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Clinical Research Study

The Bad Reputation of Digoxin in Atrial Fibrillation—Causality or Bias? Nationwide Nested Case-Control Study ☆,☆☆

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ABSTRACT

Aims: Studies have reported excess risk of mortality associated with digoxin in atrial fibrillation (AF). This study sought to investigate if these findings could be replicated and whether a potential association could be explained by bias.

Methods: Using Danish Nationwide registers, a nested-case control study from 2012 to 2022 was conducted in a cohort of patients with AF. Cases were defined as death of any cause and the exposure was treatment with digoxin compared with beta blockers/verapamil. To investigate bias, additional analyses with negative control outcomes as case definitions—in which we would not expect a plausible association (eg, nursing home admission)—were employed. Associations were reported as hazard ratios (HRs) with 95% confidence intervals (95% CI).

Results: A total of 59,748 cases were identified and matched 1:10 with controls (53% men, median age: 84 [IQR: 77-89]). Digoxin was associated with increased rates of mortality in the entire cohort (HR 1.85, 95% CI 1.78-1.92) as well as subgroups such as patients with heart failure (HR 1.84, 95% CI 1.65-2.06), diabetes (HR 1.85, 95% CI 1.6-2.14), and kidney disease (HR 1.37, 95% CI 1.04-1.8). Significant associations with all negative control outcomes were also found, most notably nursing home admissions (HR 1.79, 95% CI 1.67-1.93).

Conclusion: Digoxin use was associated with increased mortality in AF. However, negative control outcomes were also associated with digoxin use indicating that the described association between digoxin and mortality is likely not causal and being prescribed digoxin is merely a marker of more advanced disease and frailty.

Introduction

Patients with atrial fibrillation (AF) often suffer from an increased resting heart rate due to inappropriately frequent ventricular contractions requiring treatment.[1] Common interventions for rate-control in AF includes digoxin, a cardiac glycoside, which has been used for medical purposes for centuries.[2] Digoxin is excreted renally and has a relatively narrow therapeutic interval putting patients at a theoretical risk of supratherapeutic serum concentrations and intoxication. Digoxin toxicity comprises several symptoms including fatigue, gastrointestinal symptoms (eg, nausea, vomiting), electrolyte disturbances as well as an increased incidence of arrhythmias and death.[3,4]

Consequently, reports from both post hoc analyses of trial data designed for different research questions as well as observational studies have described increased mortality in patients treated with digoxin leading to severe concerns regarding the safety of digoxin.[5–17] Recently, this discussion was reinvigorated by concerns regarding increased mortality in patients with an implantable cardiac device treated with digoxin.[8] However, these studies coexist with neutral reports, and are almost exclusively nonrandomized comparisons prone to bias, especially without appropriate comparator groups. Importantly, due to its mechanism of action and few contraindications, digoxin is often prescribed for medically frail patients difficult to account for by covariate adjustment.[18–21] Due to these conflicting results, the controversy, and the widespread

Abbreviations: AF, Atrial fibrillation; IQR, Interquartile range; HR, Hazard ratio; CI, Confidence interval; IHD, Ischemic Heart Disease; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; PAD, Peripheral artery disease; RAS, Renin-Angiotensin system; AAD, Antiarrhythmic Drug; NSAID, Nonsteroidal anti-inflammatory drug.

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☆☆ Tweet: In this nationwide study of atrial fibrillation patients, digoxin was associated with all-cause death but also several negative control outcomes. Is digoxin's growing bad reputation merely due to unmeasured confounding?

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use of digoxin, we sought to use Danish nationwide registers to examine the risks of mortality associated with digoxin in AF patients as well as investigate if a potential association could be explained by bias and patient selection. The latter was examined using negative control outcomes: pneumonia, septicemia, dehydration or acute kidney injury, and nursing home admission.[22]

Methods

Data Sources

The present study was performed using the Danish nationwide clinical and administrative registers and databases. These data sources have been used extensively for research purposes and are described in more detail elsewhere.[23–26] Briefly, in Denmark, all citizens are registered with a unique identifying number. Using this identifier, residents can be followed on an individual level using numerous clinical and administrative databases (eg, demographic variables, hospital contacts coded with one or more diagnoses according to the International Classification of Diseases 10th edition, filled drug prescriptions, operations and procedures, death and migration, and nursing home admissions). Enrollment into the described registers is mandatory ensuring more or less nationwide coverage.

