

Digoxin use and outcomes after myocardial infarction in patients with atrial fibrillation

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Abstract

Digoxin is used for rate control in atrial fibrillation (AF), but evidence for its efficacy and safety after myocardial infarction (MI) is scarce and mixed. We studied post-MI digoxin use effects on AF patient outcomes in a nationwide registry follow-up study in Finland. Digoxin was used by 18.6% of AF patients after MI, with a decreasing usage trend during 2004–2014. Baseline differences in digoxin users ($n = 881$) and controls ($n = 3898$) were balanced with inverse probability of treatment weight adjustment. The median follow-up was 7.4 years. Patients using digoxin after MI had a higher cumulative all-cause mortality (77.4% vs. 72.3%; hazard ratio [HR]: 1.19; confidence interval [CI]: 1.07–1.32; $p = 0.001$) during a 10-year follow-up. Mortality differences were detected in a subgroup analysis of patients without baseline heart failure (HF) (HR: 1.23; $p = 0.019$) but not in patients with baseline HF (HR: 1.05; $p = 0.413$). Cumulative incidences of HF hospitalizations, stroke and new MI were similar between digoxin group and controls. In conclusion, digoxin use after MI is associated with increased mortality but not with HF hospitalizations, new MI or stroke in AF patients. Increased mortality was detected in patients without baseline HF. Results suggest caution with digoxin after MI in AF patients, especially in the absence of HF.

KEYWORDS

atrial fibrillation, cardiovascular pharmacology, digitalis glycosides, ischemic heart disease, pharmacoepidemiology

1 | INTRODUCTION AND BACKGROUND

Digoxin is a cardiac glycoside that has been in clinical use for decades. In the past, it was widely used in the treatment of heart failure (HF), but more recently its use

has declined, and it is currently mainly used as a second-line therapy to achieve rate control in patients with atrial fibrillation (AF). Digoxin is eliminated, largely unchanged, in the urine. Despite its lack of metabolism by the cytochrome P450 enzymes, digoxin is subject to P-glycoprotein-mediated drug interactions, and drugs

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that inhibit P-glycoprotein—such as clarithromycin, itraconazole and verapamil—can increase digoxin concentrations to toxic levels.¹ Due to digoxin's narrow therapeutic range and its pharmacokinetics that are affected by many patient-specific factors, therapeutic drug monitoring is frequently utilized in digoxin therapy.²

There is an ongoing controversy surrounding the impact of digoxin on clinical outcomes. The randomized DIG trial in the 1990s found no association between digoxin use and mortality, although it did find a link between digoxin use and reduced HF hospitalizations, in HF patients with normal sinus rhythms.³ However, digoxin was later associated with increased mortality in HF.^{4,5} The data concerning the effects of digoxin in AF are scarce, with no randomized studies available and meta-analyses of studies suggesting either increased mortality⁵ or not enough data for conclusions.⁴ Older studies from the 1990s found a correlation between digoxin use and increased mortality after myocardial infarction (MI).^{6–8} However, current knowledge about the potential impact of digoxin on clinical outcomes after MI is very limited. Two recent studies of acute coronary syndrome⁹ and STEMI¹⁰ patients found no association between digoxin and short-term mortality, but there are no recent long-term data on the influence of digoxin on outcomes after MI. Thus, we investigated the impact of digoxin therapy on long-term post-MI outcomes in AF patients.

