



## Cardiac left ventricular ejection fraction in men and women with schizophrenia on long-term antipsychotic treatment

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### ABSTRACT

Patients with schizophrenia exhibit a higher cardiovascular mortality compared to the general population which has been attributed to life-style factors, genetic susceptibility and antipsychotic medication. Recent echocardiographic studies have pointed to an association between clozapine treatment and reduced left ventricular ejection fraction (LVEF), a measure that has been inversely associated with adverse outcomes including all-cause mortality. Cardiovascular magnetic resonance (CMR) is considered the reference method for LVEF measurement. The aim of the present study was to investigate the LVEF in patients with schizophrenia on long-term treatment with antipsychotics and healthy controls. Twenty-nine adult patients with schizophrenia on long-term medication with antipsychotics and 27 age-, sex- and body mass index-matched healthy controls (mean ages 44 and 45 years, respectively) were recruited from outpatient psychiatric clinics in Uppsala, Sweden. The participants were interviewed and underwent physical examination, biochemical analyses, electrocardiogram and CMR. Men with schizophrenia on long-term antipsychotic treatment showed significantly lower LVEF than controls ( $p = 0.0076$ ), whereas no such difference was evident among women ( $p = 0.44$ ). Specifically, clozapine-treated male patients had 10.6% lower LVEF than male controls ( $p = 0.0064$ ), whereas the LVEF was 5.5% below that of controls among male patients treated with non-clozapine antipsychotics ( $p = 0.047$ ). Among medicated men with schizophrenia, we found significantly lower LVEF compared to healthy individuals, suggesting the need of routine cardiac monitoring in this patient group. This is the first study showing a significant negative association between treatment with non-clozapine antipsychotics and LVEF.

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### 1. Introduction

It is currently established knowledge that there is an increased overall as well as cardiovascular disease (CVD) mortality among patients with schizophrenia with CVD deaths occurring at least ten years earlier in patients compared to the general population (Crump et al., 2013; Ringen et al., 2014; Westman et al., 2017). Further, CVDs are the leading cause of death among patients with schizophrenia causing more excess deaths than suicide (Westman et al., 2017). It has been hypothesized that the elevated CVD mortality is attributable to life-style factors, such as smoking, lack of exercise, poor diet and socio-economic poverty,

to shared genetic susceptibility between schizophrenia and CVDs, and to antipsychotic medicines having obesogenic or other detrimental effects (Ringen et al., 2014). The hypothesized negative cardiac effect of antipsychotics has been challenged by a recent study showing a non-elevated risk of CVD death and a decreased overall mortality among patients on second generation antipsychotics compared to non-users of antipsychotics (Kiviniemi et al., 2013). A decreased overall mortality among patients on haloperidol or second generation antipsychotics compared to patients on placebo has also been reported (Khan et al., 2013), and clozapine treatment specifically has been related to lower all-cause mortality compared to treatment with other antipsychotics (Tiihonen et al., 2009). On the other hand, antipsychotics in general and clozapine in particular have been reported to be associated with frequent subclinical cardiac dysfunction, as reflected by a decreased left ventricular ejection fraction (LVEF) measured with echocardiographic modalities (Chow et al., 2014; Korkmaz et al., 2016).

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LVEF refers to the percentage of blood that is ejected out of the left ventricle with each cardiac contraction. LVEF is an important systolic functional parameter and can be quantified by different modalities including echocardiography (ECHO) and cardiovascular magnetic resonance (CMR). LVEF normal values assessed by CMR are considered to be 57–77% (Kawel-Boehm et al., 2015). According to the guidelines from the European Society of Cardiology and the American Society of Echocardiography, LVEF >50% and >55%, respectively, are considered normal (Lang et al., 2005; McMurray et al., 2012; Tsao et al., 2016). CMR is regarded as the reference standard for LVEF measurement due to high image quality and volumetric data (Wood et al., 2014), whereas transthoracic ECHO has been reported to have limitations in assessing grades of left ventricular dysfunction compared to CMR (Alexis et al., 2017). We thereby consider that the assessment of LVEF with CMR in physically asymptomatic patients with schizophrenia on antipsychotics compared to healthy controls is of importance for the understanding of the established higher CVD mortality and overall mortality in this patient group. We hypothesize that physically asymptomatic patients with schizophrenia on long-term medication with antipsychotics exhibit a reduced LVEF compared to healthy controls, and that the LVEF reduction is not restricted to patients receiving clozapine but can also be found in patients on non-clozapine antipsychotics. Considering the observed differences in CVD mortality and susceptibility to cardiovascular risks of antipsychotics between men and women with schizophrenia (Fors et al., 2007; Seeman, 2009; Westman et al., 2017), we further hypothesize that putative LVEF differences between patients and controls are gender-dependent.

