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Effectiveness of Paroxetine Versus Non-Paroxetine Selective Serotonin Reuptake Inhibitors on Mortality and Heart Failure Following Myocardial Infarction: An Active Comparator Population-Based Cohort Study

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ABSTRACT

Background: Animal studies suggest that paroxetine, unlike other selective serotonin reuptake inhibitors (SSRIs), may attenuate post-myocardial infarction (MI) heart failure. We examine the effectiveness of paroxetine versus non-paroxetine SSRIs on the risk of post-MI mortality and heart failure in a clinical setting.

Method: We conducted a nationwide population-based cohort study based on Danish medical registries. Using an active comparator design, we compared the effectiveness of paroxetine with non-paroxetine SSRI drugs on post-MI outcomes. This included all patients hospitalized for MI in Denmark during 1995–2020 who had redeemed an SSRI prescription within 90 days prior to admission and measured outcome variables after a 180-day follow-up period. We calculated cumulative incidences as a measure of risk and used Cox regression to compute hazard ratios (HRs) for all outcomes, adjusting for sex, age group, individual comorbidities, and comedications.

Results: We identified 13 053 patients receiving treatment with an SSRI at the time of hospital admission for MI. Cumulative incidences were lower for paroxetine SSRI users compared with non-paroxetine SSRI users for all-cause mortality (24.7% versus 33.8% (difference: −9.1% [95% CI: −12.4; −5.8])) and cardiovascular death (15.9% versus 22.7% (−6.8% [95% CI: −9.6; −4.0])), but not for heart failure (11.0% versus 11.8% (−0.7% [95% CI: −3.13; 1.65])). Adjusted hazard ratios (aHRs) showed no substantial differences for all-cause mortality (aHR 0.9 [95% CI: 0.8–1.1]), cardiovascular death (aHR 0.9 [95% CI: 0.8–1.1]), or heart failure (aHR 1.0 [95% CI: 0.8–1.3]).

Conclusion: Paroxetine was not associated with clinically significant improvement in post-MI outcomes compared with non-paroxetine SSRI drugs.

All author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Summary

- Animal studies suggest that paroxetine, unlike other selective serotonin reuptake inhibitors, may attenuate post-myocardial infarction heart failure.
- Conducting a nationwide population-based cohort study based on Danish medical registries, we compared the effectiveness of paroxetine with non-paroxetine SSRI drugs on post-myocardial infarction outcomes.
- We examined paroxetine vs. non-paroxetine SSRI treatment in 13053 patients suffering from myocardial infarction.
- After adjusting for sex, age group, individual comorbidities, and comedications, there was no difference in heart failure, all-cause mortality, or cardiovascular death between groups.
- We were unable to translate the preclinical findings to a meaningful clinical application in our observational study.

1 | Introduction

Myocardial infarction (MI) is a major cause of morbidity and mortality in the Western world [1]. MI may lead to congestive heart failure through a complex and multifactorial process involving myocardial infarct size and left ventricular remodeling, which correlates with prognosis and mortality in MI survivors [2].

Left ventricular remodeling begins shortly after an MI and often precedes clinical symptoms of heart failure [3]. The surge in reactive oxygen species (ROS) following reperfusion may be an essential step in the pathophysiology of left ventricular remodeling [4, 5]. Inhibition of ROS production following MI attenuates left ventricular remodeling in an in vivo mouse model of MI [6], supporting a key role for ROS in remodeling.

We have previously demonstrated the ability of paroxetine, a selective serotonin reuptake inhibitor (SSRI), to reduce ROS and attenuate post-MI left ventricular remodeling in an in vivo rat model [7]. Unlike other SSRIs, paroxetine has an antioxidant moiety. Hence, the direct attenuation of ROS is likely not a drug class effect [8–10].