2 | MATERIALS AND METHODS

2.1 | Study design

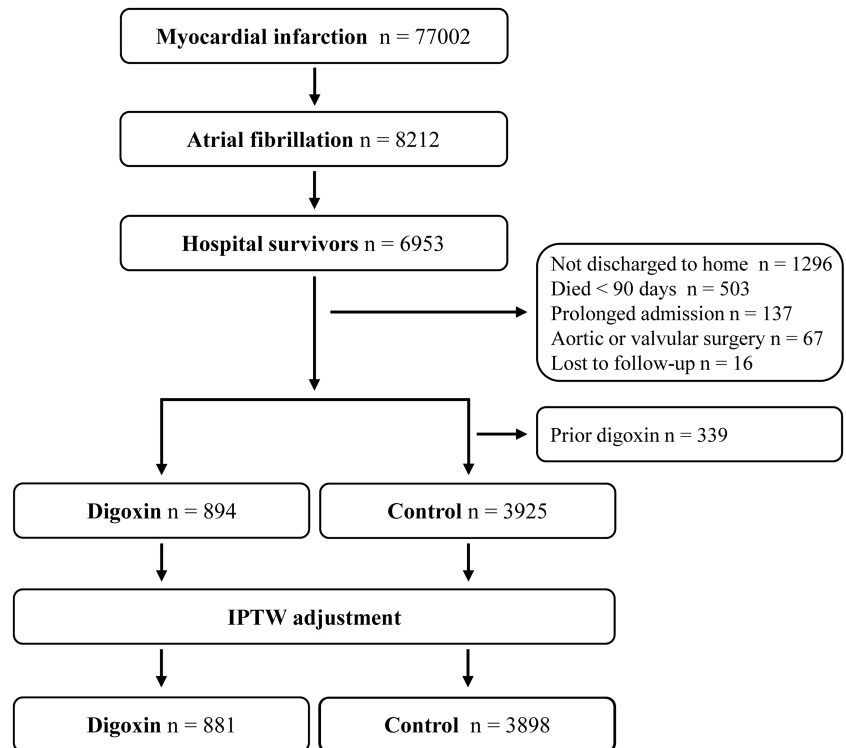
We studied the impact of digoxin on the outcomes of AF patients after MI. The inverse probability of treatment weight (IPTW) method was used to create comparable study groups.¹¹ The primary outcome of interest was all-cause mortality. Secondary outcomes were cardiovascular mortality, HF hospitalization, stroke and new MI. Consecutive MI patients with AF admitted to hospitals between 1 April 2004 and 31 December 2014 were studied using a combination of nationwide mandatory registries. Study patients were identified from the Care Register for Healthcare in Finland (CRHF), which includes data on all hospital admissions and interventional procedures in Finland.¹² All hospitals in Finland equipped with a coronary catheterization laboratory and treating MI patients ($n = 20$) were included in the study. Hospital-surviving patients with out-of-hospital MI admitted to medical, surgical or intensive care wards were included. To capture only patients with the ability and need to purchase post-MI medications, patients who

died within 90 days after discharge, patients not discharged to their homes or to home-like facilities (including nursing homes), and patients with prolonged (>90 days) admissions were excluded (Figure 1). In addition, patients lost to follow-up ($n = 17$) and those treated with non-coronary cardiac surgery were excluded (Figure 1). Subgroup analyses were performed for patients with and without HF at baseline. Index MI was defined as the use of an ICD-10 code I21 as the primary discharge diagnosis. AF was defined as the use of an ICD-10 code I48 during the index admission. Cardiovascular medications are only available from pharmacies by prescription in Finland. Digoxin usage after MI was defined as drug purchase within 90 days after discharge. No digoxin therapy was defined as not having purchased digoxin 90 days before MI or 90 days after discharge. Initial digoxin dosage was defined as the tablet strength of the first digoxin prescription purchase after MI. Definitions of outcomes, comorbidities, baseline features and prescription medications are presented in the Supporting Information.

2.2 | Data sources and permissions

The CRHF Registry and Finnish Cancer Registry were obtained from the National Institute for Health and Welfare of Finland (permission no: THL/2245/5.05.00/2019). Mortality and cause of death data were obtained from a nationwide cause of death registry held by Statistics Finland (permission no: TK-53-484-20). Prescription medication purchase data (including ATC codes and purchase dates) and drug reimbursement permission data were obtained from the Social Insurance Institution of Finland (permission no: 91/522/2015). The collection and reporting of data within the included registries are mandated by law; therefore, the data from these registries provide a full picture of the Finnish population. Follow-up started at 90 days and ended 10 years after MI. Follow-up data were available up to 31 December 2018. Because this was a retrospective registry study, no informed consent was required, nor were the participants contacted. The legal basis for the processing of personal data is public interest and scientific research (EU General Data Protection Regulation 2016/679 (GDPR), Article 6 (1)(e) and Article 9(2)(j); Data Protection Act, Sections 4 and 6). The data that support the findings of this study are available with permission from Findata (www.findata.fi). Restrictions apply to the availability of these data, which were used under licence for this study. The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.¹³

FIGURE 1 Study flowchart. IPTW, inverse probability of treatment weight



2.3 | Statistical analysis

Effect sizes in the baseline characteristics between the study groups were evaluated using standardized mean differences (SMD). Logistic regression was used to create propensity scores based on age, sex, alcohol abuse, anaemia, cerebrovascular disease, chronic pulmonary disease, coagulopathy, dementia, depression, insulin-dependent diabetes, non-insulin-dependent diabetes, HF, hypertension, hypothyroidism, liver disease, malignancy, metastatic cancer, paralysis, peripheral vascular disease, psychotic disorder, rheumatic disease, renal failure, valvular disease, revascularization by PCI or CABG, ST-elevation MI, cardiovascular pharmacotherapy after MI (ADP-inhibitor, anticoagulant, ACEi/ARB, aldosterone antagonist, antiarrhythmic, beta blocker, calcium channel blocker, statin), treating hospital, and study year. IPTWs were calculated using propensity scores.¹¹ To improve the balancing, patients with non-overlapping propensity scores (1 in the digoxin group and 32 in the control group) were excluded, and IPTWs were stabilized.¹⁴ Separate propensity scoring and IPTW calculations were performed for subgroups of patients with and without diagnosed HF up until the time of index MI admission. Unmeasured confounding was estimated by calculating the *E* value.¹⁵

