

ORIGINAL REPORT

Use of quinine and mortality-risk in patients with heart failure—a Danish nationwide observational study[†]

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ABSTRACT

Purpose Leg cramps are common in patients with heart failure. Quinine is frequently prescribed in low doses to these patients, but safety of this practice is unknown. We studied the outcomes associated with use of quinine in a nationwide cohort of patients with heart failure.

Methods Through individual-level-linkage of Danish national registries, we identified patients discharged from first-time hospitalization for heart failure in 1997–2010. We estimated the risk of mortality associated with quinine treatment by time-dependent Poisson regression models.

Results A total of 135 529 patients were included, with 14 510 patients (11%) using quinine at some point. During a median time of follow-up of 989 days (interquartile range 350–2004) 88 878 patients (66%) died. Patients receiving quinine had slightly increased mortality risk, adjusted incidence rate ratio (IRR) 1.04 (95% confidence interval [CI] 1.01 to 1.07). The risks differed according to concomitant β -blocker treatment. For patients treated with both quinine and β -blockers IRR was 1.15 (95% CI 1.09 to 1.21) vs. 0.99 (95% CI 0.96 to 1.03) for patients treated with quinine but not β -blockers. The risks were highest shortly after initiation of therapy: for the first 14 days of treatment IRR was 2.12 (95% CI 1.54 to 2.93) for patients in treatment with β -blockers and 1.17 (95% CI 0.86 to 1.59) for patients not treated with β -blockers.

Conclusions Use of quinine was common and associated with increased mortality in heart failure, especially if administered together with β -blockers and shortly after treatment initiation. Mechanisms underlying the findings remain to be established. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—quinine; heart failure; mortality; pharmacoepidemiology

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INTRODUCTION

Leg cramps are common among elderly individuals and are often due to electrolyte imbalances, impaired peripheral blood flow,¹ use of diuretics,² and extracellular

volume depletion—characteristics also found in patients with heart failure. Leg cramps are, however, often idiopathic.¹ The anti-malaria drug quinine is frequently prescribed in low doses to remedy leg cramps despite lack of data on the safety associated with this practice.

Quinine treatment for leg cramps was for many years considered a harmless treatment because of the low doses used but has been questioned lately. In 2006 the U.S. Food and Drug Administration (FDA) ordered pharmaceutical companies to discontinue marketing quinine for unapproved indications³ and again in 2010 issued a warning against prescribing quinine

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[†]The study has been presented at the ESC congress in Munich in 2012, where it was chosen for the highlight of the congress session

off-label for leg cramps due to concerns of potentially serious adverse effects including pancytopenia⁴ and prolonged QT-interval.⁵ In August 2012 FDA nevertheless reported that 92% of quinine use was still due to off-label indications, such as leg cramps and muscle pain.⁶

The effects of quinine on leg cramps and muscle pain are believed to be mediated by quinine's sodium and potassium channel blocking properties—mechanisms that may also be of importance to cardiac electrical conduction and function.⁷ Indeed, the dextrorotatory isomer of quinine, quinidine, is an old class 1A antiarrhythmic drug, which can cause heart failure, prolonged QT-interval, heart block, and fatal torsade de pointes ventricular tachycardia and is therefore not often used anymore.⁸ Because quinine has a similar but weaker toxicity profile as quinidine we wanted to investigate the association between quinine with risk of mortality in a large and temporary cohort of patients with heart failure.

METHODS

The Danish nationwide administrative registries contain complete data on a variety of health-care related variables. All Danish inhabitants are given a personal and permanent civil registration number at time of birth or immigration. The analyses were made by cross-linking the administrative registries by each patient's unique registration number. For the present analyses, we linked four of these registries.

From the Danish National Patient Registry we obtained information on all hospitalizations in Denmark since 1978. Hospitalization and discharge dates were available to us along with discharge diagnoses coded according to the International Classification of Diseases (ICD) system (the 8th version was used until 1993 and the 10th version was used hereafter). For the present study, we identified all individuals hospitalized for the first time with heart failure (primary or secondary discharge diagnosis) between 1997 and 2010; ICD-10 codes I50, I42, I11.0, or J81.9. The registry did not allow us to distinguish between heart failure patients with preserved ejection fraction from heart failure patients with reduced ejection fraction.

