] To emulate a trial where patients with AF are randomized to amiodarone treatment, we based this analysis on all patients with incident AF included in the study. Patients exposed to amiodarone before AF diagnosis and those diagnosed with ILD or PLC before or within

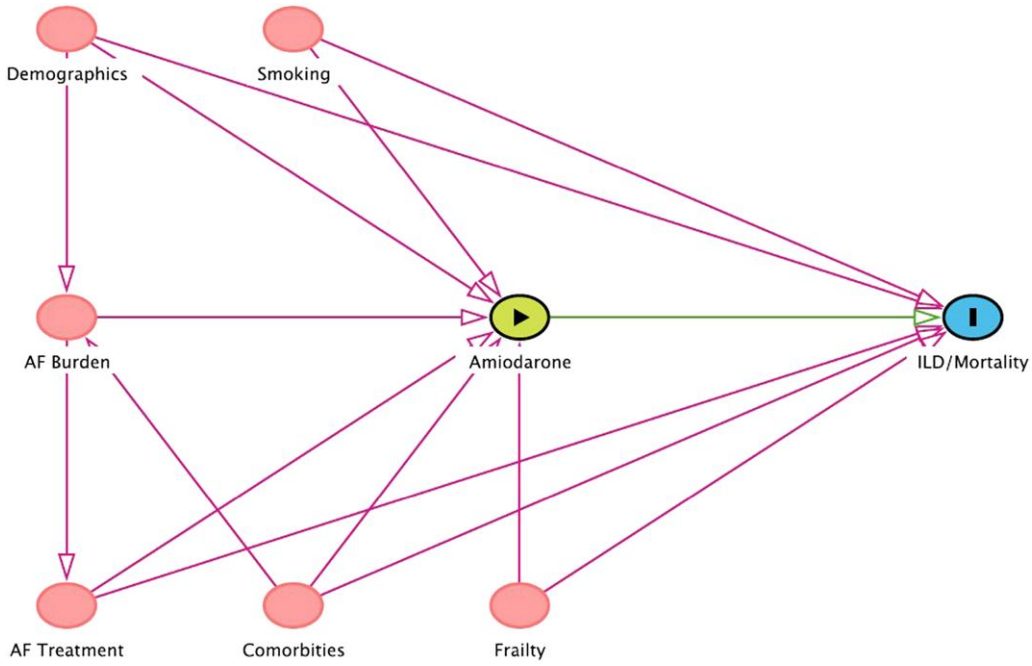


Figure 2 Directed acyclic graphs of the assumptions on relationship between variables. Patient demographics: age, ethnicity, sex, and socioeconomic status. AF treatment: beta-blockers, antiarrhythmics other than amiodarone (propafenone, flecainide, and sotalol), and systemic oral anticoagulation (warfarin, dabigatran, rivaroxaban, and apixaban). Comorbidities: diabetes, chronic obstructive pulmonary disease, liver disease, rheumatic disease, renal disease, cerebrovascular accident, myocardial infarction/history of ischaemic heart disease, and congestive heart failure. Frailty: prior malignancy, dementia, and tendency for hospitalizations

30 days of amiodarone exposure were excluded from this analysis. We allowed a 'grace period' of 1 year for all included patients, during which they could have been assigned to amiodarone intervention or remain as controls. Amiodarone intervention was defined as 60 consecutive days of documented amiodarone exposure during the first year after AF diagnosis. Patients who had ILD or PLC during the grace period were randomly assigned to one of the groups (treatment or control). Intention-to-treat and as-treated analyses were performed. In the intention-to-treat, patients were censored at the earliest among the following: (i) last date of follow-up (31 December 2022), (ii) 10 years after AF diagnosis, or (iii) at a competing event date. For the as-treated analysis, patients were censored if they commenced amiodarone treatment for controls and, alternatively, for the treatment group, if there were more than 60 days between sequential amiodarone drug dispensing unless the last dispensing included a non-standard prescription with more than 30 tablets (in such cases, patients were censored if the number of amiodarone tablets had not covered 50% of the time).

Study covariates

All study covariates were based on information recorded prior to amiodarone therapy initiation or equivalent matched time for the amiodarone-unexposed controls. Age was considered the baseline age at which amiodarone or matched-control therapy was initiated. Admissions were calculated as the cumulative number of admissions 5 years before the initiation of exposure (amiodarone or matched-control). Socioeconomic status relied on a five-rank categorical scale based on CHS records.[17] All medical conditions (based on ICD-9 codes and an internal coding system) and drug exposures were based on records before (up to 6 months) the index exposure date.

Outcome data

The primary outcome was newly diagnosed ILD. Secondary outcomes were PLC and all-cause mortality. Also, the associations between amiodarone exposure and referrals to pulmonary care clinics, a large variety of pulmonary-related conditions (asthma, chronic obstructive pulmonary disease, and pneumonia), and potential adverse effects (hypothyroidism, hyperthyroidism, and liver toxicity) were examined.

Interstitial lung disease was defined based on relevant ICD-9 codes for ILD or drug-associated lung disease (ICD-9 codes: 508.8, 515–516.9, and 518.89). Primary lung cancer was identified based on ICD-9 codes 162.x and 231.2. All-cause mortality was determined based on mortality documentation during the follow-up period until 31 December 2022, as recorded and cross-validated with the national computerized registry of the Ministry of Interior. A table delineating all the diagnoses and ICD-9 codes used for outcome determination are provided in Supplementary data online, *Supplement S2*.

Statistical analysis

Baseline characteristics of the study population are presented as medians (interquartile range) for continuous variables, counts, and percentages for categorical variables. The Mann–Whitney *U* and χ^2 tests were applied to compare the variables' distribution.