The risk of ischemic heart disease is increased in depressive patients, and the prognosis of MI patients is adversely affected by the presence of depression [11–13]. A randomized double-blinded trial with 300 patients demonstrated that 24 weeks of treatment with the SSRI escitalopram after MI reduced the risk of major adverse cardiac events to 40.9% from 53.6%, compared with placebo, after a median follow-up of 8.1 years (hazard ratio [HR]: 0.69) [14].

No studies have investigated the effectiveness of paroxetine on mortality and heart failure following MI in a clinical care setting. We used an active comparator design to examine the association of current paroxetine treatment versus non-paroxetine SSRI treatment on mortality and heart failure following MI.

2 | Methods

2.1 | Design and Setting

We conducted this nationwide population-based cohort study in Denmark, with a population of approximately 5.6 million persons during the 1995–2020 study period. The Danish National Health Service provides tax-supported health care, ensuring unfettered access to general practitioners and hospitals for all Danish inhabitants [15]. Accurate linkage of all registries at the individual level is possible in Denmark owing to the unique central personal registry number assigned to each Danish citizen at birth and to residents upon immigration [16]. In this study, we linked information from The Danish National Patient Registry (DNPR), The Danish National Prescription Registry, The Danish Register of Causes of Death, and The Danish Civil Registration System.

2.2 | Myocardial Infarction Patients

In Denmark, care for patients with acute MI and heart failure is provided by Danish public hospitals. All hospital data are registered in the DNPR [17]. We used the DNPR to identify all patients with a first-time inpatient diagnosis of MI during the study period. The DNPR has recorded information on dates of admission and discharge from all Danish non-psychiatric hospitals since 1977 and from emergency room and outpatient hospital clinic visits since 1995 [17]. Therefore, first-time MI is defined as first time since 1977 when the registry was established.

Each hospital discharge or outpatient visit is recorded in the DNPR with one primary diagnosis and one or more secondary diagnoses classified according to the *International Classification of Diseases*, *Eighth Revision* (ICD-8) through 1993 and the *Tenth Revision* (ICD-10) thereafter [17]. We identified MI patients using both primary and secondary discharge diagnoses. Across several validation studies, positive predictive values > 90% have been reported for coding of the diagnosis of MI [18]. All ICD and Anatomical Therapeutic Chemical (ATC) classification system codes used in the study are provided in Tables S1 and S2.

2.3 | Paroxetine and Non-Paroxetine SSRI Use

We used the Danish National Prescription Registry to identify all prescriptions redeemed by study participants for SSRIs [19]. Pharmacies in Denmark use electronic accounting systems to obtain reimbursement from the National Health Service. For each redeemed prescription, the date of purchase and the amount and type of drug prescribed according to the ATC classification system are transferred to the Danish National Prescription Registry.

We defined current users as patients who redeemed a prescription for paroxetine or a non-paroxetine SSRI drug within 90 days before hospitalization for MI. A diagnosis for depression was not mandatory. Patients who had redeemed a prescription for both paroxetine and a non-paroxetine SSRI during this period were excluded from the analysis. We used a 90-day window to

ensure current use at the time of MI, as prescriptions for SSRIs are rarely provided for longer than 90-day periods in Denmark. Therefore, if the patients take the medication as prescribed, a prescription reimbursed within 90 days of MI admission will ensure current SSRI use.

2.4 | Outcomes

The primary study outcomes were incident heart failure, all-cause mortality, and cardiovascular death during the 180 days following MI. The choice of a follow-up period of 180 days was based on an expected larger effect on ROS modulation closer to the MI event. Cardiovascular death was defined as underlying cause-specific mortality registered as venous thromboembolism, myocardial infarction, stroke, heart failure, arrhythmia, or valvular heart disease.

Additionally, we examined the following individual causes of death: venous thromboembolism, myocardial infarction, stroke, arrhythmia, heart valve disease, respiratory disease, and chronic obstructive pulmonary disease. Causes of death were obtained from the Danish Register of Causes of Death [20].