From the Danish Registry of Medical Product Statistics we obtained information on all dispensed prescriptions for pharmacologic agents since 1995. We used the following Anatomical Therapeutic Chemical (ATC) Classification System codes to identify use of quinine (P01BC01), renin-angiotensin-system (RAS) inhibitors (C09), beta blockers (C07), statins (C10A), thiazides (C03A), loop diuretics (C03C), spironolactone/epplereno-

ne (C03D), calcium-channel blockers (C08), digoxin (C01AA05), vitamin K antagonists (B01AA0), aspirin (B01AC06), and clopidogrel (B01AC04). We also obtained information on dispensing dates, strength, and quantity of dispensed medications for all agents. The Danish Registry of Medical Product Statistics has been shown to be very accurate.⁹

From the National Population Registry we obtained information on vital status, age, and gender for all individuals and from the National Causes of Death Registry we obtained information on causes of deaths.

Population and study endpoints

In order to ensure equal time for all patients to claim prescriptions for new medications after hospitalization, we only included patients alive 30 days after discharge. We started the observational time 30 days after discharge (from now on denoted 'study baseline') and followed patients for the risk of all-cause mortality until maximally 31 December 2010. As sensitivity, we performed an analysis where only cardiovascular-related mortalities were included (ICD-10 codes I01-I99). Due to lack of information for 2009 and 2010 we only included patients hospitalized in 1997–2008 and followed patients until maximally 31 December 2008 in this analysis.

Comorbidities and pharmacotherapy

We classified patients as having a specific comorbidity if they had a discharge diagnosis available within a 10-year period prior to actual observational time, meaning that comorbidities were updated continuously. The diagnosis of diabetes was obtained from claimed prescriptions for glucose-lowering medications (anatomical therapeutic classification [ATC] code A10) at some point between 90 days prior to hospitalization and 30 days after discharge, in accordance with previous work.^{10–12} We classified patients as being in treatment with concomitant cardiovascular pharmacotherapy, including β -blockers, if they had claimed at least one prescription of the specific drug at some point during 180 days prior to study baseline. In that context, previous work has shown that the proportion of heart failure patients commencing treatment with a new heart failure drug more than 30 days after discharge from first-time hospitalization for heart failure is small.¹³

We updated use of quinine continuously and calculated treatment exposure by considering the amount of tablets dispensed divided by the time interval between up to three claimed prescriptions, allowing the daily dosages to vary between 100 mg and 200 mg. If the amount of claimed tablets between prescription

intervals resulted in calculations of daily dosages exceeding 200 mg per day, we assumed that excessive tablets were saved and used during the first uncovered period. Because malaria is a very rare condition in Denmark (the numbers of affected individuals in the whole Danish population was 91 in 2008 and 54 in 2009),¹⁴ the indication for quinine in this study population was most likely leg cramps, which is, apart from malaria, the only labeled indication for quinine in Denmark. As the effect of quinine on leg cramps has been shown to be sustained for at least two weeks after treatment cessation, and to avoid “false breaks” during treatment, all treatment periods were lengthened by 14 days.¹⁵ We used loop diuretic dosages as a proxy for severity of heart failure and updated loop diuretic dosages continuously. We used an algorithm similar to that described for quinine to calculate dosages. This method has been used previously and has shown to correlate very well with mortality, but not with renal function in heart failure.^{16,17}

Statistics

We used the Chi-square test and the *t*-test for comparisons of characteristics between quinine and non-quinine users at baseline. We applied Cox proportional hazard regression models to investigate factors associated with initiation of quinine during follow-up among patients who had not been treated with quinine prior to study baseline.

We used multivariable Poisson regression models to calculate incidence rate ratios associated with use of quinine. All variables from Table 1 and actual calendar year were included in the analyses. Prior to analyses, we divided time into bands of 0.065 years (\approx 24 days), 0.125 years (\approx 46 days), 0.25 years (\approx 91 days), 0.5 years (\approx 183 days), and 0.75 years (\approx 274 days), and 1 year after study baseline, and hereafter in 1-year periods until 31 December 2010. We updated comorbidity, age, and treatment with loop diuretics at the start of each of these bands. We hereafter created separate bands for each shift in treatment with quinine throughout the study period. Pre-specified interaction analyses were performed between quinine and ischemic heart disease and between quinine and β -blockers, as we hypothesized that these two groups may have differential outcomes associated with influences of quinine on the heart conduction system. Due to interactions between quinine and use of β -blockers (but not with ischemic heart disease) we analyzed incidence rate ratios associated with use of quinine separately for patients with and without concomitant β -blocker treatment by inclusion of dummy variables where

appropriate. We tested assumptions of no interactions and no time dependency and found models valid unless otherwise specified.