The study population comprised paired patient couples according to amiodarone exposure status, defined by the documented prescription and regular monthly dispensing in the amiodarone-treated arm. To estimate the average treatment effect in the treated among the different populations, the inverse probability treatment weighting (IPTW) methodology was used.[18] Variables included in the IPTW were predetermined by two experts (G.T. and M.H.) using a directed acyclic graph (DAG) to represent causal effects between variables. The causal model connecting consistent low-dose amiodarone exposure with ILD or mortality is depicted in *Figure 2*. In the DAG, arrows between variables indicate causation, and unconnected variables have no direct causal association. All statistical analyses in balancing between study groups were performed with consideration of the DAG framework and including chosen covariates to minimize the bias of the estimands of amiodarone exposure on study outcomes. To

overcome potential frailty differences between study populations, the following baseline covariates included in the IPTW modelling were age (by quintiles), number of admissions prior to commencement of follow-up (by quintiles), socioeconomic rank status (by rank), smoking status, antiarrhythmic therapy other than amiodarone, beta-blocker treatment, liver disease, malignancy, rheumatic disease, renal disease, stroke, peripheral vascular disease, myocardial infarction, congestive heart failure, diabetes, dementia, and chronic obstructive pulmonary disease.

Absolute standardized mean difference and Kolmogorov–Smirnov statistics were used to evaluate covariate balance. Balance was determined based on acceptable .1 and .05 thresholds, respectively. Next, IPTW Kaplan–Meier curves were constructed using the Aalen–Johansen estimator, and three effect estimands were computed: (i) hazard ratio (HR) as a weighted risk assessment for the complete follow-up, (ii) risk ratios (RR), and (iii) risk differences (RD) for each year of follow-up, based on the Kaplan–Meier estimator. The confidence intervals (CI) around the Kaplan–Meier curves were computed based on robust standard errors, and a nonparametric percentile bootstrap method with 500 repetitions was used for the effect estimands. All analyses followed an 'on-treatment' approach where all events were accounted for from the first dispensing date and up to 42 days following the last recorded dispensing date, or 10 years of regular amiodarone dispensing, equally for each matched pair. An intention-to-treat based on the entire study population was performed, irrespective of amiodarone adherence and unrelated to variable gaps in treatment during follow-up, and a sensitivity analysis emulating a target trial was carried out. All analyses followed the same statistical procedure as the primary analysis. Additionally, since the study period overlaps with the COVID-19 pandemic, which primarily involved acute pulmonary disease, another sensitivity analysis, confined to the pre-pandemic era, was conducted, truncating follow-up time to 1 January 2020, when the pandemic was first reported in Israel.

For all analyses, significance was set at a two-sided *P*-value of ≤.05. Statistical analyses were performed using R: Core Team, statistical software version 4.1.2 [(R Foundation for Statistical Computing, Vienna, Austria), RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/].

Results

Study population

During the study period, 278 625 new cases of AF as a primary diagnosis were identified. A total of 45 164 individuals had documented amiodarone prescription and dispensing after AF diagnosis throughout the study period. After matching to amiodarone-unexposed patients in a 1:1 ratio, according to the pre-specified above-mentioned matching criteria, and excluding couples with recorded study outcomes before the index exposure date, 33 958 patients were retained in each group. Of the at-risk matched cohort, 6039 amiodarone-exposed patients were identified to have consistent amiodarone dispensing throughout the follow-up term without interruption and were included in the final analysis with their matched amiodarone-unexposed controls. The median time from AF diagnosis to amiodarone therapy initiation was 232 days (interquartile range 28–1426 days), and the median daily amiodarone-defined dose during the study was 200 mg q.d. (interquartile range 196–205 mg q.d.). The flowchart of the study is depicted in *Figure 1*.

Baseline characteristics

Baseline characteristics of the final study population are presented in *Table 1*.

Patients exposed to amiodarone had higher rates of diabetes; previous cardiovascular, peripheral vascular, and cerebrovascular diseases; prior malignancy; background rheumatic disease; and background chronic renal disease ($P < .05$ for all). Also, amiodarone-exposed patients had marginally higher smoking rates ($P = .093$) and were most likely to suffer from chronic obstructive pulmonary disease ($P < .05$). Amiodarone-exposed patients were slightly less likely to have background dementia ($P = .006$). Notably, patients treated with amiodarone were more likely to be treated with beta-blockers (87.3% vs. 66.5%), other antiarrhythmic medications (24.6% vs. 12.6%), and systemic anticoagulation (68.8% vs. 31.4%, $P < .001$ for all). The covariate balancing Love plot used to compare outcomes across study groups is provided in Supplementary data online, Supplement S3. Overall, all covariates were adequately balanced.

Pulmonary surveillance

Active pulmonary surveillance rates were assessed using documentation of patients' first visit to pulmonary assessment (lung function tests or pulmonologist examination). After IPTW, amiodarone-exposed patients tended to be referred more and earlier to pulmonology assessments (HR 1.60, 95% CI 1.31, 2.26; $P < .001$).

Interstitial lung disease

During a median follow-up of 4.2 years, ILD was diagnosed in 242 (2.0%) of the patients. After IPTW, amiodarone exposure was not significantly related to an increased risk of ILD (HR 1.45, 95% CI 0.97, 2.44; $P = .09$). The IPTW-based survival curves of ILD across study groups are presented in *Figure 3A*. Fifty-six patients diagnosed with ILD in the amiodarone exposure group discontinued amiodarone dispensing around their diagnosis (up to 60 days after ILD diagnosis). The RR and RD for each year are reported in Supplementary data online, Supplement 4. When observing yearly RR differences, amiodarone exposure was associated with a very mild increase in RR starting from the second year of exposure (RR: 1.0065, 95% CI 1.0005, 1.0115), which remained similarly higher until after the eighth year of exposure (RR: 1.0190, 95% CI 1.0041, 1.0342), after which, in the ninth and tenth years of exposure resumed to be indifferent. Between the second and eighth years of exposure, the number needed to harm to cause one ILD case with amiodarone ranged from 55 (eighth year) to 156 patients (second year).