Information on heart failure diagnoses was retrieved from the DNPR, using primary and secondary inpatient and outpatient clinic diagnoses. The positive predictive value of the heart failure diagnosis coding is lower than for MI (approximately 80%) [17]. We used the Danish Civil Registration System to obtain information on all-cause mortality [16]. The Danish Civil Registration System has recorded changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.

2.5 | Comedications

Concurrent use of other drugs that may potentially affect MI prognosis was identified from the Danish National Prescription Registry. For analysis purposes, redemption of prescriptions for comedications had to occur within 90 days before admission for MI. Comedications included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, spironolactone, beta blockers, calcium channel blockers, diuretics, nitrates, statins, aspirin, P2Y12-inhibitors, vitamin K antagonists, direct oral anticoagulants, systemic glucocorticoids, and non-steroidal anti-inflammatory drugs.

2.6 | Comorbidities

We retrieved data from the DNPR on comorbidities from 1977 to the index date. Data on comorbidities are registered at hospital discharge or outpatient visit in the same manner as described for myocardial infarction. Comorbidities are registered any time prior to the MI. These data provided information on known prognostic factors and other potential confounders that may be associated with the type of SSRI use and study outcomes. Comorbidities included cardiovascular comorbidities (angina pectoris, atrial fibrillation or flutter, valvular heart disease, hypercholesterolemia, myocarditis, cardiomyopathy, hypertension, stroke, and intermittent claudication) and non-cardiovascular comorbidities (cancer, obesity, diabetes mellitus, chronic pulmonary disease, alcoholism-related diseases, myxedema, anemia, and chronic kidney disease).

2.7 | Statistical Analysis

We characterized paroxetine and non-paroxetine SSRI users in the MI cohort at baseline according to sex, age group (<50, 50–59, 60–69, 70–79, and ≥ 80 years), calendar period of MI diagnosis (1995–2003 and 2004–2020), individual comorbidities, and comedication use. For the mortality analyses (all-cause and cardiovascular death), we followed all patients from their hospital admission date until death, emigration, or 180 days follow-up, whichever came first. For the heart failure analyses, we followed all patients until a heart failure diagnosis, death, emigration, or 180 days follow-up, whichever came first. Additionally, we performed sensitivity analyses on the length of SSRI treatment prior to admission (30 or 60 days) to identify possible selection bias or problems with non-adherence. Sensitivity analyses on the length of follow-up (30, 90, or 365 days) were conducted to evaluate if patients received the heart failure diagnosis temporally related to the acute ischemia event (30 and 90 days) or if the 180 days follow-up was too short to develop heart failure (365 days). In another sensitivity analysis, we excluded patients with heart failure at the time of admission as they would likely not benefit from the hypothesised effect of paroxetine. Additionally, we added a sensitivity analysis in which comorbidities were registered 180 days prior to MI, to ensure we did not adjust for a modifier.

We calculated cumulative incidences as a measure of the risk of heart failure and cardiovascular death, considering death as a competing risk. HRs and adjusted HRs (aHRs) with corresponding 95% confidence intervals (CIs) were calculated using a multivariable ordinary and stratified Cox proportional hazards regression models to compute hazard ratios for all-cause mortality, cardiovascular death, and heart failure comparing paroxetine users and non-paroxetine SSRI users among MI diagnosed patients. The model was adjusted for sex, age group, individual comorbidities, and the comedications listed in Table 1. We evaluated the proportional hazard assumption using log–log plots and found no evidence of violation. To evaluate effect modification, we performed analyses stratified by calendar period of MI diagnosis, sex, age groups, comorbidities, and comedication use. As mandated by Statistics Denmark, we did not report exact numbers or analyze cumulative incidences if an outcome contained five or fewer patients, due to the potential for breach of anonymity.

To examine if patients changed their SSRI medication after hospitalization for MI, we tabulated redemption of paroxetine and other SSRI prescriptions 90 days before and 365 days after MI.