We performed four sensitivity analyses to ensure robustness of our findings. First, we performed a non-time-dependent Cox proportional hazard regression model to investigate the association between baseline use of quinine and risk of mortality. In this model, we analyzed use of quinine by the intention-to-treat principle, and we adjusted the model for all variables presented in Table 1. Second, we performed a case-crossover analysis to assess the acute effects associated with quinine. In this analysis, we calculated the odds ratios for having started quinine shortly prior to death by using conditional logistic regression models. We only considered patients who met the endpoints (i.e., dead patients, “cases”), and they served as their own controls during a period prior to the endpoint, which eliminated control-selection bias.¹⁸ In this particular analysis we did not include patients who had used quinine prior to study baseline, as we wanted to investigate the acute effects of quinine treatment and eliminate survivor-bias. The length of case/control periods was set to 15 days, and we used four control periods for each case. Third, we performed an analysis where we only included deaths from cardiovascular causes, in an attempt to capture some of the putative sudden cardiac arrests. Fourth, we ran all the analyses excluding patients with use of potassium-sparing diuretics (ATC C03D) to make sure that the association between quinine and mortality was not driven by a potential sicker segment of patients.

SAS version 9.2 (SAS institute, Cary, NC, USA) was used for all analyses. A two-sided *p*-value of less than 0.05 was considered significant. We did not adjust for the numbers of tests performed.

RESULTS

We included a total of 135 529 patients. Of these, 14 510 patients (11%) used quinine at some point throughout the study period (i.e. between observational start and end). A total number of 5337 patients were in treatment with quinine at baseline. Among quinine users at baseline, median cumulative quinine treatment length prior to baseline was 680 (IQR 145–1543) days. Quinine users at baseline were slightly older, more often women, and had more comorbidity, compared to patients not using quinine at baseline. Notably, the proportion of patients who used vs. not used quinine at baseline was comparable for all the studied years (Table 1).

Table 1. Baseline characteristics

	Quinine users (n = 5337)	Non-quinine users (n = 130 192)	p-Value for difference
Gender, male	2095 (39%)	70 025 (54%)	<0.001
Age (years)	78 (\pm 10)	74 (\pm 13)	<0.001
<i>A history of:</i>			
Atrial fibrillation	1485 (28%)	39 271 (30%)	<0.001
Diabetes	1124 (21%)	19 557 (15%)	<0.001
Acute myocardial infarction	1123 (21%)	28 477 (22%)	0.15
Rheumatic disease	194 (4%)	4040 (3%)	0.03
Renal disease	430 (8%)	6105 (5%)	<0.001
Cerebrovascular disease	840 (16%)	17 088 (13%)	<0.001
Cancer	311 (6%)	6377 (5%)	0.01
Chronic ischemic heart disease	2117 (40%)	45 603 (35%)	<0.001
Peripheral artery disease	434 (8%)	6472 (5%)	<0.001
<i>Concomitant medications:</i>			
Beta-blockers	2019 (38%)	60 343 (46%)	<0.001
ACE inhibitors	2902 (54%)	75 467 (58%)	<0.001
Statins	1401 (26%)	35 579 (27%)	0.08
Aspirin	3228 (60%)	71 936 (55%)	<0.001
Clopidogrel	408 (8%)	11 210 (9%)	0.01
Vitamin K antagonists	966 (18%)	28 495 (22%)	<0.001
Digoxin	1721 (32%)	41 668 (32%)	0.71
Aldosterone receptor antagonists	1518 (28%)	30 973 (24%)	<0.001
Calcium channel blockers	1699 (32%)	34 816 (27%)	<0.001
Thiazides	1349 (25%)	30 124 (23%)	<0.001
Insulin	500 (9%)	7269 (6%)	<0.001
<i>Heart failure severity:</i>			
No loop diuretics	1131 (21%)	38 686 (30%)	
Loop diuretics \leq 40 mg/day	2063 (39%)	55 638 (43%)	
Loop diuretics >40–80 mg/day	611 (12%)	12 428 (10%)	
Loop diuretics >80–160 mg/day	423 (8%)	7107 (5%)	
Loop diuretics >160 mg/day	1109 (21%)	16 333 (13%)	
<i>Year of hospitalization:</i>			
1997–1998	723 (14%)	19 449 (15%)	0.05
1999–2000	852 (16%)	21 109 (16%)	
2001–2002	878 (16%)	21 280 (16%)	
2003–2004	851 (16%)	19 293 (15%)	
2005–2006	746 (14%)	17 430 (13%)	
2007–2008	675 (13%)	16 603 (13%)	
2009–2010	612 (11%)	15 028 (12%)	