Primary lung cancer

At a median follow-up of 4.1 years, PLC was diagnosed in 97 patients (0.8%). After IPTW, amiodarone exposure was not related to increased risk of PLC [adjusted hazard ratio (aHR) 1.18, 95% CI 0.76, 2.08; $P = .53$]. The IPTW-based survival curves of PLC across study groups are presented in *Figure 3B*. When observing yearly RR differences, amiodarone exposure was not associated with PLC during all follow-up years (see Supplementary data online, Supplement S4).

All-cause mortality

At a median follow-up of 4.9 years, all-cause death occurred in 2185 (18.1%). After IPTW, amiodarone exposure was related to a lower risk of all-cause death (aHR 0.65, 95% CI 0.60, 0.72; $P < .001$). The IPTW-based survival curves of PLC across study groups are presented in *Figure 3C*. The association between amiodarone exposure and lower risk of mortality was consistent throughout study years, with RRs ranging from 0.9582 (95% CI 0.9462, 0.9696) in the first year to 0.8501 (95% CI 0.7976, 0.9025) in the eighth year. The number needed to treat with amiodarone to prevent one mortality case was stable and ranged between 10 (eighth year) and 24 patients (first year).

Table 1 Baseline characteristics of the matched study population

	Control ($n = 6039$)	Amiodarone ($n = 6039$)	Entire ($n = 12\,078$)	Significance
Sex (female)	3118 (51.6%)	3118 (51.6%)	6326 (51.6%)	1
Age (years)	72.1 (64.2, 79.4)	74.4 (66.9, 80.7)	73.3 (65.4, 80.0)	<0.001
Ethnicity (Jewish)	5036 (83.4%)	5049 (83.6%)	10 085 (83.5%)	0.920
Socioeconomic status (low)	1581 (26.2%)	1424 (23.6%)	3005 (24.9%)	0.004
Smokers	1504 (24.9%)	1586 (26.3%)	3090 (25.6%)	0.093
Malignancy	638 (10.6%)	785 (13.0%)	1833 (14.2%)	0.0301
Prior cerebrovascular disease	1316 (21.8%)	1668 (27.6%)	2984 (24.7%)	<0.001
Pulmonary disease[a]	1748 (28.9%)	2183 (36.1%)	3931 (32.5%)	<0.001
Congestive heart failure	1005 (16.6%)	2291 (37.9%)	3296 (27.3%)	<0.001
Dementia	458 (7.6%)	380 (6.3%)	838 (6.9%)	0.006
Diabetes	2000 (33.1%)	2514 (41.6%)	4514 (37.4%)	<0.001
Significant hepatic disease	10 (0.2%)	12 (0.2%)	22 (0.2%)	0.831
Rheumatic disease	290 (4.8%)	365 (6.0%)	655 (5.4%)	0.003
Renal disease	806 (13.3%)	1332 (22.1%)	2138 (17.7%)	<0.001
Prior myocardial infarction	676 (11.2%)	1560 (25.8%)	2236 (18.5%)	<0.001
Peripheral vascular disease	603 (10.0%)	876 (14.5%)	1479 (12.2%)	<0.001
Beta-blocker therapy	4017 (66.5%)	5272 (87.3%)	9289 (76.9%)	<0.001
Antiarrhythmic therapy	759 (12.6%)	1484 (24.6%)	2243 (18.6%)	<0.001
Anticoagulation therapy	1894 (31.4%)	4157 (68.8%)	6051 (50.1%)	<0.001

[a]Chronic obstructive pulmonary disease or asthma.

Exploratory outcomes related to amiodarone exposure

The association between amiodarone exposure and other possible side effects and clinical outcomes was explored. After IPTW, amiodarone exposure was associated with an increased risk of hyperthyroidismHR 5.7, 95% CI 3.90, 8.34), hypothyroidism (HR 8.7, 95% CI 6.93, 11.00), hepatic disorder (HR 2.67, 95% CI 1.83, 3.91), incident asthma (HR 1.34, 95% CI 1.00, 1.79), and incident pneumonia (HR 1.37, 95% CI 1.17, 1.60). Amiodarone exposure was not associated with chronic obstructive pulmonary disease (HR 1.18, 95% CI 0.94, 1.48) nor adult respiratory distress syndrome (HR 1.22, 95% CI 0.85, 1.74).

Sensitivity analyses

Three sensitivity analyses were performed to support the validity of the primary analysis.

The sensitivity analysis results among the entire population, regardless of consistency of amiodarone use, are provided in Supplementary data online, Supplement S5. Briefly, interrupted amiodarone exposure was associated with a slightly greater risk of ILD and PLC and had a reduced risk of death as in the primary analysis.

When including only the pre-COVID-19 pandemic era, no associations were found between amiodarone exposure and ILD (HR 1.33, 95% CI 0.83, 2.14, $P = .33$) or PLC (HR .93, 95% CI 0.54, 1.62, $P = .74$), but the association between amiodarone exposure and lower risk for all-cause mortality remained (HR 0.66, 95% CI 0.59, 0.74, $P < .001$).