## 2. Materials and methods

### 2.1. Subjects

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Regional Ethical Review Board in Uppsala, Sweden—approval numbers: 2013/206 (09-10-2013), 2013/206/2 (04-03-2015). Written informed consent was obtained from all subjects.

The study initially included 30 patients with schizophrenia and 30 healthy control individuals matched for age, sex and body mass index (BMI). The patients were recruited from outpatient psychiatric clinics in Uppsala, Sweden, and were all physically asymptomatic. All but one patient were treated with long-term antipsychotic medication (median duration of treatment 16.5 years, interquartile range 10–25 years; duration of treatment >10 years for 23/29 patients). The 29 medicated patients (18 men and 11 women) were included in the study. Twenty patients were diagnosed with paranoid schizophrenia (ICD-10: F20.0), six with undifferentiated schizophrenia (ICD-10: F20.3), one with residual schizophrenia (ICD-10: F20.5), one with schizophrenia, unspecified (ICD-10: F20.9) and one with simple-type schizophrenia (ICD-10: F20.6). Eight patients were on clozapine and 21 were on non-clozapine antipsychotics. Particularly, five of the patients who were medicated with clozapine were on clozapine monotherapy, two on clozapine and aripiprazole and one on clozapine and risperidone. In the non-clozapine group, 14 patients were on second generation antipsychotics (five on olanzapine, three on aripiprazole, one on risperidone, two on paliperidone, one on risperidone and quetiapine, one on risperidone and paliperidone and one on aripiprazole and quetiapine), six were on first generation antipsychotics (three on perphenazine, two on flupentixol and one on haloperidol) and one on perphenazine and aripiprazole. If a patient was medicated with both clozapine and another antipsychotic agent, the patient was classified in the clozapine group.

The healthy controls were recruited using the following procedure. In a first step, possible control subjects with the same age and gender as the patients were assigned randomly from a nation-wide population register. In the next step, they were interviewed regarding psychiatric and somatic morbidity as well as body weight and height for matching purposes. After preliminary inclusion they underwent baseline investigations. Three of the controls were excluded due to present or past psychiatric diagnoses and/or psychiatric medication and 27 controls (17 men and 10 women) were included in the study. None of the patients or controls had a history of CVD.

Exclusion criteria for both patients and controls were medical history of CVD, hypertension, diabetes, neoplastic disease, organic brain disease or chronic kidney disease (glomerular filtration rate < 30), previous or current use of antihypertensive, antidiabetic or antihyperlipidemic agents, and DSM-IV alcohol or other substance abuse or dependence. All participants were interviewed regarding health history, pharmacological treatment history, current or previous diseases in the family (parents and siblings), physical activity, dietary and smoking habits. They were further assessed with the Structured Clinical Interview for DSM-IV-Axis 1 Disorders (SCID 1) (Spitzer et al., 1992) and the Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993). The Leisure Time Physical Activity Instrument (LTPAI) and Physical Activity at Home and Work Instruments (PAHWI) (Mannerkorpi and Hernelid, 2005) provided data on the average hours of light, moderate and vigorous activity. These hours were then added together to produce the physical activity during one week. All participants underwent physical examination, anthropometric measurements and electrocardiogram (ECG) and were judged to be medically healthy.

### 2.2. Biochemical analyses

Whole blood samples were collected from patients and controls between 8 and 10 a.m. after at least 8 h of absence of food intake. The biochemical analyses were performed in the Department of Clinical Chemistry and Pharmacology at Uppsala University Hospital and are listed in Table 1.

### 2.3. CMR image acquisition

Imaging was performed on a 1.5 Tesla MRI system (Achieva, Philips Medical Systems, Best, the Netherlands) with a 25 mT/m gradient system, using the standard SENSE cardiac coil in the supine position and retrospectively gated vector ECG for cardiac triggering.

Cine images were acquired during breath holding using a steady state free precession sequence covering the left ventricular myocardium from the apex to the atria in 8 mm thick short axis slices with a 2.5 mm slice gap, an acquired in-plane resolution of  $2.27 \times 1.81$  mm and 18 phases recorded per cardiac cycle. Two slices were acquired per breath hold. The temporal resolution varied between the subjects depending on their heart rates.