During a median observational time of 989 (interquartile range [IQR] 350–2004) days, additionally 9173 patients claimed at least one prescription of quinine, of which 6598 had not been treated with quinine prior to study baseline. Median time to treatment initiation from study baseline was 634 (IQR 224–1341) days. Predictors for initiation of quinine included female gender, higher age, greater severity of heart failure, and greater burden of comorbidity, in particularly renal disease, diabetes, cancer, and peripheral artery disease. Also being in treatment with spironolactone, thiazides, high doses of loop diuretics, and insulin were predictors for initiation of quinine treatment (Figure 1). Of patients using quinine throughout the study period, approximately 40% were found to be long-term users (Figure 2).

Outcomes

The median time of follow-up was 989 (IQR 350–2004) days. During this period, 88 878 (66%) patients

died. Total observation time and numbers of events stratified by β -blocker treatment for patients with and without quinine are shown in Table 2.

Overall, quinine was associated with an adjusted incidence rate ratio of 1.04 (95% confidence interval 1.01–1.07) for all-cause mortality (Figure 3). Patients initiating quinine for the first time after study baseline (i.e. those who had not been exposed to quinine previously) had a substantial higher incidence rate ratio associated with quinine compared with patients who had been exposed to quinine prior to study baseline (p for difference between new users and pre users <0.001), 1.19 (1.14–1.24) vs. 0.96 (0.92–0.99). Patients who used β -blockers also had a higher incidence rate ratio associated with quinine, compared with patients who did not use β -blockers, 1.15 (1.09–1.21) vs. 0.99 (0.97–1.03), p for difference <0.001). Per se, however, β -blocker treatment was associated with an adjusted incidence rate ratio of 0.78 (0.77–0.79) in the study cohort. For patients initiating quinine for the first