The analyses were performed using SAS V. 9.4 (SAS Institute Inc., Cary, North Carolina, USA). The study was approved by the Danish Data Protection Agency (record number:

TABLE 1 | Characteristics of patients hospitalized with a first-time diagnosis of myocardial infarction during 1995–2020, by paroxetine and non-paroxetine SSRI use, Denmark, 1995–2020.

	Paroxetine users ($n = 698$)		Non-paroxetine SSRI users ($n = 12\,355$)	
	n	%	*n*	%
Gender				
Male	282	40.4	5494	44.5
Female	416	59.6	6861	55.5
Age, years				
< 50	70	10.0	663	5.4
50–59	132	18.9	1258	10.2
60–69	155	22.2	2084	16.9
70–79	185	26.5	3523	28.5
≥ 80	156	22.3	4827	39.1
Calendar period of diagnosis/index date				
1995–2003	282	40.4	3759	30.4
2004–2020	416	59.6	8596	69.6
Cardiovascular disease	308	44.1	7316	59.2
Angina pectoris	142	20.3	3059	24.8
Atrial fibrillation or flutter	60	8.6	1695	13.7
Valvular heart disease	28	4.0	837	6.8
Hypercholesterolemia	50	7.2	1215	9.8
Myocarditis	≤ 5		24	0.2
Cardiomyopathy	7	1.0	141	1.1
Hypertension	183	26.2	4345	35.2
Stroke	56	8.0	2564	20.8
Intermittent claudication	24	3.4	641	5.2
Non-cardiovascular disease	230	33.0	4999	40.5
Cancer	16	2.3	497	4.0
Obesity	17	2.4	281	2.3
Diabetes mellitus	16	2.3	571	4.6
Chronic pulmonary disease	139	19.9	2487	20.1
Alcoholism-related disease	18	2.6	325	2.6
Myxedema	22	3.2	383	3.1
Anemia	38	5.4	1447	11.7
Chronic kidney disease	22	3.2	802	6.5
Comedications	502	71.9	9750	78.9
SSRI drugs	698	100	12 355	100
Paroxetin	698	100	0	0
Fluoxetine	0	0	775	6.3
Citalopram	0	0	8212	66.5
Sertraline	0	0	2113	17.1
Fluvoxamine	0	0	40	0.3
Escitalopram	0	0	1333	10.8
Cardiovascular drugs				
Angiotensin-converting enzyme inhibitors	495	70.9	9656	78.2
Angiotensin receptor blockers	119	17.0	2193	17.7
Spironolactone	79	11.3	1312	10.6
Beta blockers	28	4.0	600	4.9
Calcium channel blockers	128	18.3	2389	19.3
Furosemide	131	18.8	2519	20.4
Bumetanide	117	16.8	3118	25.2
Nitrates	85	12.2	1722	13.9
Statins	119	17.0	2438	19.7
Acetylsalicylic acid	163	23.4	3883	31.4
P2Y12-inhibitors	22	3.2	590	4.8
Warfarin	20	2.9	481	3.9
Direct oral anticoagulants	7	1.0	165	1.3
Systemic glucocorticoids	56	8.0	1321	10.7
Non-steroidal anti-inflammatory drugs	140	20.1	2042	16.5

Note: ≤ 5 stands for "less than or equal to 5." This convention is used rather than the exact number to prevent identification of individuals, as mandated by Statistics Denmark.
Abbreviation: SSRI, selective serotonin reuptake inhibitor.

2016-051-000001). According to Danish legislation, no approval from an ethical committee or patient informed consent are required for registry-based studies in Denmark.

3 | Results

3.1 | Descriptive Characteristics

The total number of MI cases during the study period was 212 399. Among these, we identified 698 paroxetine SSRI users and 12 355 non-paroxetine SSRI users (Table 1). The sex distribution was similar between the two groups (40% of paroxetine SSRI users and 45% of non-paroxetine SSRI users were male). The average age of paroxetine users was 68.5 years; the average age of non-paroxetine SSRI users was 74.2 years. Overall, the non-paroxetine SSRI group had more comorbidities than the paroxetine SSRI group. However, there were no differences in pulmonary or chronic obstructive pulmonary disease between the groups.