### 2.4. CMR image analysis

Left ventricular function was assessed (by CEB) on a workstation with commercially available analysis software (MR Workspace 2.6.3.5, Philips Medical Systems, Best, the Netherlands). Quantification was performed on all short-axis images where LV myocardium was present. The endocardial and epicardial contours of the LV myocardium were traced in end diastole, defined as the first phase following the ECG R-wave; and in end systole, defined visually as the phase with the smallest LV volume. Border definition of the epicardial contour was accomplished by manual tracing using a mouse. The endocardial contour was generated with computer assistance, where a manually drawn contour is automatically adapted to the underlying image. The papillary muscles were included in the endocardial contour when attached to the ventricular wall. Papillary muscles not attached to the wall were included in the

**Table 1**  
Differences in clinical and background characteristics, and biochemical parameters between patients with schizophrenia and healthy controls. Correlations with left ventricular ejection fraction (LVEF).

	Patients		Controls		ANOVA <sup>a</sup> or L-R test <sup>b</sup> <i>p</i> value	Correlation with LVEF	
	N	Mean (SD) or %	N	Mean (SD) or %		Direction (+ or –)	<i>p</i> value
Gender (women %)	29	37.9	27	37	0.945	+ <sup>c</sup>	0.026
Age (years)	29	44 (7.2)	27	45 (6.6)	0.578	+	0.311
Body Mass Index (kg/m <sup>2</sup> )	29	29.6 (4.3)	25	28.7 (4.2)	0.457	+	0.600
Smoking status (%)	29	37.9	27	18.5	0.104	+	0.897
Systolic blood pressure (mmHg)	29	130.6 (15.0)	25	131.9 (14.4)	0.748	–	0.479
Diastolic blood pressure (mmHg)	29	80.9 (7.8)	25	84.2 (11.3)	0.213	+	0.169
Physical activity (hours of exercise/week)	28	15.8 (11.9)	26	26.3 (16.0)	0.008	+	0.112
Diet index	29	6.9 (2.1)	25	6.7 (2.5)	0.774	–	0.927
Family history of diabetes (%)	29	24.1	24	16.7	0.502	+	0.678
Family history of cardiovascular disease (%)	29	41.4	24	58.3	0.218	–	0.720
AUDIT <sup>d</sup> points	29	1.9 (2.8)	26	3.9 (2.6)	0.008	–	0.113
Glucose (mmol/L)	29	6.1 (0.8)	25	5.8 (0.7)	0.145	–	0.470
Glycated hemoglobin (mmol/mol)	29	36.3 (3.7)	24	33.1 (3.7)	0.003	+	0.861
Triglycerides (mmol/L)	29	1.6 (0.8)	25	1.3 (0.6)	0.264	–	0.482
Low-density lipoprotein (mmol/L)	29	3.5 (0.8)	25	3.4 (0.8)	0.659	+	0.456
High-density lipoprotein (mmol/L)	29	1.2 (0.3)	25	1.3 (0.3)	0.293	+	0.438
C-reactive protein (mg/L)	29	4.7 (5.5)	25	1.7 (1.7)	0.013	+	0.023
Heart rate (beats per minute)	29	81.3 (13.2)	27	67.3 (10.3)	<0.0001	–	0.732
Corrected QT interval (ms)	29	436.6 (21.3)	27	426.2 (21.2)	0.074	–	0.293

<sup>a</sup> Analysis of variance.

<sup>b</sup> Likelihood ratio test.

<sup>c</sup> Women had significantly higher LVEF than men.

<sup>d</sup> AUDIT: alcohol use disorder identification test.

LV blood volume. The contours were drawn up to the aortic valve and joined by a straight line through the blood pool. LVEF was computed assuming a myocardial density of 1.05 g/mL (Sandstede et al., 2000)

### 2.5. Statistical analysis

To test whether there was a difference in LVEF between patients and controls, we compared the average LVEF between the two groups with an analysis of variance (ANOVA). In this initial analysis, diagnosis and gender were treated as class variables, and their interaction was subsequently included to test whether the effect of diagnosis depended on gender. To test the differential effect of clozapine and non-clozapine antipsychotics, the patients were sub-divided into those treated with clozapine and those treated with other antipsychotics. Mean differences between patients and controls were compared with least square mean contrasts.