Study Population and Study Design

We conducted a nationwide nested case-control study including patients in Denmark diagnosed with atrial fibrillation. As such, all adult patients with AF in Denmark (above 18 years and below 100 years of age) who were alive 180 days after AF diagnosis were included in the study population (or nest) (Figure 1). The 180-day blanking period was introduced to make sure that all identified cases would be with AF in the entirety of the exposure window. Eligible subjects were included from 2012 to 2022. For the analysis concerning nursing home admissions, all patients who were already at a nursing home at baseline were excluded. Please see the following for elaboration on case definitions.

Case Definition

We conducted analyses using several preplanned case definitions (or outcomes) pertaining to the outlined research questions. For the main analysis (mortality) we used a case definition defined at the date of verified death in the described administrative registers. Controls were identified from the cohort of patients with AF using exact risk set sampling with replacement. Matching variables were age, sex, and time since AF diagnosis (Supplemental Figure S1).

To further investigate whether patients treated with digoxin could be prone to residual confounding and selection bias (ie, digoxin prescription being a marker of more advanced disease), several negative control outcomes were defined.[22] Thus, we employed several case definitions, in which we would not expect a plausible association as the exposure (digoxin) should have no causal relation to these outcomes. Accordingly, any significant association with these outcomes could indicate fundamental differences between the two comparator groups, independent from the investigated exposure, impossible to fully account for statistically and underline a biased comparison. The case definitions in question were hospital admissions with pneumonia, septicemia, dehydration and acute kidney injury, as well as being admitted to a nursing home.

Exposure and Variable Definitions

The principal variable of interest, or exposure variable, was treatment with digoxin defined by claimed prescriptions of oral formulations of digoxin at any pharmacy in Denmark within 180 days prior to the date of the outcome among cases and corresponding data among controls. All claimed prescriptions of the drug, irrespective of tablet strength (ie, 62.5 μg or 250 μg), were included in the study. Patients were defined as exposed if they had a claimed prescription of digoxin within 180 days prior to the date of interest (date of case definition). Additionally, to show temporal trends in digoxin use during the study period, average claims of digoxin prescription among all included patients were calculated and depicted graphically, by history of heart failure as well.

Due to the fact that AF patients not receiving any treatment are likely inherently different than patients being prescribed digoxin, we chose an active comparator design, in which the nonexposed patients included in the comparator group had to be in treatment with a comparable rate-limiting drug.[27] Hence, the nonexposed patients in the study had to be in treatment with either a beta blocker (metoprolol, atenolol, bisoprolol, nebivolol, labetalol, carvedilol, propranolol, pindolol, and sotalol) or a nondihydropyridine calcium channel blocker (verapamil) as these are commonly used in Denmark.[28]

As previously done, comorbidities were defined as a registered diagnosis in a period of up to five years prior to the date of interest (date of case definition) and concomitant pharmacotherapy was defined by claimed prescriptions 180 days prior to the date of interest. Included comorbidities were ischemic heart disease, heart failure, stroke, diabetes mellitus, chronic kidney disease, prior cancer, chronic obstructive pulmonary lung disease, hypertension, and thyroid disease. Diabetes and hypertension were defined using claimed prescriptions used in the treatment of these conditions.

Included concomitant pharmacotherapy was renin-angiotensin-system inhibitors, diuretics, acetyl-salicylic acid, antiplatelet agents, amiodarone, class 1c antiarrhythmics, nitrates, nonsteroid anti-inflammatory drugs, and oral anticoagulants.

Statistical Methodology

All cases and sampled controls were described at the date of interest using summary statistics with median and interquartile range (IQR) for continuous variables and counts and percentages for dichotomous variables. The average use of digoxin use within a year was calculated among patients alive and uncensored at the beginning of each calendar year using the Ghosh and Lin method to estimate the mean with 95% confidence interval (95% CI) of recurrent events in a setting with death as a notable competing risk.[29,30] History of heart failure was redefined for each patient by the beginning of each calendar year as any previous hospital visit for heart failure.