3.2 | Post-MI All-Cause Mortality, Cardiovascular Death, and Heart Failure

We observed a lower 180-day cumulative incidence among paroxetine users than among non-paroxetine SSRI users for all-cause mortality (24.7% versus 33.8%, (difference: −9.1% [95% CI: −12.4; −5.8])) and for cardiovascular death (15.9% versus 22.7%, (−6.8% [95% CI: −9.6; −4.0])). For heart failure, we observed no difference (11.0% versus 11.8% (−0.7% [95% CI: −3.13; 1.65])) (Table 2). The crude hazard ratios for all-cause mortality, cardiovascular death, and heart failure were lower for paroxetine users than for non-paroxetine users. However, after adjustment, no clinically important differences were observed between the groups for all-cause mortality (aHR 0.9 [95% CI: 0.8–1.1]), cardiovascular death (aHR 0.9 [95% CI: 0.8–1.1]), and heart failure (aHR 1.0 [95% CI: 0.8–1.3]).

Sensitivity analyses on length of SSRI treatment prior to admission (Tables S3 and S4), length of follow-up (Tables S5–S7), and the analysis that excluded patients with heart failure at time of admission (Table S8), were consistent with the main results.

The analysis stratified by calendar periods (1995–2003 and 2004–2020) did not reveal a difference in aHRs for heart failure or mortality between paroxetine and non-paroxetine SSRI users (Table S9). Additionally, the results remained robust in analyses stratified by gender, age, comorbidity, and comedication use. However, results for patients < 60 years pointed to a beneficial effect of paroxetine on all-cause mortality (aHR 0.6 [95% CI: 0.3–1.1], Tables S10 and S11).

A negligible number of changed medication between paroxetine and non-paroxetine SSRIs (0.1% and 3.4%, respectively) within 365 days after their MI diagnosis. However, approximately a quarter of the patients discontinued their SSRI medication (26.5% and 32.8%), but most patients continued their medication (64.9% and 66.8%) (Table S12).

Registering comorbidities 180 days earlier to avoid adjusting for a mediator did not change the results (Table S13).

4 | Discussion

In this nationwide population-based cohort study, we found no difference in all-cause mortality, cardiovascular death, and heart failure among patients with MI who used paroxetine versus non-paroxetine SSRIs after adjusting for sex, age group, individual comorbidities, and comedication use.

Previous research has shown that treatment with SSRIs increases psychological quality of life [10], but does not lower all-cause mortality in heart failure patients [10, 21]. In patients suffering from acute MI, treatment with the SSRI escitalopram improves all-cause mortality outcomes compared to placebo [14], possibly due to attenuation of circulating ROS [22], which inhibits post-MI remodeling [4, 5]. Our study builds upon these findings by showing that paroxetine does not add clinically important additional benefit compared to the class effect of SSRI treatment, despite its unique ability to function as an antioxidant. This may be due to the several, and perhaps more important, pleiotropic effects of SSRIs in addition to their antidepressant qualities. SSRIs exert an anti-adrenergic effect on the heart, improving post-MI heart rate variability, which reduces mortality [23, 24]. Additionally, SSRIs decrease vasomotor tone [25] and platelet activation [26], which may improve heart failure outcomes. However, SSRI treatment also may increase the risk of bleeding in patients receiving antiplatelet therapy [27] following MI, which may impact post-MI mortality.

The ability of non-paroxetine SSRI treatments to indirectly lower circulating ROS [22] in patients suffering from a psychiatric disorder, as well as their other beneficial effects, may overshadow or match the direct antioxidant effect of paroxetine. These class effects of SSRIs may partly explain our neutral findings. Additionally, the doses used in proof-of-concept animal studies are far above the standard dose used to treat depression in a clinical care setting [7]. Therefore, the antioxidant effect of paroxetine may have been negligible at the lower doses utilized in this study.