Differences between study groups were analysed using Jonckheere–Terpstra, *t* and chi-square tests. Trends were tested using the Cochrane–Armitage test. Outcomes

were studied using the stabilized IPTW-adjusted Kaplan–Meier method and robust Cox regression modelling with sandwich-type estimators. The association of initial digoxin dosage with outcomes was studied with multivariable Cox modelling. The median follow-up period for the survivors was 7.4 (interquartile range [IQR]: 5.3–10) years. Cause-specific hazard models were applied in the outcome analyses. Schoenfeld residuals were used to confirm proportional hazard assumptions. The number needed to harm (NNH) was calculated as previously described.¹⁶ The results are given in terms of mean, median, percentage and hazard ratio (HR) with a 95% confidence interval (CI) or \pm SD. Statistical significance was defined as a *p* value <0.05. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used to carry out the analyses.

3 | RESULTS

The mean age of the study patients was 76.7 (SD: 9.4, range: 40–100) years, with no difference between digoxin users and controls (*p* = 0.259, Table 1). Digoxin therapy was applied more frequently to women and to patients with HF (Table S1). Patients treated with digoxin were less frequently revascularized by percutaneous coronary intervention and had a lower frequency of ADP-inhibitor usage but a higher frequency of anticoagulation and beta blocker usage after MI (Table S1). The proportion of AF

TABLE 1 Baseline features of inverse probability of treatment weight (IPTW)-adjusted myocardial infarction patients with atrial fibrillation with and without post-infarction digoxin therapy

Variable	Digoxin n = 881	Control n = 3898	p value	SMD
Age, years (SD)	77.2 (9.3)	76.9 (9.4)	0.314	0.041
Women	53.1%	54.9%	0.317	0.036
Comorbidities				
Alcohol abuse	2.1%	2.5%	0.503	0.025
Anaemia	4.7%	4.7%	0.916	0.004
Cerebrovascular disease	16.7%	17.2%	0.738	0.012
Chronic pulmonary disease	14.1%	15.1%	0.454	0.027
Coagulopathy	0.5%	0.6%	0.787	0.010
Dementia	7.1%	6.2%	0.339	0.034
Depression	10.9%	11.0%	0.920	0.004
Diabetes	31.5%	30.5%	0.556	0.021
Insulin dependent	11.5%	10.4%	0.329	0.035
Non-insulin dependent	20.0%	20.1%	0.941	0.003
Heart failure	50.5%	49.6%	0.311	0.004
Hypertension	64.8%	64.7%	0.956	0.002
Hypothyroidism	5.4%	5.4%	0.999	0.0001
Liver disease	1.1%	1.0%	0.885	0.005
Malignancy	14.2%	14.1%	0.934	0.003
Metastatic tumour	0.2%	0.1%	0.711	0.013
Paralysis	0.5%	0.6%	0.864	0.006
Peripheral vascular disease	11.7%	10.8%	0.448	0.027
Prior CABG	5.6%	5.5%	0.952	0.008
Prior myocardial infarction	25.2%	23.9%	0.389	0.031
Psychotic disorder	2.6%	2.6%	0.954	0.002
Rheumatic disease	7.9%	7.6%	0.791	0.010
Renal failure	4.7%	4.6%	0.857	0.007
Valvular disease	10.6%	10.5%	0.977	0.001
ST-elevation MI	26.6%	26.1%	0.754	0.011
Revascularization	36.4%	37.8%	0.437	0.028
PCI	29.4%	29.8%	0.806	0.009
CABG	7.6%	8.4%	0.424	0.029
Pharmacotherapy after MI				
ADP-inhibitor	38.5%	39.8%	0.447	0.028
Anticoagulant	66.0%	66.0%	0.999	0.0001
ACEi or ARB	66.3%	67.0%	0.689	0.015
Aldosterone antagonist	7.8%	7.4%	0.729	0.013
Antiarrhythmic	4.5%	4.1%	0.565	0.021
Beta blocker	81.9%	83.7%	0.179	0.048
Ca blocker	20.8%	21.6%	0.605	0.019
Statin	67.5%	68.7%	0.467	0.026

(Continues)

TABLE 1 (Continued)

Variable	Digoxin <i>n</i> = 881	Control <i>n</i> = 3898	<i>p</i> value	SMD
Treating hospital (<i>n</i> = 20)			0.684	0.026
Year			0.436	0.041

Abbreviations: ADP, adenosine diphosphate; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; SMD, standardized mean difference.