QUININE IN HEART FAILURE, MORTALITY-RISK

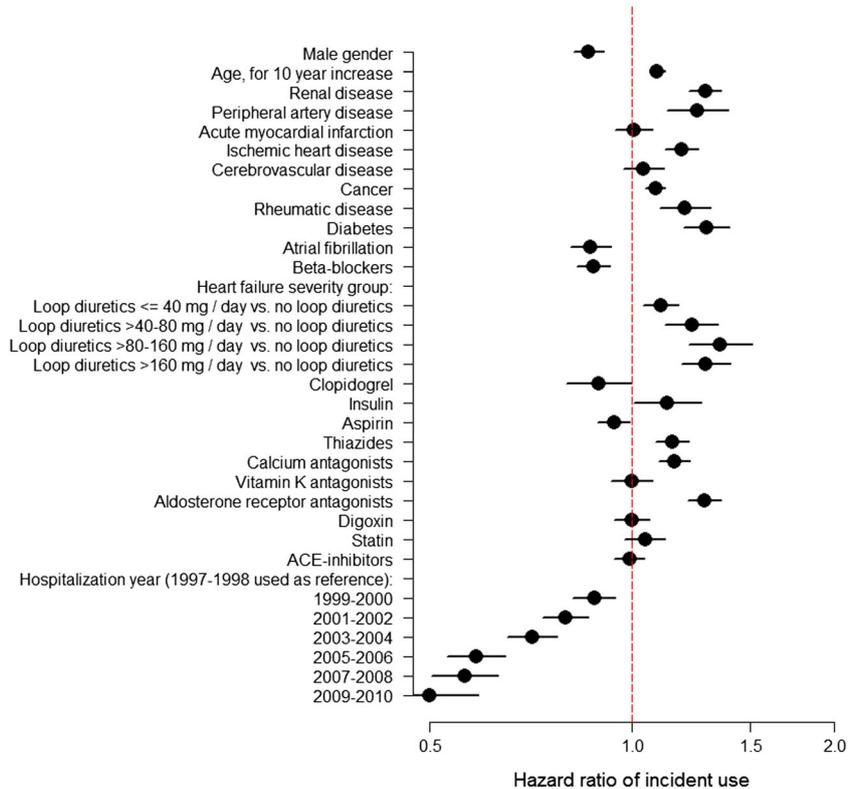


Figure 1. Predictors for initiating quinine treatment during follow-up according to selected baseline characteristics

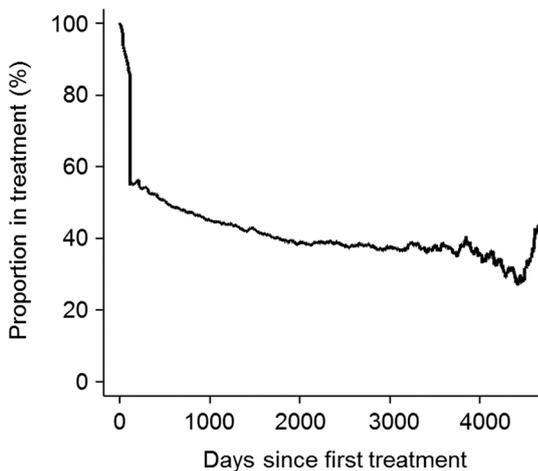


Figure 2. Temporal patterns for quinine use. Figure illustrates the proportion of patients remaining in treatment after their first claimed prescription (or study baseline for those who were in treatment at study baseline)

time after baseline, a particular steep increase in incidence rate ratio associated with quinine was found for the first 14 days of treatment among those treated with β -blockers (2.12 [1.54–2.93]), but not for those treated without β -blockers (1.17 [0.86–1.59]), p for difference =0.01. Excluding potassium-sparing

diuretics from any of the analyses yielded very similar results (online supplemental Table 1).

The association between use of quinine and all-cause mortality was not dependent on when during the observational period patients were exposed (p for interaction between time since hospitalization and use of quinine=0.45). The associations were furthermore not modified by use of digoxin, loop diuretic group, renal disease, gender, age, ischemic heart disease, or peripheral artery disease (p for interactions >0.05).

Sensitivity analyses

In the non-time-dependent Cox regression model, baseline use of quinine was associated with a hazard ratio of 1.09 (1.06–1.12) for mortality. Similar to the main analysis, use of β -blockers modified this association (p for difference <0.001), hazard ratio 1.20 (1.14–1.26) associated with quinine for those who used β -blockers and 1.04 (1.01–1.08) for those who did not use β -blockers.

Time dependent analyses without 14-day treatment prolongation yielded nearly identical results as the main analyses.

Table 2. Observational time and events

	Beta blockers (<i>n</i> = 62 362)		No beta blockers (<i>n</i> = 73 167)	
	No quinine	Quinine	No quinine	Quinine
Numbers ever exposed	61 835	5803	72 288	8707
Numbers deaths	30 951	1743	52 840	3344
Observational time (years)	230 066	8348	248 673	13 368
Incidence rates (<i>n</i> /100 PY)	13.5 (13.3–13.6)	20.9 (19.9–21.9)	21.2 (21.1–21.4)	25.0 (24.2–25.9)