Our population-based study was performed within a tax-supported uniformly organized health care system, minimizing the risk of selection and referral biases [15]. Although the positive predictive value for heart failure coding recorded in the DNPR is modest, it is likely much higher among patients suffering from MI. Moreover, it is unlikely that coding errors would be associated with a specific SSRI drug. Misclassification of heart failure diagnoses would therefore be non-differential and bias the results toward the null.

SSRI prescription was not linked to a depression diagnosis. There are other, less common indications for starting treatment with SSRIs (e.g., anxiety and obsessive-compulsive disorder). However, we were not able to discriminate indications for SSRI initiation from the prescription database. Because the other indications for use of SSRI drugs are also prevalent among patients suffering from depression, we cannot verify that the treatment was initiated due to depression, even if we restricted to patients with a depression diagnosis. Our hypothesis was that the antioxidant properties of paroxetine attenuated myocardial remodeling and consequently heart failure. This effect is not likely to be related to the indication for initiating treatment.

SSRI drugs are dispensed only by prescription in Denmark. Additionally, the prescription databases are based only on dispensed prescriptions and are virtually complete [19]. Consequently, we were able to identify all patients with

TABLE 2 | Cumulative incidence and hazard ratios of heart failure, all-cause mortality, and cause-specific mortality 180 days after myocardial infarction in patients treated with paroxetine or non-paroxetine SSRIs at time of hospital admission for MI.

	Paroxetine users		Non-paroxetine SSRI users				
	No. at risk/ events	Cumulative incidence, % (95% CI)	No. at risk/events	Cumulative incidence, % (95% CI)	Difference in cumulative incidence (95% CI)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]
Heart failure	698/77	11.0 (8.9–13.5)	12 355/1451	11.8 (11.2–12.4)	−0.7 (−3.1–1.7)	0.9 (0.7–1.1)	1.0 (0.8–1.3)
All-cause mortality	698/172	24.7 (21.5–27.9)	12 355/4162	33.8 (32.9–34.6)	−9.1 (−12.4–5.8)	0.7 (0.6–0.8)	0.9 (0.8–1.1)
Cause-specific mortality							
Cardiovascular disease	698/111	15.9 (13.3–18.7)	12 355/2798	22.7 (22.0–23.4)	−6.8 (−9.6 – −4.0)	0.7 (0.6–0.8)	0.9 (0.8–1.1)
Venous thromboembolism	698/< 5		12 355/12	0.1 (0.1–0.2)	0.1 (−0.2–0.3)	1.4 (0.2–10.7)	1.5 (0.2–11.5)
Myocardial infarction	698/83	11.9 (9.6–14.4)	12 355/1893	15.3 (14.7–16.0)	−3.5 (−5.9 – −1.0)	0.8 (0.6–0.9)	1.0 (0.8–1.2)
Stroke	698/8	1.2 (0.6–2.2)	12 355/150	1.2 (1.0–1.4)	−0.1 (−0.9–0.7)	0.9 (0.4–1.8)	1.6 (0.8–3.3)
Heart failure	698/< 5		12 355/97	0.79 (0.6–0.96)	−0.5 (−0.9 – −0.1)	0.3 (0.1–1.4)	0.6 (0.1–2.3)
Arrhythmia	698/0		12 355/44	0.4 (0.3–0.5)			
Heart valve disease	698/< 5		12 355/87	0.7 (0.6–0.9)	−0.4 (−0.8–0.0)	0.4 (0.1–1.6)	0.9 (0.2–3.7)
Respiratory disease	698/25	3.6 (2.4–5.2)	12 355/382	3.1 (2.8–3.4)	0.5 (−0.9–1.9)	1.1 (0.7–1.6)	1.5 (1.0–2.3)
Chronic obstructive pulmonary disease	698/20	2.9 (1.8–4.3)	12 355/230	1.9 (1.6–2.1)	1.0 (−0.3–2.3)	1.5 (0.9–2.3)	1.82 (1.1–2.9)