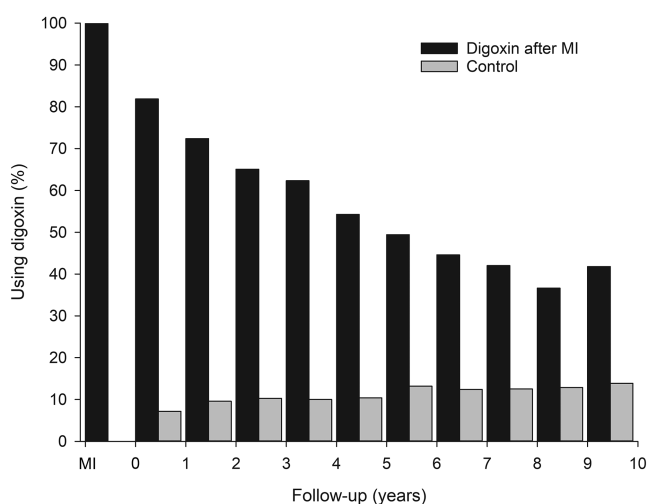


FIGURE 2 Persistence with digoxin therapy and digoxin usage in the control group during follow-up in atrial fibrillation patients after myocardial infarction (MI)

patients treated with digoxin after MI decreased from 23.4% in 2004 to 9.6% in 2014 ($p < 0.0001$ for trend), with an 18.6% usage rate during the whole study period. The continuity rate of pharmacy purchased digoxin therapy was 81.9% within the first follow-up year and gradually declined to 41.8% within the 10th follow-up year (Figure 2) ($p < 0.0001$ for trend). Less than 14% of control patients used digoxin later during the follow-up period (Figure 2). Digoxin was used prior to MI by 36.6% of the patients who used post-MI digoxin therapy. Differences in baseline features and medication usage were balanced by IPTW adjustment, resulting in 881 digoxin users and 3898 controls (Table 1).

3.1 | Mortality

During the 10-year follow-up period, 3079 patients (628 in the digoxin group) died. Patients who used digoxin therapy after MI had a higher rate of mortality during the follow-up period (Figure 3). The 1-year all-cause mortality rate was 16.5% in the digoxin group

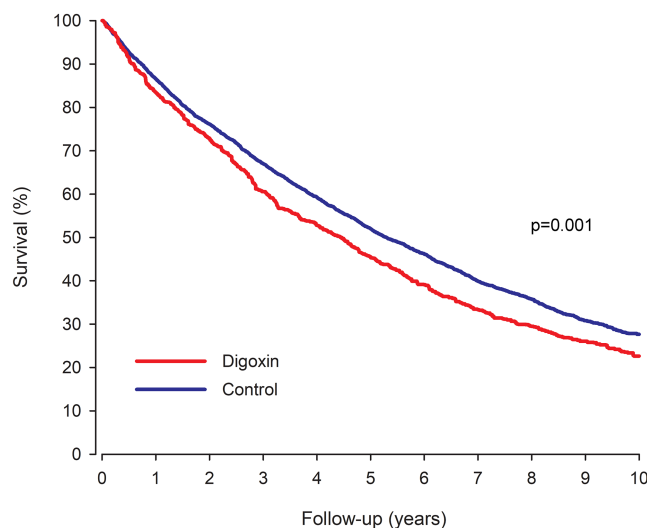


FIGURE 3 Survival of atrial fibrillation patients by digoxin use after myocardial infarction. Adjusted with inverse probability of treatment weight

versus 13.4% in the control group ($p = 0.038$), and the 5-year mortality rate was 54.4% in the digoxin group versus 48.0% in the control group ($p = 0.002$). The all-cause mortality rate within the 10-year follow-up period was 77.4% in the digoxin group versus 72.3% in the control group (HR: 1.19; CI: 1.07–1.32; $p = 0.001$). The digoxin-associated NNH for 10-year mortality after MI was 16.7 (CI: 10.7–42.0) in the total study cohort. The *E* value was 1.66 (CI: 1.34–1.97). The 10-year cardiovascular mortality was 65.1% in the digoxin group versus 59.0% in the control group (HR: 1.23; CI: 1.09–1.39; $p = 0.001$). Initial digoxin dosage after MI was not associated with mortality (Table 2).