Results of the sensitivity analysis based on target trial emulation are provided in Supplementary data online, *Supplement 6*. Overall, 199 313 patients met the inclusion and exclusion criteria and were included in this analysis. In the intention-treat analysis, there was no association between amiodarone treatment and ILD (HR 1.07, 95% CI 0.98, 1.18) or PLC (HR 0.96, 95% CI 0.84, 1.11). However, the as-treated analysis, though confined to a median follow-up time of 262 days, revealed a minor increased risk for ILD under amiodarone treatment (HR 1.15, 95% CI 1.02, 1.27) but slightly lower risk for PLC (HR 0.82, 95% CI 0.71, 0.95). Also, amiodarone exposure was consistently associated with a lower risk of all-cause death among these patients (intention-to-treat: HR 0.95, 95% CI 0.93, 0.97; as-treated: HR 0.84, 95% CI 0.82, 0.86).

Discussion

In this nationwide population-based study, among 12 078 newly diagnosed AF patients who were followed for a median time of 4.2 years, continuous and consistent low-dose amiodarone exposure was not associated with increased risk of ILD or PLC on long-term follow-up. It should be noted that amiodarone did show a small clinically marginal statistical association with increased risk of ILD between 2 and 8 years of follow-up, which, albeit statistically significant, was clinically negligible and accounted for with a maximal RR of 1.019 after 8 years of follow-

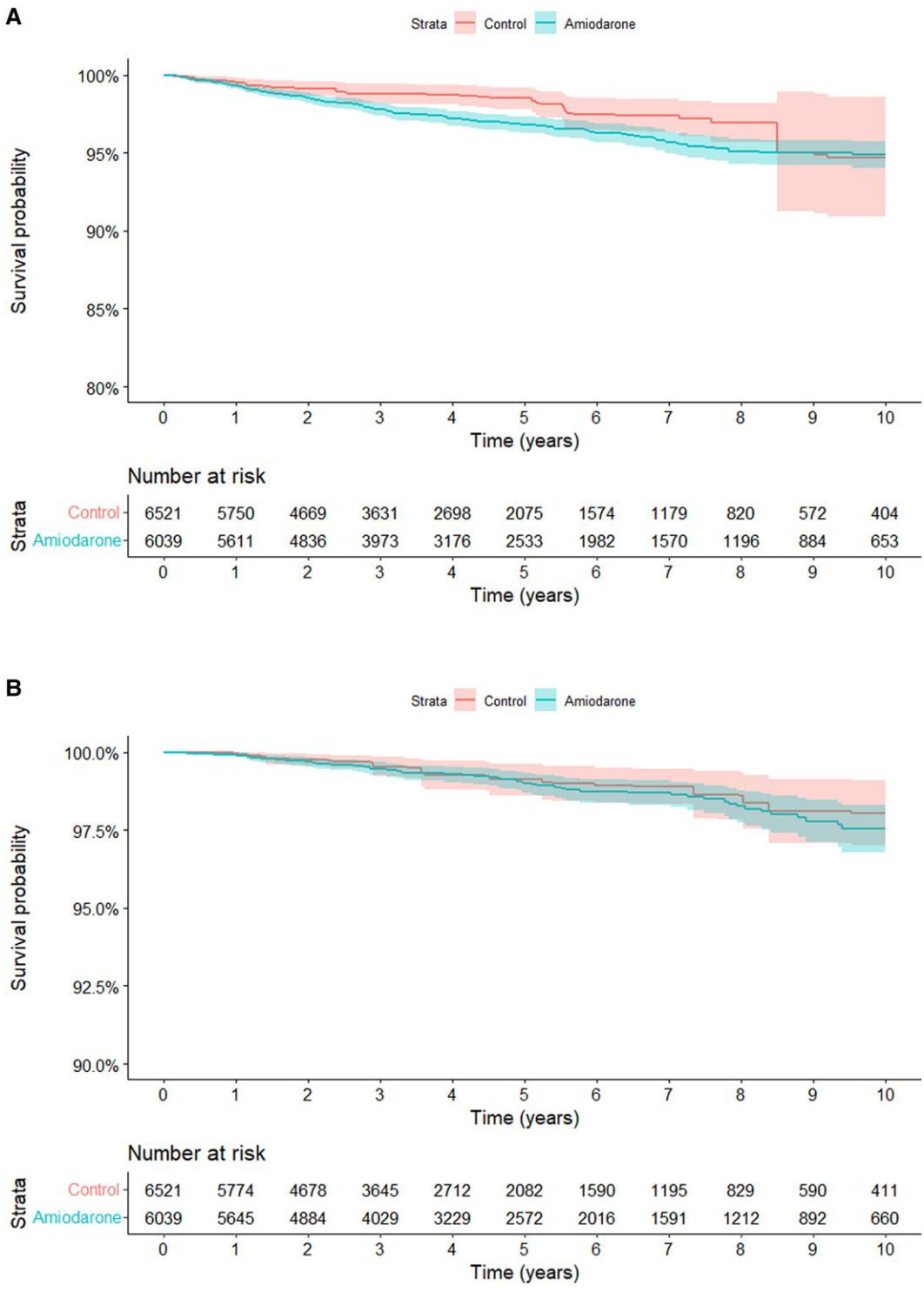


Figure 3 Kaplan–Meier curves for the primary and secondary outcomes. (*A*) Interstitial lung disease. (*B*) Primary lung cancer. (*C*) All-cause mortality

up. Remarkably, the incidences of ILD (~2%) and PLC (~0.8%) were relatively low (*Structured Graphical Abstract*). Also, mortality risk was lower among patients exposed to amiodarone and remained so for all follow-up years, implying that this did not significantly affect the patient's overall prognosis. The study results were consistent across sensitivity analyses, including a target emulation trial framework built to assess causal inference. To date, this study is the first to address the impact of consistent exposure to currently used doses of amiodarone on pulmonary safety and overall prognosis in a tightly followed contemporary population with consistent amiodarone dispensing.