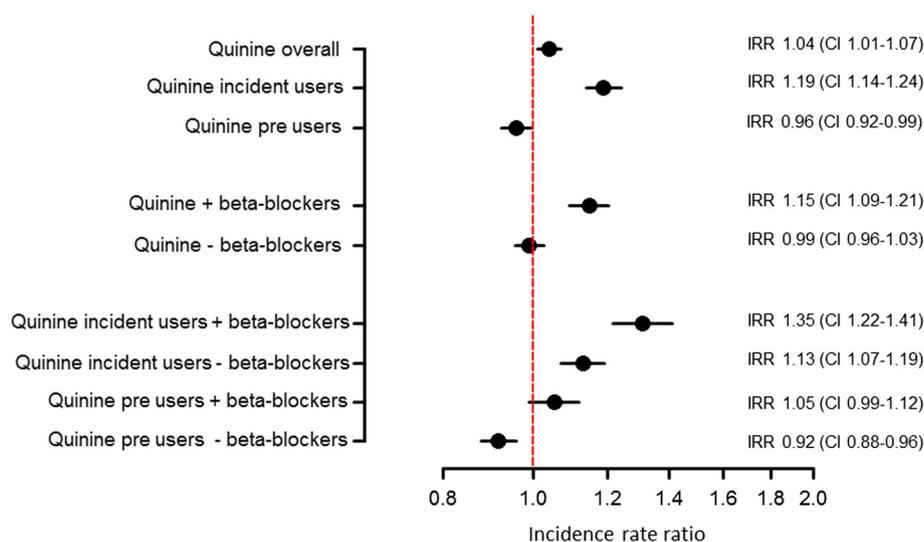


Figure 3. Adjusted incidence rate ratios (IRR) associated with use of quinine and all-cause mortality overall and in specific subgroups

The case-crossover analyses showed increased odds ratios for having started quinine treatment during 15 days prior to death among β -blocker as well as non- β -blocker treated patients, 1.47 (1.20–1.78) and 1.37 (1.17–1.59), respectively.

Repeating the main analyses with cardiovascular deaths as the outcomes, similar results were found. Overall, use of quinine was associated with incidence rate ratio 1.05 (1.01–1.08) and was higher among beta-blocker users (1.18 [1.12–1.27]) compared with non-beta-blocker users (0.98 [0.94–1.03]), *p* for difference <0.0001. The risks were highest for the first 14 days of treatment, incidence rate ratio 2.85 (2.01–4.02) and 1.15 (0.78–1.68) among patients with and without beta-blockers.

DISCUSSION

In the present nationwide cohort of heart failure patients we found that quinine was used by more than 10% of the population at some point and was associated with an increased risk of mortality, especially in patients with concomitant use of β -blockers and early

after treatment initiation. Among those who initiated quinine treatment for the first time during follow-up and also used β -blockers incidence rate ratios were more than doubled for the first 14 days of treatment. Considering the high baseline mortality rates found for patients with heart failure (i.e. 66% died during a median follow-up time of 989 days), such a high relative risk does warrant attention and needs further investigations.

In any epidemiological study there is a risk that the results are driven by confounding that have not been accounted for in the used models, but a few things would argue that our results cannot be explained by confounding alone. The case-cross-over analysis, which revealed similar results as the main analyses, uses the patient as his own control in a different time period and thereby effectively removes much confounding. The increased risk associated with starting quinine therapy as well as the lower risk in chronic users is compatible with drug toxicity. The interaction with β -blockers therapy also strengthens the result as detailed below. Altogether, we therefore find that the risk of quinine being a real danger to patients with heart failure is very high and should be taken seriously.

Mechanistically, quinine is known to be the chemical right isomer of quinidine, which is an old class 1A antiarrhythmic drug that may cause, e.g. torsades de pointes ventricular tachycardia, heart failure, and heart block.⁸ Quinine has a toxicity profile similar to that of quinidine and has, e.g. shown to possess a negative inotropic effect, to slow the rate of depolarization and conduction to a similar extent as quinidine, and to increase the action potential duration and the effective refractory period in the myocardium, although the latter to a lesser degree than quinidine.¹⁹ These features may lead to a significant depression of the intra-atrial and intra-ventricular conduction system. In this context, one interventional study which aimed to investigate the antiarrhythmic effect of quinine in humans reported that administration of quinine (1200–1600 mg) significantly increased QTc by 22 ± 59 ms and QRS-duration by 22 ± 27 ms.²⁰ Such increases are also well known for the use of quinine in malaria treatment.²¹ Also potentially contributing to adverse outcomes, quinine has shown to display alpha-adrenergic receptor blocking properties, which may cause hypotension and myocardial depression by decreasing coronary perfusion.²²

Speculatively, in combination with β -blockers low dosages of quinine could result in cardiac conduction block, especially in patients with structural heart disease, and this may explain the findings of a differential effect associated with quinine for β -blocker and non- β -blocker-treated patients in our study. Another potential explanation for the interaction could be competitive metabolism with cytochrome P-450 system by many β -blockers and quinine.²³ Despite that the magnitude of residual confounding needs to be significant to explain a two-fold increase in incidence rate ratios (as found for the first two weeks of treatment with quinine in patients with β -blockers), we can, however, not rule out that patients with reduced ejection fractions (who may have worse prognosis than patients with preserved ejection fractions) may have a higher likelihood of being treated with β -blockers, compared with patients with preserved ejection fractions and that this may underlie our findings of an interaction. Opposing such idea, however, β -blockers were associated with a significantly lowered mortality-risk per se in the present cohort.