In the subgroup analyses, significant differences in mortality were detected only in patients without baseline HF. In the subgroup with baseline HF, the 10-year all-cause mortality rate was 85.7% in the digoxin group versus 84.9% in the control group (HR: 1.05; CI: 0.93–1.18; $p = 0.413$). In patients without baseline HF, all-cause mortality was 70.9% in the digoxin group versus 64.4% in the control group (HR: 1.23; CI: 1.03–1.46; $p = 0.019$) during the 10-year follow-up.

TABLE 2 Association of initial digoxin dosage with 10-year outcomes after myocardial infarction in atrial fibrillation patients

	Outcome								
	All-cause mortality		Heart failure hospitalization		Stroke		New myocardial infarction		
	n	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Digoxin dosage									
0.0625 mg	152	Reference	0.697	Reference	0.905	Reference	0.388	Reference	0.764
0.125 mg	623	0.97 (0.76–1.22)	0.781	1.00 (0.77–1.31)	0.987	0.76 (0.49–1.18)	0.218	0.87 (0.58–1.31)	0.501
0.25 mg	119	0.88 (0.63–1.21)	0.426	1.07 (0.74–1.53)	0.730	0.66 (0.33–1.29)	0.219	0.82 (0.46–1.47)	0.511

Note: The results were adjusted for age, sex, alcohol abuse, anaemia, cerebrovascular disease, chronic pulmonary disease, coagulopathy, dementia, depression, diabetes, heart failure, hypertension, hypothyroidism, malignancy, paralysis, peripheral vascular disease, prior coronary bypass, prior myocardial infarction, psychotic disorder, rheumatic disease, renal failure, ST-elevation myocardial infarction, revascularization, pharmacotherapy (ADP-inhibitor, anticoagulant, ACEi/ARB, aldosterone antagonist, antiarrhythmic beta blocker, Ca blocker, statin) and study year. Abbreviations: CI, confidence interval; HR, hazard ratio.

3.2 | HF hospitalization

During the follow-up period, 399 patients in the digoxin group and 1795 in the control group were hospitalized with HF. The cumulative incidence of HF hospitalization was 46.0% in the digoxin group versus 45.9% in the control group at 5 years and 60.5% versus 62.3% for the digoxin group and the control group, respectively, at 10 years (HR: 1.03; CI: 0.91–1.18; $p = 0.608$) (Figure 4). The 10-year incidence of HF hospitalization in patients with baseline HF was 78.3% in the digoxin group versus 77.3% in the control group (HR: 1.02; CI: 0.88–1.17; $p = 0.835$). New HF requiring hospitalization occurred in 54.7% of patients without baseline HF in the digoxin group and in 51.0% of patients in the control group (HR: 1.22; CI: 0.98–1.52; $p = 0.068$) during the follow-up period. Initial digoxin dosage was not associated with HF hospitalization (Table 2).

3.3 | Stroke

Stroke occurred in 799 patients (153 in the digoxin group) within the follow-up period (Figure 5). The cumulative 10-year incidence of stroke was 30.5% in the digoxin group versus 29.2% in the control group (HR: 1.09; CI: 0.90–1.33; $p = 0.383$). The incidence of stroke was 25.5% in the digoxin group versus 30.5% in the control group (HR: 0.89; CI: 0.68–1.17; $p = 0.413$) in the HF subgroup and 33.3% versus 28.8% in the digoxin group and the control group, respectively, in the non-HF subgroup (HR:

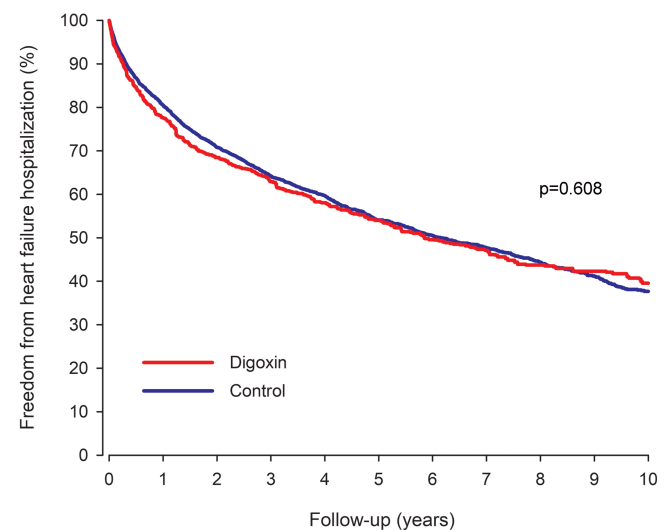


FIGURE 4 Cumulative freedom from heart failure hospitalization in atrial fibrillation patients with and without digoxin therapy after myocardial infarction. Adjusted with inverse probability of treatment weight