The employed statistical outcome design has been previously used and described in more detail.[31,32]

Briefly, within the framework of the nested case-control design, we applied multivariable, time-dependent Cox proportional hazards models. Using the constructed models and conditional logistic regression software, we derived hazard ratios (HR) with 95% CI to describe the association between digoxin exposure and the rates of the outcomes of interest compared with beta blocker or verapamil exposure. All models were adjusted for preplanned variables identified as potential confounders defined at time of earliest possible exposure, 180 days prior to outcome date or corresponding date among controls. Adjustment variables included in the multivariable model were age group, a history of ischemic heart disease, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, chronic kidney disease, cancer, and thyroid disease, and educational level. Supplementary Figure S1 provides a graphical representation of risk set sampling in the nested case-control design.

In terms of clinical interpretation, the estimates derived from the used models and nested-case control design should be interpreted as equivalents to a time-updated Cox model using the whole AF sampling population as a cohort with continuously updating exposure, demographic variables as well as comorbidity and concomitant pharmacotherapy.[33]

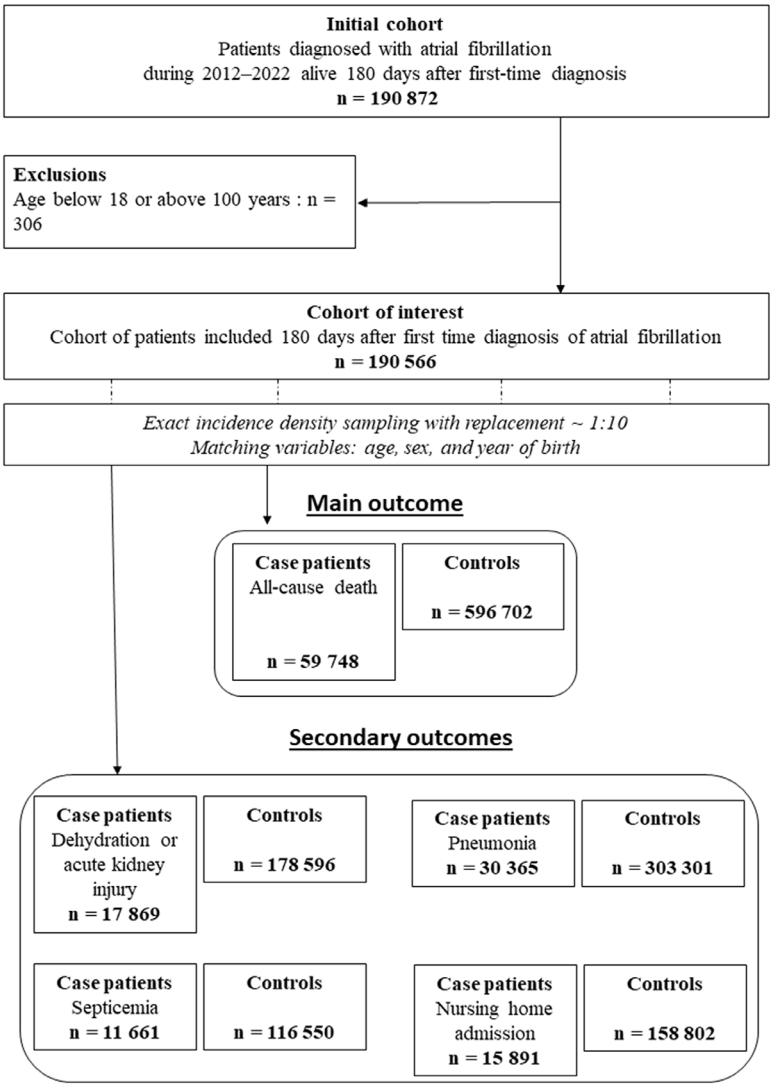

Figure 1. Flowchart.
Flow chart depicting study population inclusion and sampling of cases and controls.

Supplemental Analyses

Several subgroup analyses were performed with analyses stratified by variables in which we hypothesized the effect of digoxin exposure could be different (ie, different age groups, by sex, heart failure, diabetes, and kidney disease). To shed light on potential protopathic bias, a supplementary analysis without an active comparator was also performed (ie, comparing digoxin exposure with no exposure).[27,34] We also performed an analysis using a definition of digoxin exposure restricted to only new-users (no prior digoxin exposure). Finally, we performed an analysis using an exposure definition comprised of a combination of digoxin and beta-blocker/verapamil (beta-blocker/verapamil and digoxin vs beta-blocker/verapamil).

Ethics

Register-based data studies have been approved by the Danish Data Protection Agency and the current project is registered at the responsible institute (Approval No. P-2019-348).