Previous studies reported a higher ILD rate among patients treated with amiodarone.[6] In that era, amiodarone was prescribed in chronic

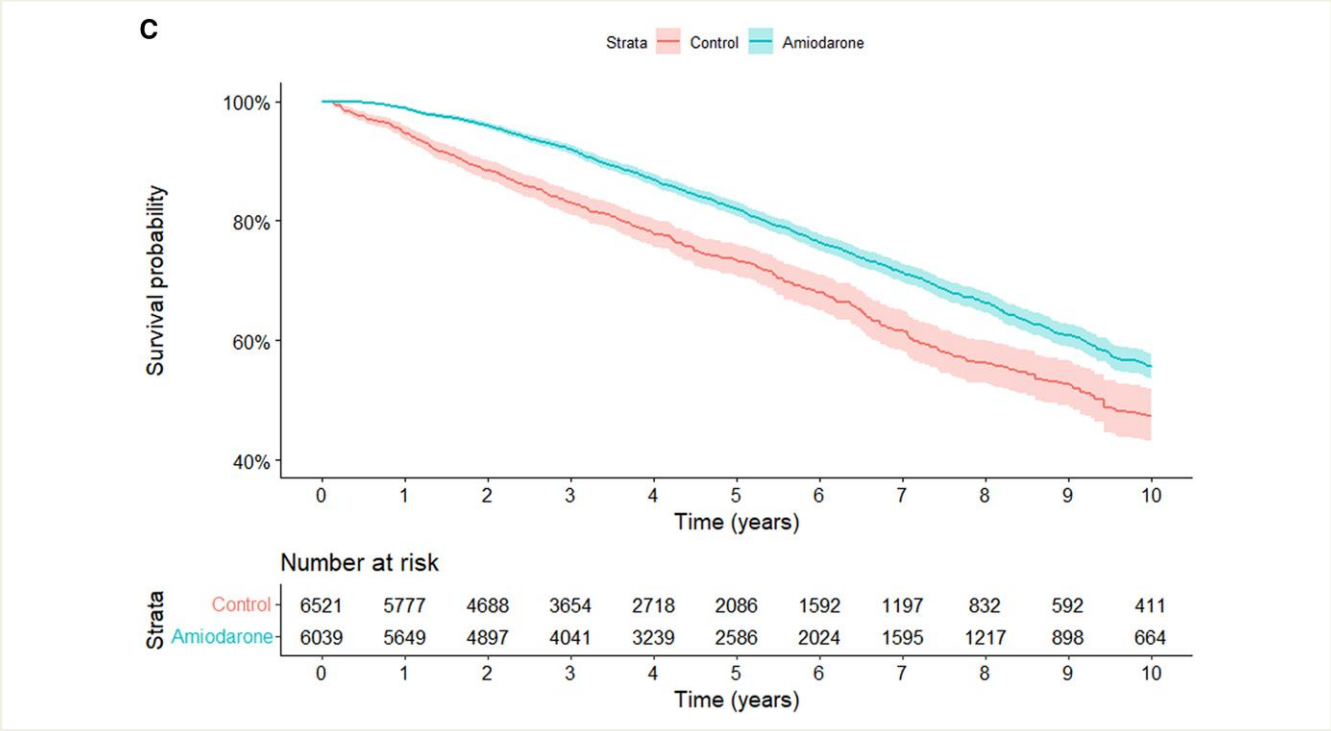


Figure 3 Continued

high doses (≥400 mg/day), contrary to the lower dose regimens which are practiced now. In previous trials, the reported incidence of amiodarone-related ILD ranges from 5% to 10% over 5 years or more.[6–8] However, a recent report found that the current amiodarone-associated ILD incidence is around 2%.[13] A randomized study among sudden cardiac death survivors, where low-dose amiodarone was used, reported a ∼10% incidence of amiodarone pulmonary toxicity.[16] However, that trial had a small sample size ($n = 228$), included a proactive pulmonary surveillance of amiodarone-treated patients, and thus was more sensitive to subclinical pulmonary adverse events, unlike the current study that relied on EHRs and comprised of a different patient population. Most importantly, of the nine patients diagnosed with ILD in that study, none died during follow-up, and, in the entire cohort, amiodarone was associated with reduced mortality, similar to this study's findings. The low incidence of ILD limits the likelihood of performing a randomized study to test this association between amiodarone and ILD. While two meta-analyses of randomized trials, including amiodarone exposure irrespective of dosage, showed an increased risk of ILD with amiodarone treatment,[19,20] another meta-analysis, including only trials with low-dose amiodarone, did not show a significant difference in the risk of ILD.[8] These inconsistent findings leave the question of the pulmonary safety of low-dose amiodarone treatment unresolved. Of note, meta-analyses are sensitive to pooling patients with different baseline risks and thus might be prone to misleading results; however, given the low incidence of ILD, considerable variability in amiodarone exposure, and limited sample size of existing studies, they are better powered to reveal possible relationships between amiodarone exposure and ILD.