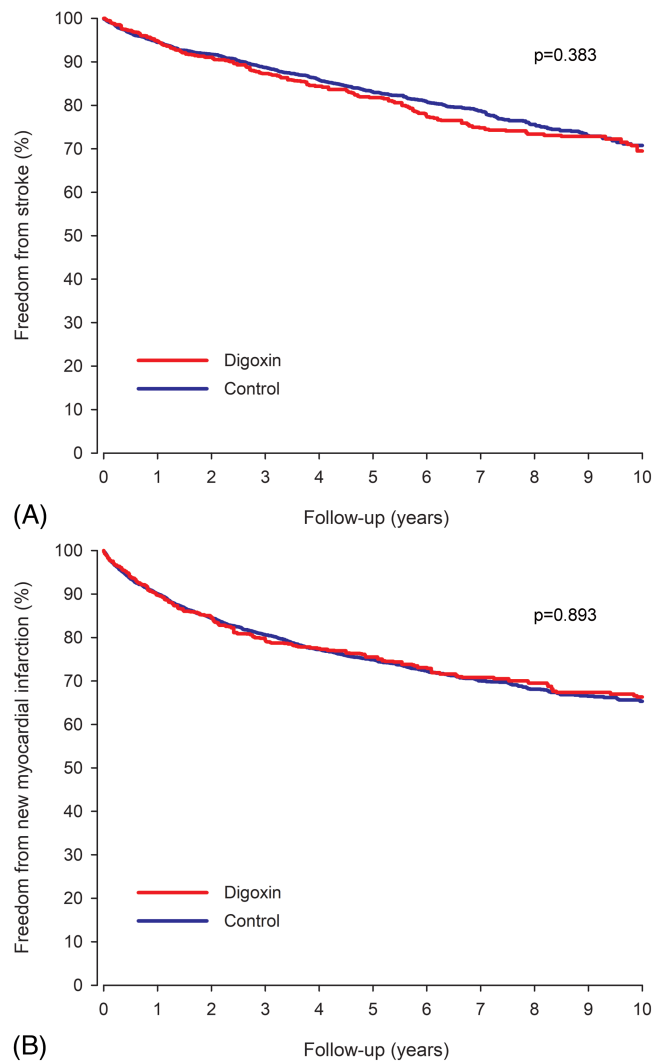


FIGURE 5 Cumulative freedom from stroke (A) and new myocardial infarction (B) in atrial fibrillation patients with and without digoxin therapy after myocardial infarction. Adjusted with inverse probability of treatment weight

1.24; CI: 0.93–1.67; $p = 0.145$) during the 10-year follow-up period. There was no association between initial digoxin dosage and stroke incidence (Table 2).

3.4 | New MI

Out of all patients, 1159 (206 in the digoxin group) had new MI with a cumulative incidence of 33.7% in the digoxin group versus 34.7% in the control group within the follow-up period (HR: 0.99; CI: 0.82–1.19; $p = 0.893$) (Figure 5). In HF patients, the 10-year incidence of new MI was 42.1% in the digoxin group versus 40.9% in the control group (HR: 1.05; CI: 0.85–1.29; $p = 0.678$). In non-HF patients, the incidence of new MI was 27.5% in the digoxin group versus 29.9% in the control group (HR:

0.86; CI: 0.64–1.16; $p = 0.329$). Initial digoxin dosage was not associated with the incidence of new MI (Table 2).

4 | DISCUSSION

This population-based study investigated the impact of digoxin on long-term outcomes after MI in AF patients. Digoxin usage was independently associated with long-term mortality but not with the occurrence of HF hospitalizations, stroke or new MI. Digoxin exerts positive inotropic effects by inhibiting cardiac Na⁺/K⁺-ATPase, which causes an increase in intracellular Na⁺, resulting in inhibition of the efflux of Ca⁺ and an increase in intracellular Ca⁺ concentration. Furthermore, digoxin has parasympathomimetic activity. These effects translate to increased cardiac contractility and slower AV-nodal conduction. Importantly, digoxin has a low therapeutic index, and high digoxin concentrations are associated with adverse effects, commonly manifesting as arrhythmias, nausea, cognitive impairment and disturbed vision.