Results

The AF cohort comprised 190,566 patients with a median age of 74 years (IQR 66-82 years) with a slight overweight of male patients (57%). Among the most prevalent comorbidities were hypertension (68%), ischemic heart disease (17%), congestive heart failure (17%), diabetes (16%), and previous stroke (12%). The majority of patients were treated with oral anticoagulants (79%), and to a lesser extent antiplatelet agents (18%). Concomitant use of antiarrhythmic drugs was not common with amiodarone being the most frequent drug (7%), and to a lesser extent class 1c antiarrhythmics (1%), sotalol (<1%), and dronedarone (<1%) (Supplementary Table S2).

We identified 59,748 cases and sampled 596,702 controls using the case-definition of mortality. Concerning secondary outcomes of dehydration/acute kidney injury, septicemia, pneumonia, and nursing home admissions, see figure (Figure 1).

The covariates were reasonably balanced between the overall cases and controls as well as the cases and controls used in the statistical models for both analyses (Table 1, Supplementary Table S3).

During the study period, the use of digoxin in the cohort decreased from an average of 132 (95% CI 127-138) claimed prescriptions pr. 100 persons within a year in 2013 to 72 (95% CI 71-74) in 2022. Further, digoxin use was more prevalent among patients with both atrial fibrillation and heart failure compared with patients without history of heart failure (Figure 2).

Examining mortality, the adjusted rates were higher among AF patients exposed to digoxin compared with patients treated with beta-blockers/verapamil (HR 1.85, 95% CI 1.78-1.92) (Figure 4).

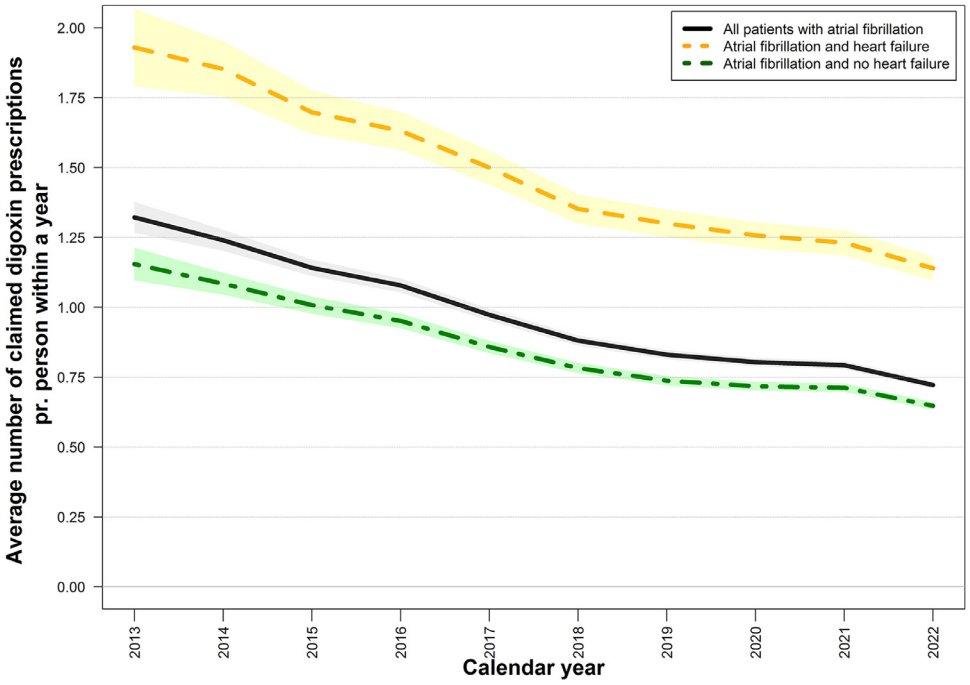

Figure 2. Temporal trends in digoxin use among patients with atrial fibrillation, by history of heart failure
Average use of digoxin was calculated among all patients with atrial fibrillation as marginal means with 95% CI, including competing risk of death, to give a measure of the recurrent event (prescription claim) for relative comparison across groups and calendar year. Every patient included and alive on 1 January in the year in question contributed to the analyses. History of heart failure was defined as any previous hospital visit prior to beginning of calendar year in question.