The current analysis is based on a population derived from a large health maintenance organization with close medical surveillance and low turnover rates. When interpreting the results of this study, it should be acknowledged that the incidence of ILD in the Israeli population is relatively low compared with the rest of the world.[21,22] A previous population-based study from Canada among patients with AF reported a slightly lower incidence of ILD than in this study but, on the other hand, showed a significantly higher risk of ILD among amiodarone-treated patients, regardless of dosage.[12] However, as mentioned earlier, this study had a significant imbalance between study groups, which were not matched by any criteria, included only elderly patients, and did not account for time since AF diagnosis and the amiodarone-free interval of the exposed population. On the other hand, a study among heart failure patients showed, concordant with this study's findings, that low-dose amiodarone therapy was not associated with an increased risk of ILD.[23] A recent multicentre study with a similar incidence of ILD as in this report showed that cumulative exposure to low-dose amiodarone was associated with increased ILD risk.[13] The study results show that consistent therapy with low-dose amiodarone is not associated with an increased risk of ILD in 10 years, although with meagre, clinically negligible association of ILD between 2 and 8 years of exposure.

In this study, focusing on the pulmonary safety of amiodarone therapy, the incidence of PLC was low and similar across the study groups. The lack of association between low-dose amiodarone use and the risk of PLC in this study concurs with previous reports showing that amiodarone is safe regarding cancer risk.[24,25] While higher doses of amiodarone were proposed to be associated with increased risk,[9] several studies, including this report, showed that amiodarone therapy in currently accepted doses is not associated with an increased risk of cancer.[24,25] Moreover, some studies suggested that amiodarone might promote anti-neoplastic effects.[26]

Amiodarone is the most effective pharmacotherapy for maintaining sinus rhythm among patients with AF, linked with reductions in AF-related procedures and costs.[1–3,27] However, due to considerable possible side effects and contradictory data on long-term clinical

benefits, most recent guidelines recommend amiodarone as a last resort for rhythm control for AF patients.[28] The recent EAST-AFNET 4 study showed that an early rhythm control strategy is associated with reduced cardiovascular risk.[4] Previous studies, such as AFFIRM and RACE, failed to show improved outcomes with this strategy.[29–31] Data on the association between amiodarone exposure and mortality are contradictory as different studies reported increased,[32] similar,[32] or reduced risk of death.[33] The results of this study, based on a real-world contemporary population of patients with newly diagnosed AF with a median follow-up of over 5 years, show that amiodarone treatment is not associated with an increased risk of death in patients with newly diagnosed AF. Moreover, in the present analysis, amiodarone was associated with a reduced risk of death after IPTW. These results should be interpreted cautiously due to the possible residual, unaccounted for, confounding, and potential systematic bias due to imbalance in medical surveillance and treatment associated with the amiodarone-treated group, as possible with any registry-based study. However, these results provide a relatively solid reassurance regarding the safety of amiodarone treatment with no signal of increased risk of death.

The analyses show that consistency of amiodarone use played a vital role in the association between amiodarone treatment and risk of ILD and PLC. This finding may indicate that the added pulmonary risk attributed to amiodarone treatment may, in part, be related to distinct patient characteristics that influence the decision to prescribe amiodarone treatment while also independently increasing the risk of pulmonary disease. Also, this finding could be explained by a higher demand for medical treatment and tighter follow-up among patients prescribed amiodarone. This study's findings highlight that consistency of amiodarone therapy, which is the closest measure to assure adherence to therapy in clinical trial design, is not associated with clinically significant increased pulmonary risk and probably diminished the unaccounted residual risk that stems from the immense differences between patients who are treated with amiodarone to those who are not. The higher incidence of known adverse effects of amiodarone therapy, such as hypothyroidism, hyperthyroidism, and hepatic disorders, supports the study's cohort's reliability and the results' validity.

Several limitations of this study should be acknowledged. First, as with any historical population-based study, one could only control for variables with recorded data, which may result in residual confounding that was not addressed in the statistical analyses. While it is plausible that patients who were treated with amiodarone might be under tighter medical surveillance and follow-up and possibly exposed to other therapeutic and pharmaceutical interventions (specifically such that may affect amiodarone metabolism or associated with pulmonary side effects) which were unaccounted for, these patients had a much higher burden of comorbidities that increased the risk of subsequent medical events and death, counterbalancing their potential residual confounding. Also, applying the IPTW approach and the high covariate balancing achieved in this study provides the closest fit of covariate balance that could be achieved in a population-based study setting while maintaining maximal sample size, which would have been significantly limited by conventional matching. Notably, the data used did not include information on genetic, occupational, and environmental exposures. While these exposures are seldom assessed in any trial, their potential effects on the outcomes related to this study might be significant. While these factors could not be accounted for given the nature of the data, socioeconomic status, and ethnicity, two factors that might partly reflect these exposures were included in the statistical analyses to balance between study groups. Second, events were based on diagnoses made in electronic medical records, thus leaving the possibility of under-reporting or misdiagnosis. However, although ILD and PLC diagnoses were not separately validated, all diagnoses in the used AF registry have been previously validated.[34] In addition, events were very inclusively classified based on adjudication by hospital and community physicians; thus, the ILD incidence reported in this study might even be higher than actual disease rates. While this study does not account for subclinical cases that could have been diagnosed under active screening in pulmonary clinics, it does reflect the clinically significant disease incidence since these cases often seek medical attention and are diagnosed within the health system. Given the clinical benefits of rhythm control and considering the lower mortality observed in this study under amiodarone adherence, it might be argued that any possible subclinical adverse effect of amiodarone should necessarily imply drug discontinuation. Lastly, the current study aimed to assess possible causality between low-dose amiodarone use and ILD during follow-up and thus included patients treated with low-dose amiodarone continuously and might represent a subpopulation of patients who are distinct from those who take amiodarone irregularly. However, given the focus of this study and considering the vast differences between patients who are treated with amiodarone to those who are not, it may be argued that this is the first study to most-closely address the association between prolonged amiodarone exposure and these outcomes. Also, it might be argued that choosing exposures based on the consistency of amiodarone use and non-exposures based on never being exposed to amiodarone may be prone to collider or indication bias. Thus, we performed a sensitivity analysis using a target trial emulation framework, which findings are consistent with those of the primary analysis revealing no to marginally increased risk of ILD, no excess risk for PLC, and a lower risk of all-cause death with amiodarone exposure. While this sensitivity analysis is subjective to substantially shorter follow-up time due to the inherent attributes of the as-treated target emulation network and the natural course of patients with AF, who frequently are treated at some point with amiodarone due to accumulation of background morbidities or increased disease burden, its consistency with the primary analysis results provide reassurance concerning the robustness of the data and the findings of the study. The strengths of the study are its large sample size representing contemporary real-world medical practice, the assurance of consistent amiodarone exposure during follow-up, eliminating misclassification of diagnoses attribution, completeness of follow-up, and access to imaging, laboratory, and hospitalization, as well as community data. Other strengths of the study are the matching of the patients by time since AF diagnosis and the truncation of time following amiodarone discontinuation in both study groups, which minimize the chances of lead-time and misclassification biases.