There is an ongoing controversy about the potential increase in mortality with digoxin treatment. The largest and most recent randomized digitalis trial, the 1990s DIG trial, found digoxin to have a neutral effect on mortality in HF patients,³ and a meta-analysis of previous randomized trials showed similar results.⁴ However, observational studies have found increased mortality with digoxin in HF,⁵ but the association weakens with more detailed baseline adjustments.⁴ Studies on the impact of digoxin in AF are fewer, with no randomized controlled trials (RCTs) available. Meta-analyses have suggested both that digoxin increases the risk of mortality⁵ and that there is not enough data to draw conclusions⁴ about the effects of digoxin in AF patients. The ongoing randomized DIGIT-HF trial will provide contemporary evidence for the efficacy and safety of digoxin in HF with and without AF.¹⁷

Uncertainty about the impact of digoxin is reflected in guideline recommendations. Most recent European Society of Cardiology (ESC) HF guidelines recommend digoxin only for treatment of HF patients with rapid heart rate and reduced ejection fraction.¹⁸ The HF guidelines of the AHA/ACC give a level IIaB recommendation for the reduction of HF hospitalizations.¹⁹ The AF guidelines of the ESC recommend digoxin or beta blockers as a first-line therapy to control heart rate in patients with reduced ejection fraction and digoxin as a second-line therapy in patients with normal or near normal myocardial contractility.²⁰ AHA/ACC/HRS guidelines recommend digoxin only as a second-line therapy for rate control in AF patients with HF.²¹ Digoxin is recommended by the ESC for rate control in the acute phase

of STEMI with extensive myocardial damage or severe left ventricular dysfunction,²² but guidelines give no recommendations regarding digoxin use after MI.^{22,23}

The potential impact of digoxin on clinical outcomes after MI has been less studied, and there is currently a definite gap in evidence concerning how to use digoxin after the acute phase of MI. To the best of our knowledge, there are no RCTs or ongoing studies on digoxin after acute MI in AF patients. The DIGIT-HF trial will provide important information about digoxin but will exclude patients with recent MI.¹⁷ Previous studies enrolling in the early 1990s found increased mortality after MI in digoxin users.^{6–8} Post hoc analysis of the DIG trial also indicated an association between long-term digoxin use and mortality in patients with previous MI.²⁴ In contrast, an analysis of the AFFIRM study enrolling AF patients in the 1990s found no independent association between digoxin use and mortality in the subgroup of MI patients.²⁵ Similarly, a pooled analysis of CARPICON, EPHEBUS, OPTIMAAL and VALIANT post-MI trials enrolling in the late 1990s and early 2000s found no association between digoxin and all-cause mortality in a 3-year follow-up of AF patients.²⁶ However, the recent data are limited to short-term follow-up periods. Garvia-Rubira et al. found that previous digoxin treatment did not influence the in-hospital mortality of acute coronary syndrome patients,⁹ and Metawee et al. observed no association between digoxin and 30-day mortality in STEMI patients.¹⁰ We found that post-MI digoxin usage was significantly associated with increased long-term mortality after MI in AF patients, with an NNH of 16.7 for death after adjustment for many potential confounders. To our knowledge, the current study, with a median follow-up period of 7.4 years, is the first contemporary long-term analysis of digoxin use and clinical outcomes after acute MI, and it is among the first to focus on AF patients.

In the sensitivity analysis, we found post-MI digoxin use to be associated with increased mortality in patients without a baseline diagnosis of HF but not in those with an HF diagnosis. This finding agrees with previous RCTs of digoxin's neutral effect on mortality in HF.⁴ In addition, a previous observational Swedish study found that digoxin use was associated with an increase in 1-year mortality in AF patients without baseline HF but not in those with baseline HF.²⁷ The detrimental post-MI impact of digoxin is also linked to patients without systolic HF.²⁶ However, because an HF diagnosis may be omitted in acute MI when the patient has reduced contractility but not symptomatic HF, these subgroup results should be interpreted with caution, especially regarding the lack of HF.

In healthy persons, ventricular arrhythmias induced by digoxin are rare. Myocardial damage, remodelling,

and scarring after MI, in addition to potential residual ischaemia, expose patients to ventricular tachyarrhythmias and sudden cardiac death.¹ Parasympathomimetic activity of digoxin may contribute to proarrhythmic autonomic dysfunction.²⁸ Although digoxin concentrations are typically monitored, digoxin's therapeutic index is extremely narrow, and adverse effects can occur at therapeutic concentrations as well.² Thus, it is mechanistically plausible that post-MI patients are more susceptible to the potentially hazardous adverse effects of digoxin.