Table 1
Characteristics for Cases and Controls

	Controls (n = 596702)	Cases (n = 59748)
Age, years [IQR]	84 [77, 89]	84 [77, 89]
Men	318174 (53.3)	31868 (53.3)
IHD	112022 (18.8)	13726 (23.0)
HF	108583 (18.2)	17096 (28.6)
Stroke	76803 (12.9)	9326 (15.6)
Diabetes	92238 (15.5)	13470 (22.5)
COPD	59318 (9.9)	12730 (21.3)
CKD	41869 (7.0)	8269 (13.8)
Cancer	92515 (15.5)	15688 (26.3)
Hypertension	427320 (71.6)	45240 (75.7)
PAD	16565 (2.8)	3613 (6.0)
Thyroid disease	52646 (8.8)	6084 (10.2)
Calcium antagonists	152819 (25.6)	13002 (21.8)
RAS-inhibitor	272662 (45.7)	24118 (40.4)
Diuretics	303650 (50.9)	36364 (60.9)
Antiplatelets	92711 (15.5)	11097 (18.6)
Anticoagulants	470119 (78.8)	42941 (71.9)
Amiodarone	21039 (3.5)	2962 (5.0)
Class 1C AAD	3214 (0.5)	76 (0.1)
Nitrates	31343 (5.3)	4170 (7.0)
NSAID	38036 (6.4)	3810 (6.4)
Education* Unknown	24,820 (4.2)	2,855 (4.8)
Vocational	204913 (34.3)	19976 (33.4)
Elementary/high school	255958 (42.9)	28493 (47.7)
Higher education	111011 (18.6)	8424 (14.1)

* Highest achieved level of education.Characteristics defined at the earliest time of exposure, ie, 180 days prior to the outcome among cases and corresponding date among controls. Numbers are totals (%) unless indicated otherwise.IHD = ischemic heart disease; HF = heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; PAD = peripheral artery disease; RAS = renin-angiotensin system; AAD = antiarrhythmic drug; NSAID = nonsteroidal anti-inflammatory drug.

When examining predefined subgroups, we found comparable results with higher rates of mortality between digoxin exposed patients and patients treated with beta-blockers/verapamil (Figure 2). This was the case in all subgroups hypothesized as high-risk patients. As such, we found similar rates to the main analysis in patients with heart failure (HR 1.84, 95% CI 1.65-2.06), diabetes (HR 1.85, 95% CI 1.60-2.14), and kidney disease (HR 1.37, 95% CI 1.04-1.80). We found the most pronounced association with digoxin exposure in younger patients < 78 years of age (HR 2.59, 95% CI 2.44-2.76) (Figure 2).

Regarding the predefined secondary negative control outcomes, we found that being exposed to digoxin conferred increased rates of all defined outcomes including pneumonia (HR 1.40, 95% CI 1.32-1.48), septicemia (HR 1.55, 95% CI 1.41-1.70), as well as nursing home admission (HR 1.79, 95% CI 1.67-1.93) (Figure 4).

Supplementary Analyses

Performing the main analysis without requiring an active comparator (ie, not requiring the control to be in treatment with either betablocker or verapamil) yielded similar results to the main analysis (HR 1.52, 95% CI 1.49-1.55).

Restricting our case exposure definition to only AF patients with first-time exposure to digoxin (new-users) accentuated the association with digoxin exposure compared with the main analysis (HR 4.64, 95% CI 4.13-5.21)

Combination therapy (digoxin and beta-blocker/verapamil vs beta-blocker/verapamil) revealed comparable results to the main analysis (HR 1.53, 95% CI 1.49-1.57).

Discussion

In this nationwide nested case-control study, we found that digoxin use has decreased markedly among patients with AF in recent years—irrespective of heart failure history (Figure 2). Further, patients treated with digoxin had increased rates of mortality compared with patients treated with other rate-limiting drugs consistent among all subgroups. However, this association was likely not causal as digoxin treated patients also had increased rates of unrelated outcomes (negative control outcomes) such as pneumonia, septicemia, dehydration/acute kidney injury, and admission to nursing homes (Figure 4). As such, our results clearly indicate that being prescribed digoxin should be considered a marker of advanced disease and frailty.