In conclusion, this study showed that amiodarone treatment with currently used doses among patients with AF was associated with a no to very slight increase in long-term risk of ILD and no increased risk for PLC in patients with AF. While amiodarone exposure was associated with a meagre, clinically negligible, increased risk of ILD between 2 and 8 years of treatment, this risk was outbalanced in the long term. Also, patients exposed to amiodarone had no increased risk of all-cause death. If validated by others, the results of this study might warrant a change in the pulmonary follow-up policy of patients initiated with amiodarone therapy and may encourage an increase in its use for rhythm control in AF.

Supplementary Data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

G.T. previously received speaker's fee from Novo Nordisk and travel support for scientific meeting from Bayer. G.T. received a limited research grant from the Israeli Heart Society. H.A. previously received travel support for scientific meeting from Bayer. L.K. previously received a research grant from Pfizer Inc. via the BMS/Pfizer European Thrombosis Investigator Initiated Research Program (ERISTA). M.H. received a research grant from Pfizer Inc. and is a part of the Pfizer Inc. advisory board for AF screening. M.H. received an unrestricted educational grant to conduct research from the Michel Mirowski international fund. M.H. is a member of the European Heart Rhythm Association national cardiac societies committee and the chairperson of the Israeli working group on electrophysiology and pacing.

Data Availability

The data of this study are available to share under the policies of data privacy and confidentiality regulations of Clalit Health Services.

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Ethical Approval

This study was approved by the Institutional Committee on Human Research of Soroka University Medical Center, Beersheva, Israel.

Pre-registered Clinical Trial Number

This trial relied on historical database and does not require pre-registration.