Elevated serum digoxin concentration (SDC) is linked to increased mortality.^{29–31} Contrary to our expectations, we found no association between initial digoxin dosage after MI and long-term clinical outcomes. Because laboratory data were not available, we were unable to study SDCs. After reports of higher SDCs associated with mortality, measurement of SDC after digoxin initiation, followed by dose adjustment as needed, became a clinical routine in Finland's centralized healthcare system. Furthermore, clinical laboratories in Finland have updated their normal range for SDC to reflect the accumulating clinical evidence. Concurrently, recent data from the United States show a decreasing trend in digoxin toxicity and adverse outcomes.³² Thus, the observed neutral association between initial digoxin dosage and clinical outcomes likely reflects an awareness of patient-specific factors, such as kidney function and age, that affect SDC and improved monitoring rather than biological effects.

The DIG trial found that digoxin was associated with reduced HF hospitalizations in HF patients with normal sinus rhythms,³ and a meta-analysis shows a similar effect.⁴ However, data on AF patients is much more limited.⁴ In our data on AF patients, there was no association between post-MI digoxin use and HF hospitalizations. This is in line with the previous findings in post-MI AF patients²⁶ and AF patients without baseline HF.³³ We also found digoxin to have no association with the occurrence of stroke or new MI, indicating that digoxin does not significantly influence thrombogenesis in clinical use. These associations were previously rarely studied.⁴ An analysis of AF patients in the AFFIRM study found digoxin to be associated with stroke risk, but the patients were not anticoagulated.³⁴ In the more recent ENGAGE AF-TIMI 48 trial using anticoagulation, there was no association between digoxin use and risk of stroke or MI in AF patients.³³

Our study has strengths and limitations. We used a combination of previously validated nationwide mandated-by-law registries^{35,36} with complete follow-up on the primary clinical outcome. Propensity scoring and IPTW were used to balance differences in major risk factors and concurrent medications between the study groups. It is nevertheless possible that unrecognized

residual confounders may have impacted the results, although propensity scoring with IPTW is one of the strongest methods to control confounding factors. Based on the *E* value, the observed higher all-cause mortality in digoxin users could be explained by an unmeasured confounding associated with both digoxin use and all-cause mortality by a risk ratio of 1.7-fold each, above and beyond the measured confounders, but weaker confounding could not do so.¹⁵ Medication usage was studied with a standard method using drug purchase data from a database covering all prescription drug purchases in Finland,³⁷ but we did not have data on the actual usage of purchased medications, nor was it possible to study the temporal changes in the drug therapies. Furthermore, the available data limited the analysis of digoxin dosage to the initial tablet strength and did not account for tablet splitting, alternate day dosing, or the use of multiple tablets per day. We did not have access to ECG recordings, and presence of AF was based on ICD-10 coding. Furthermore, we did not have information regarding the AF type (e.g., new onset, paroxysmal, persistent or permanent), but because there appear to be no significant differences in outcome between AF types after MI,³⁸ we consider this limitation to be unlikely to cause significant bias. In addition, we did not have data on ejection fraction, preventing the subclassification of HF into HF_rEF and HF_pEF.¹⁸ Inaccuracies in administrative databases are a limitation that is likely to affect digoxin users and controls in a similar fashion and are thus not expected to have major influence over the key findings of this study. Our study was designed as intention-to-treat-type analysis and the persistence with digoxin gradually decreased during the follow-up. Therefore, our results may differ from the on-treatment impact of digoxin in long-term follow-up. As previously noted, RCTs are the golden standard of drug studies, and observational studies must always be interpreted with caution.^{24,39}

Our results have clinical implications regarding post-MI medication in AF patients. Digoxin is currently used mainly for rate control in AF patients. Current results, along with older studies, suggest that rate control in AF after MI should be handled by beta blockers rather than digoxin. In addition to lowering the baseline heart rate, beta blockers limit the abrupt heart rate increases that occur during exercise, unlike digoxin, and most importantly, beta blockers improve outcomes after MI.^{20,22,23} In addition, digoxin and beta blockers have comparable impacts on quality of life in AF patients with rate control.⁴⁰ In clinical reality, however, there are situations in which beta blockers alone or combined with calcium channel blockers are not effective enough, or adverse drug effects prevent their use, and digoxin usage is thus unavoidable.

In conclusion, our study shows that digoxin usage after MI is associated with increased long-term risk of mortality in patients with AF. Notably, in a subgroup analysis, an increased risk of death with digoxin usage was detected in patients without baseline HF but not in those with HF. Digoxin usage was not associated with HF hospitalizations, new MIs or stroke after MI. Our results suggest that digoxin should be used with caution after MI in AF patients, especially if HF is not present.

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CONFLICT OF INTEREST

None.

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