The published data pertaining to the risk of mortality in patients being prescribed digoxin are conflicting; however, with an overwhelm-

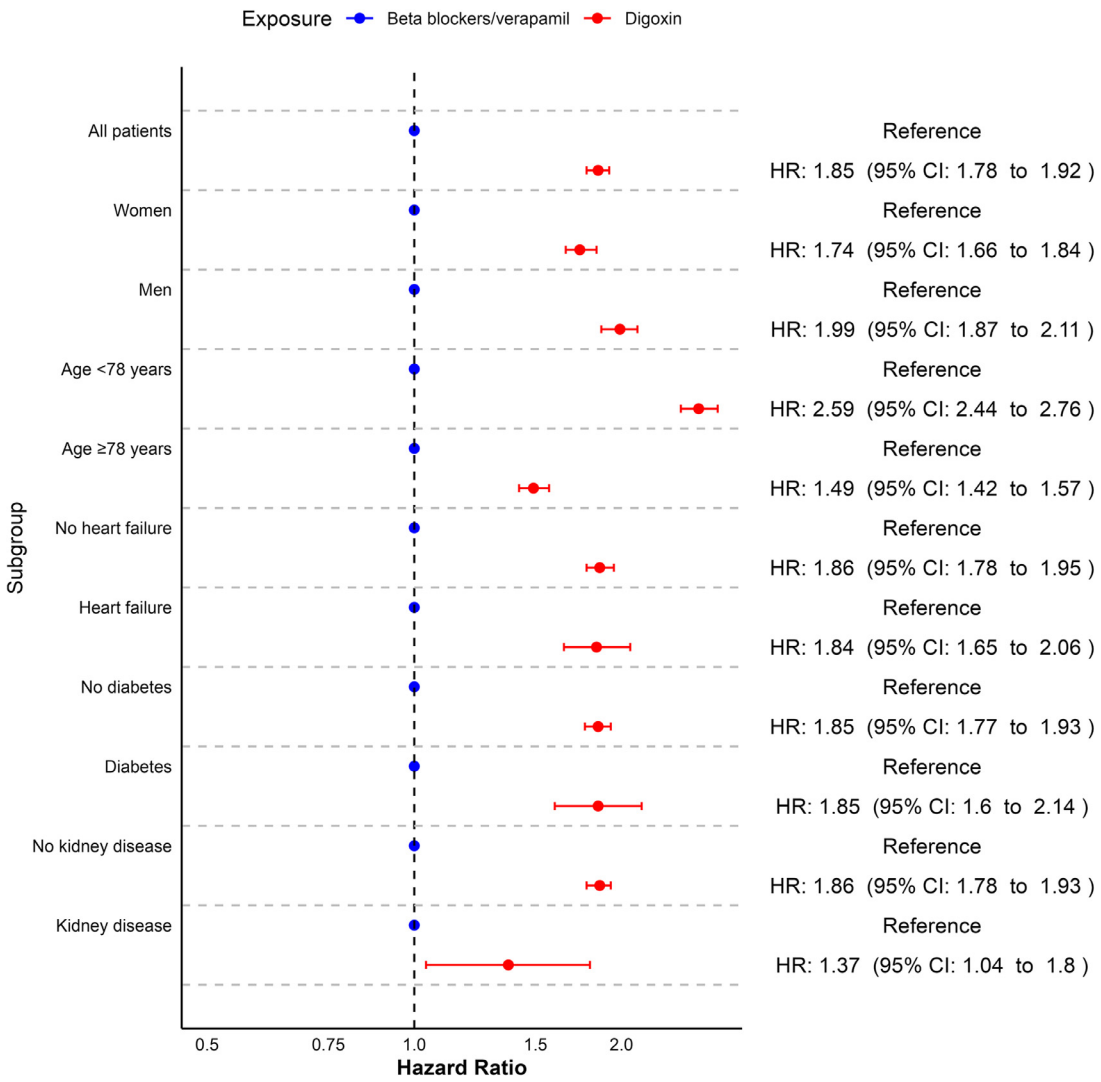

Figure 3. Hazards of all-cause death associated with concomitant rate control treatment, by subgroups of interest.
Forest plot showing the association between digoxin exposure and the adjusted rates of mortality both in the entire study population as well as in predefined subgroups. HRs were calculated from the nested case-control data using conditional logistic regression associating the outcome (all-cause death) with concomitant rate-control treatment (digoxin vs beta blockers/verapamil) using software for conditional logistic regression. Exposure was defined as a claimed prescription within 180 days prior to the date of the outcome or corresponding date among controls. Adjustment variables included in the multivariable model were medical history of ischemic heart disease, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, chronic kidney disease, cancer, and thyroid disease; age; and educational level. HR = hazard ratio; CI = confidence interval.