As in the beginning of this study period, use of β -blockers for heart failure was not common, but with the large randomized clinical trials showing that β -blockers effectively prevented adverse outcomes in congestive heart failure around late 1990s and start of 2000s,²⁴ guidelines changed and now β -blockers are recommended to most patients with heart

failure.²⁵ Thus, given that β -blocker therapy nowadays comprises a standard element in the management of heart failure and that more than 10% of heart failure patients may be exposed to quinine, the number of patients that may potentially be harmed by this practice is significant. Noteworthy, in 2006, 2010, and 2012 FDA issued warnings against the use of quinine off-label for leg cramps due to concerns for serious adverse side effects. Although the likelihood of initiating quinine was shown to decrease throughout our study period, the practice of using quinine for relief of leg cramps seem to continue both in Denmark and in the U.S.^{3,4,6} FDA recently estimated that in 2011 51 800 patients redeemed a prescription for quinine from U.S. outpatient retail pharmacies for unapproved indications.⁶

STRENGTH AND LIMITATIONS

The major strengths of the present study included the large sample size of 135 529 patients with 14 510 patients using quinine. The use of Danish registries for identifying patients with heart failure has been proved to be very sensitive (99%), when validated against criteria based on symptoms, clinical signs, and echocardiography.²⁶

Despite the availability of updated loop diuretic dosages and a variety of other potential confounding variables, it cannot be excluded that the association between quinine and increased mortality-risks in part may have been influenced by residual confounding-by-indication. Specifically, we lacked data on left ventricular function, electrolyte status, blood glucose and lipid levels, and creatinine values, as well as data on electrocardiograms prior to and after administration of quinine, and we do not know how many patients died of sudden cardiac arrest. Our estimates on risks associated with quinine relied on calculations from claimed prescriptions, and we cannot be certain as to when or whether patients actually used quinine. A further limitation was that quinine is available over-the-counter in Denmark. Therefore, the actual number of patients using quinine may be greater than estimated.

CONCLUSION AND CLINICAL IMPLICATIONS

This nationwide study showed that quinine treatment in an unselected cohort of patients with heart failure is common and associated with increased risk of mortality. A particularly high increase in risk of mortality

associated with quinine was found for patients treated concomitantly with β -blockers and especially within the first 14 days after quinine treatment initiation, regardless of how long after hospital admission the treatment was initiated. These results suggest that the common practice of using quinine for symptom relief of leg cramps should only be done after careful consideration, weighing the potential risks against the, questionable, benefit. Quinine is available as over-the-counter medicine in many countries, and based on our study we believe that revision of this practice may be appropriate.

CONFLICT OF INTERESTS

CA has received a travel grant from AstraZeneca. GG has received speaker fees from AstraZeneca but unrelated to the topic of the current study.

KEY POINTS

- Use of quinine was common and associated with increased mortality in heart failure.
- Especially if administered together with β -blockers.
- Increased risk was found shortly after treatment initiation.
- Mechanisms underlying the findings remain to be established

ACKNOWLEDGEMENTS

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ETHICS STATEMENT

The study was approved by the Danish Data Protection Agency (No. 2007-41-1667). Registries were de-identified by Statistics Denmark but included unique coded identification numbers that enabled individual-level linkage between registries. Retrospective registry-based studies in which individuals cannot be identified do not need ethical approval in Denmark.

AUTHOR CONTRIBUTIONS

AG and CA were responsible for data analyses. AG wrote the initial draft of the manuscript. CA takes full responsibility for the accuracy of analyses and integrity of the data. All authors contributed to study design, interpretation of the data, and critical revision of the manuscript. All authors approved the final manuscript.

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QUININE IN HEART FAILURE, MORTALITY-RISK

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