Note: ≤ 5 denotes "less than or equal to 5." This convention is used rather than the exact number to prevent identification of individuals, as mandated by Statistics Denmark.
Abbreviations: CI, confidence interval; SSRI, selective serotonin reuptake inhibitor.
[a]Adjusted for age, sex, calendar year, comedications, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, myocarditis, cardiomyopathy, hypertension, stroke, intermittent claudication, cancer, obesity, diabetes mellitus, chronic pulmonary disease, alcoholism-related diseases, myxedema, anemia, and chronic kidney disease.

redeemed prescriptions for SSRIs. By using a 90-day window for the last redemption, all patients are expected to have been in active treatment. Any misclassification of drug exposure due to non-adherence or discontinuation of treatment would attenuate the estimate of association toward unity.

This cohort study, based on data from medical registries, is inherently non-experimental. Such designs cannot establish causality with certainty due to the risk of residual confounding. By using an active comparator design, we sought to control for confounding by indication. However, some clinical indications or regional guidelines still may have led to one drug being chosen over another.

Additionally, despite extensive adjustment for potential confounders, residual confounding factors may have remained. These include lifestyle, socioeconomic status, or severity of depression. Furthermore, because of temporal trends in prescribing, paroxetine use was relatively more prevalent during the initial part of the study period (1995–2003) and relatively less prevalent during the latter part (2004–2020). Despite this difference, the results of analyses stratified by calendar period were comparable to those of the main analyses.

The study was conducted in a Danish setting with a mainly Caucasian population and a tax-supported, uniformly organized healthcare system with equal and unfettered access to healthcare services. This may limit the generalizability when compared to a population with a different ethnic composition and healthcare system.

4.1 | Conclusion

In this population-based cohort study, treatment with paroxetine before and during hospital admission for MI did not improve post-MI risk of heart failure or death compared to treatment with non-paroxetine SSRI drugs, despite promising preclinical studies.

4.2 | Plain Language Summary

Selective serotonin reuptake inhibitors (SSRIs) are antidepressants commonly used to treat depression as well as other psychiatric disorders. Unlike other SSRIs, animal studies suggest that the specific SSRI, paroxetine, may attenuate heart failure developed after a heart attack. We aimed to examine the effectiveness of paroxetine versus non-paroxetine SSRIs on the risk of death and heart failure after a heart attack in a clinical setting. Conducting a nationwide population-based cohort study based on Danish medical registries, we compared the effectiveness of paroxetine with non-paroxetine SSRI drugs on improving outcomes after a heart attack. We identified 13 053 patients receiving treatment with an SSRI at the time of hospital admission for a heart attack. Hazard ratios adjusted for sex, age group, individual comorbidities, and comedications showed no substantial differences in all-cause mortality (0.9 [95% CI: 0.8–1.1]), cardiovascular death (0.9 [95% CI: 0.8–1.1]), or heart failure (1.0 [95% CI: 0.8–1.3]). In conclusion, we were unable to translate the preclinical findings to a meaningful clinical effect in our observational study.

Author Contributions

The manuscript was conceptualized by T.R.L. and J.S. The study was designed by T.R.L., H.T.S., H.E.B., and J.S. Data analyses were performed by P.S. and interpretation by all authors. The first draft was written by T.R.L. and J.S. All authors contributed to the discussion of the data and approved the final version of the manuscript.

Acknowledgments

Dr. Sørensen is the guarantor of this work, has full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the analyses.

Disclosure

The Department of Clinical Epidemiology, Aarhus University, receives funding for other studies in the form of institutional research grants to (and administered by) Aarhus University. None of these studies has any relation to the present study.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.