ing body of evidence from both large registers as well as trial data suggesting increased risks of mortality associated with digoxin treatment.[5–17] Nevertheless, the estimates underlying these conclusions are exclusively based on nonrandomized comparisons and several publications have hypothesized that the association could be due to bias and residual confounding difficult to adjust for in the available datasets.[18–21] Moreover, when trying to infer causality from observational data (eg, concluding that a pharmacological effect of a drug is harmful), thorough methodological considerations regarding the choice of comparator group are important to minimize the risk of inferring potentially biased conclusions. Nevertheless, recent interesting data revealed a markedly increased risk of mortality in patients with an implantable cardiac device treated with digoxin leading to suggestions not to prescribe digoxin all together.[8,35]

The probably most granular randomized evidence pertaining to digoxin use in patients with heart failure was the DIG trial reporting a neutral effect on mortality and a significant reduction in heart failure hospital admissions.[36] Rigorous re-analysis of these data in the light of the plethora of publications describing the hazards of prescribing digoxin reported their analysis to indicate that digoxin should be considered primarily a marker of disease gravity and, consequently, a marker of a potentially worse prognosis.[18] The DIG trial is an older trial and how the results translate to AF patients in contemporary practice is not known. However, the data presented in the present paper fully support this conclusion and is substantiated by several negative control outcomes which infer that the relationship between mortality and digoxin is likely not causal as digoxin should not cause increased risks of pneumonia or, especially, admissions to nursing homes from a mechanistic point of view. The causal chain is likely opposite as frail patients with a lower functional level who are susceptible to infections as well as likely to be admitted to a nursing home will often be prescribed digoxin by their practitioner. Further, if a real causal relationship existed between digoxin treatment and the risk of dying, stronger associations in subgroups at higher theoretical risk of side-effects would be expected—eg, patients with chronic kidney disease or older patients—which was not the case in this study.

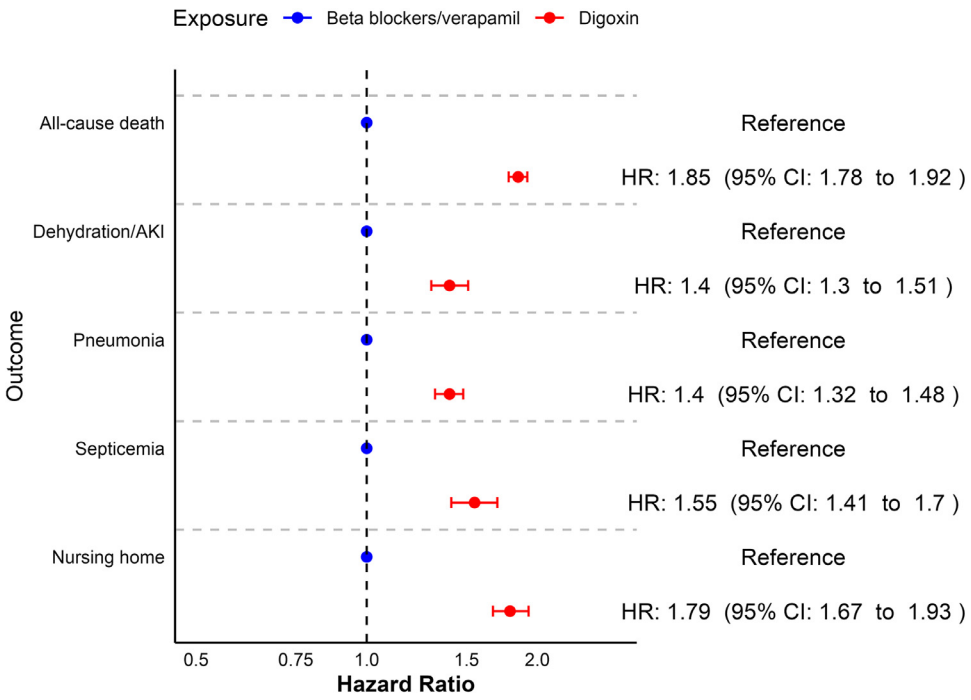

Figure 4. Hazards of all-cause death and negative control outcomes associated with concomitant rate control treatment.
Forest plot showing the association between digoxin exposure and the adjusted rates of mortality and negative control outcomes (ie, dehydration/acute kidney injury, pneumonia, septicemia, and nursing home admissions). Statistical methods as in Figure 3. HR = hazard ratio; CI = confidence interval.