References

1. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, *et al.* Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med* 2005;**352**:1861–72. https://doi.org/10.1056/NEJMoa041705
2. AFFIRM First Antiarrhythmic Drug Substudy Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. *J Am Coll Cardiol* 2003;**42**:20–9. https://doi.org/10.1016/S0735-1097(03)00559-X
3. Zimetbaum P. Amiodarone for atrial fibrillation. *N Engl J Med* 2007;**356**:935–41. https://doi.org/10.1056/NEJMct065916
4. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, *et al.* Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305–16. https://doi.org/10.1056/NEJMoa2019422
5. Schwaiblmair M, Berghaus T, Haeckel T, Wagner T, von Scheidt W. Amiodarone-induced pulmonary toxicity: an under-recognized and severe adverse effect? *Clin Res Cardiol* 2010;**99**:693–700. https://doi.org/10.1007/s00392-010-0181-3
6. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. Recognition and pathogenesis (part I). *Chest* 1988;**93**:1067–75. https://doi.org/10.1378/chest.93.5.1067
7. Dusman RE, Stanton MS, Miles WM, Klein LS, Zipes DP, Fineberg NS, *et al.* Clinical features of amiodarone-induced pulmonary toxicity. *Circulation* 1990;**82**:51–9. https://doi.org/10.1161/01.CIR.82.1.51
8. Vorperian VR, Havighurst TC, Miller S, January CT. Adverse effects of low dose amiodarone: a meta-analysis. *J Am Coll Cardiol* 1997;**30**:791–8. https://doi.org/10.1016/S0735-1097(97)00220-9
9. Su VYF, Hu YW, Chou KT, Ou SM, Lee YC, Lin EYH, *et al.* Amiodarone and the risk of cancer: a nationwide population-based study. *Cancer* 2013;**119**:1699–705. https://doi.org/10.1002/cncr.27881
10. Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. *JAMA* 2007;**298**:1312–22. https://doi.org/10.1001/jama.298.11.1312
11. Goldschlager N, Epstein AE, Naccarelli GV, Olshansky B, Singh B, Collard HR, *et al.* Practical guide for clinicians who treat patients with amiodarone: 2007. *Heart Rhythm* 2007;**4**:1250–9. https://doi.org/10.1016/j.hrthm.2007.07.020
12. Jackevicius CA, Tom A, Essebag V, Eisenberg MJ, Rahme E, Tu JV, *et al.* Population-level incidence and risk factors for pulmonary toxicity associated with amiodarone. *Am J Cardiol* 2011;**108**:705–10. https://doi.org/10.1016/j.amjcard.2011.04.024
13. Kwok WC, Ma TF, Chan JWM, Pang HH, Ho JCM. A multicenter retrospective cohort study on predicting the risk for amiodarone pulmonary toxicity. *BMC Pulm Med* 2022;**22**:128. https://doi.org/10.1186/s12890-022-01926-y
14. Yamada Y, Shiga T, Matsuda N, Hagiwara N, Kasanuki H. Incidence and predictors of pulmonary toxicity in Japanese patients receiving low-dose amiodarone. *Circ J* 2007;**71**:1610–6. https://doi.org/10.1253/circj.71.1610
15. Goodman DC, Goodman AA. Medical care epidemiology and unwarranted variation: the Israeli case. *Isr J Health Policy Res* 2017;**6**:9. https://doi.org/10.1186/s13584-017-0135-6
16. The CASCADE Investigators. Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE study). *Am J Cardiol* 1993;**72**:280–7. https://doi.org/10.1016/0002-9149(93)90673-Z
17. Filc D, Davidovich N, Novack L, Balicer RD. Is socioeconomic status associated with utilization of health care services in a single-payer universal health care system? *Int J Equity Health* 2014;**13**:115. https://doi.org/10.1186/s12939-014-0115-1
18. Hernán MA, Wang W, Leaf DE. Target trial emulation: a framework for causal inference from observational data. *JAMA* 2022;**328**:2446–7. https://doi.org/10.1001/jama.2022.21383
19. Ruzieh M, Moroi MK, Aboujamous NM, Ghahramani M, Naccarelli GV, Mandrola J, *et al.* Meta-analysis comparing the relative risk of adverse events for amiodarone versus placebo. *Am J Cardiol* 2019;**124**:1889–93. https://doi.org/10.1016/j.amjcard.2019.09.008
20. Piccini JP, Berger JS, O'Connor CM. Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. *Eur Heart J* 2009;**30**:1245–53. https://doi.org/10.1093/eurheartj/ehp100
21. Kolonics-Farkas AM, Šterclová M, Mogulkoc N, Lewandowska K, Müller V, Hájková M, *et al.* Differences in baseline characteristics and access to treatment of newly diagnosed patients with IPF in the EMPIRE countries. *Front Med* 2021; **8**:2559. https://doi.org/10.3389/fmed.2021.729203
22. Sauleda J, Núñez B, Sala E, Soriano JB. Idiopathic pulmonary fibrosis: epidemiology, natural history, phenotypes. *Med Sci (Basel)*. 2018;**6**:110. https://doi.org/10.3390/medsci6040110
23. Singh SN, Fisher SG, Deedwania PC, Rohatgi P, Singh BN, Fletcher RD. Pulmonary effect of amiodarone in patients with heart failure. *J Am Coll Cardiol* 1997;**30**:514–7. https://doi.org/10.1016/S0735-1097(97)00157-5
24. Siemers LA, MacGillivray J, Andrade JG, Turgeon RD. Chronic amiodarone use and the risk of cancer: a systematic review and meta-analysis. *CJC Open* 2021;**3**:109–14. https://doi.org/10.1016/j.cjco.2020.09.013
25. Rasmussen PV, Dalgaard F, Hilmar Gislason G, Torp-Pedersen C, Piccini J, D'Souza M, *et al.* Amiodarone treatment in atrial fibrillation and the risk of incident cancers: a nationwide observational study. *Heatr Rhythm* 2020;**17**:560–6. https://doi.org/10.1016/j.hrthm.2019.11.025
26. Steinberg E, Fluksman A, Zemmour C, Tischenko K, Karsch-Bluman A, Brill-Karniely Y, *et al.* Low dose amiodarone reduces tumor growth and angiogenesis. *Sci Rep* 2020;**10**:18034. https://doi.org/10.1038/s41598-020-75142-1
27. Lumer GB, Roy D, Talajic M, Couturier A, Lambert J, Frasure-Smith N, *et al.* Amiodarone reduces procedures and costs related to atrial fibrillation in a controlled clinical trial. *Eur Heart J* 2002;**23**:1050–6. https://doi.org/10.1053/euhj.2001.2986
28. Hindricks G, Potpara T, Dagres N, Bax JJ, Blomström-Lundqvist C, Boriani G, *et al.* 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498. https://doi.org/10.1093/eurheartj/ehaa612
29. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, *et al.* A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;**347**:1834–40. https://doi.org/10.1056/NEJMoa021375
30. Saksena S, Slee A, Waldo AL, Freemantle N, Reynolds M, Rosenberg Y, *et al.* Cardiovascular outcomes in the AFFIRM trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management): an assessment of individual antiarrhythmic drug therapies compared with rate control with propensity score-matched analyses. *J Am Coll Cardiol* 2011;**58**:1975–85. https://doi.org/10.1016/j.jacc.2011.07.036
31. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, *et al.* A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825–33. https://doi.org/10.1056/NEJMoa021328
32. Ullal AJ, Than CT, Fan J, Schmitt S, Perino AC, Kaiser DW, *et al.* Amiodarone and risk of death in contemporary patients with atrial fibrillation: findings from the Retrospective Evaluation and Assessment of Therapies in AF study. *Am Heart J* 2015;**170**:1033–-1041.e1. https://doi.org/10.1016/j.ahj.2015.07.023
33. Sim I, McDonald KM, Lavori PW, Norbutas CM, Hlatky MA. Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death. *Circulation* 1997;**96**:2823–9. https://doi.org/10.1161/01.CIR.96.9.2823
34. Reges O, Weinberg H, Hoshen M, Greenland P, Rayyan-Assi H, Tsadok MA, *et al.* Combining inpatient and outpatient data for diagnosis of non-valvular atrial fibrillation using electronic health records: a validation study. *Clin Epidemiol* 2020;**12**:477–83. https://doi.org/10.2147/CLEP.S230677