Supplemental analyses revealed an accentuated risk of mortality in new users of digoxin. The mechanism underlying this association is not known, however, it is likely that new-users are more prone to be recently diagnosed with AF in relation to concurrent disease or procedures known to be likely to affect overall prognosis (recent surgery, infections, or hospitalizations in general)—although the 180-day blanking period should mitigate this. It is also noteworthy, that it did not seem to have any effect on the magnitude of the estimate whether patients were in treatment with a combination with other rate-lowering drugs.

Digoxin is present as a recommended treatment option for rate control in patients with AF in the most recent European Society of Cardiology guideline and is widely used in clinical practice.[1,28] Although, as data from this study indicate, the use of digoxin seems to have decreased notably in recent years—both among atrial fibrillation patients with and without history of heart failure. As digoxin do not possess the same negative inotropic pharmacodynamic properties as other rate-limiting drugs, digoxin is often a drug of choice for acute rate-control in patients with heart failure or in patients without access to an immediate echocardiographic evaluation of left ventricular systolic function. However, due to its many interactions with other cardioactive substances, and narrow therapeutic interval susceptible to potentially toxic serum concentrations, there is a theoretical mechanism to how digoxin could confer an overall increased risk of adverse events. Nevertheless, as described, our results do not support this notion.

Interestingly, post hoc data from the ROCKET-AF trial described a significant interaction with sex reporting increased hazards of all-cause and vascular mortality in male patients.[16] Moreover, data from the AFFIRM trial as well as reports from the RIKS-HIA study indicated a potential interaction with heart failure with increased hazards of mortality in the subgroup of patients with AF without heart failure treated with digoxin.[5,14] Reassuringly, we were not able to reproduce any of these findings—granted that this could be a results of a more restrictive prescription practice regarding digoxin following results from these trials.

In the absence of high-quality randomized data on the safety of digoxin in patients with AF, the only available evidence stems from post hoc analyses from trials designed to test different hypotheses as well as analyses of observational data. Most of these studies report increased risks associated with digoxin. However, often causality cannot be inferred from these analyses and our data strongly support the notion that the hazards associated with digoxin are not due to the drug itself but rather bias and residual confounding. Consequently, we do not find evidence to support any restraints in the prescription of digoxin as a rate-lowering drug in AF when indicated due to concerns of excess mortality. This is especially vital to illuminate due to the findings of decreasing digoxin use among patients with known heart failure as well.

Limitations

The Danish nationwide registers are generally of high quality and have been extensively used for research, however, several limitations should be mentioned. The risk of misclassification bias do always exist in large registers but a plethora of the diagnoses have been manually validated (including AF) with high positive predictive values.[37,38] It is a limitation that we were not able to stratify between paroxysmal and persistent AF since the indication for digoxin treatment should be stronger in patients with persistent AF skewing the comparison. However, this potential bias is present in all observational studies on this topic likely adding to the confounding possibly explaining the findings. Pertaining to the exposure in question (digoxin treatment), adherence was assumed whenever a patient claimed the prescription. The available data regarding digoxin prescriptions included the strength of the drug and number of tablets in each package, however, the exact dosage of digoxin was not available. Moreover, we did not have access to relevant biochemical data such as estimated glomerular filtration rates as well as serum-digoxin measurements. Anthropometric data such as body mass index and blood pressure as well as smoking and dietary habits were also not available. Finally, residual or unmeasured confounding is inherent to the used data and study design (observational study) and cannot be avoided.

Conclusions

In this nationwide nested-case control study, we found that digoxin treatment in patients with AF was associated with increased mortality. This result was consistent across all relevant subgroups (eg, heart failure, sex, and kidney disease). However, the positive association is likely due

to bias and residual confounding as we found similar associations to several negative control outcomes in which a casual association would seem implausible (ie, pneumonia, septicemia, admission to nursing homes). Conclusively, our data underline that being prescribed digoxin is probably a marker of disease severity and the relationship between digoxin and mortality is likely not causal.

Data Availability Statement

Under Danish law, the data used for this paper cannot be made shared or made available.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Anders Holt: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jarl Emanuel Strange:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Conceptualization. **Morten Lock Hansen:** Writing – review & editing, Visualization, Validation, Supervision. **Morten Lamberts:** Writing – review & editing, Visualization, Validation, Supervision, Methodology. **Peter Vibe Rasmussen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ajmo.2025.100093.

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