In the next step, the effects of systematic differences in risk factors between the patients and controls were accounted for by adding potential confounders into the model using analysis of covariance (ANCOVA). Risk factors with significant differences between the two groups were examined for their association with LVEF in univariate and multivariate analyses. Risk factors that showed an association with LVEF that was consistent with the previously established relationships between these factors and CVD risk (Supplementary material) were kept in the model.

Residuals from the final model were normally distributed (with a near identical variation) in patients and controls ( $p > 0.90$ , Shapiro-Wilk W test), and were independent of the predicted value (as assessed by visual examination of the scatter plot).

### 3. Results

Patients showed lower physical activity and AUDIT scores as well as higher glycated hemoglobin (HbA1c), C-reactive protein (CRP) and heart rate at rest compared to controls (Table 1).

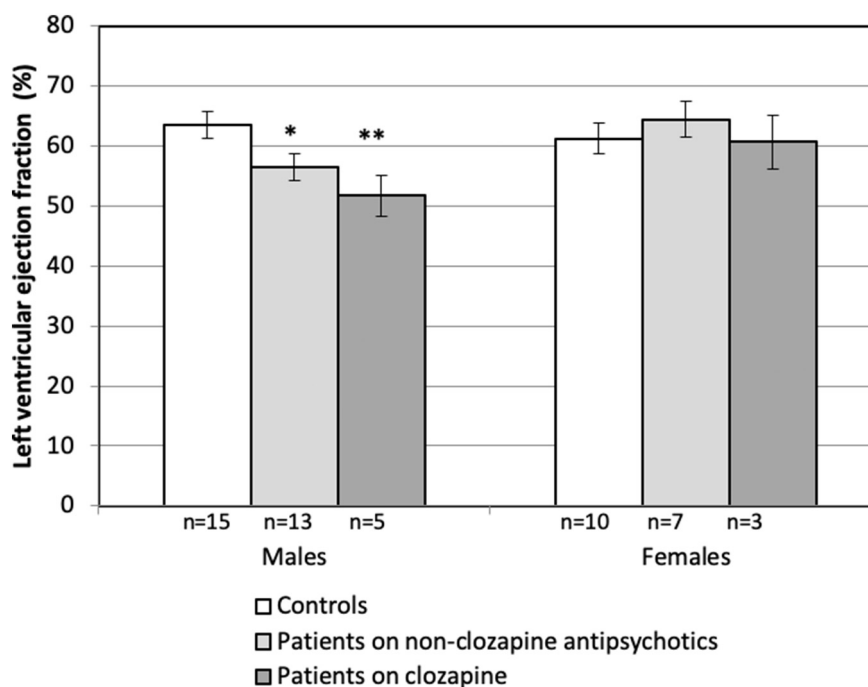
The initial ANOVA showed that patients on average tended to have lower LVEFs than controls (3.4%,  $p = 0.10$ ), and that men had a significantly lower LVEF than women (5.1%,  $p = 0.023$ ). However, the difference between patients and controls depended on gender ( $p = 0.025$  for the interaction). Thus, male patients showed significantly lower

LVEF than male controls ( $p = 0.0076$ ), whereas no such difference was evident among women ( $p = 0.44$ ). Male patients treated with clozapine had, on average, 10.6% lower LVEF than male controls ( $p = 0.0064$ ), whereas the ejection fraction was 5.5% below that of controls among male patients treated with other antipsychotics ( $p = 0.047$ ).

Five of the measured risk factors for CVD (AUDIT score, physical activity, CRP, HbA1c and heart rate) differed systematically between patients and controls, as assessed by univariate analysis (Table 1). Two of these factors (AUDIT score and physical activity) showed an association with LVEF in the final model that was consistent with previously observed relationships between the risk factors and CVD (Supplementary material). That is, LVEF decreased with increasing use of alcohol and increased with physical activity. Thus, to account for group differences with respect to physical activity and alcohol use in the comparisons between patients and controls, these two risk factors were added as covariates to the model. As smokers were more frequent in the patient group than in the control group, this factor was also added to the statistical model. The remaining three risk factors (the levels of CRP and HbA1c, and the heart rate) showed a positive, or negligible, association with LVEF (in univariate and multivariate models), and it was not considered reasonable to account for these relationships in the analysis.

Controlling for group differences with respect to physical activity, alcohol use and smoking, improved the fit of the statistical model somewhat (as indicated by a higher adjusted  $r^2$  value), but did not change the conclusions of the initial analysis. That is, male patients still had a significantly lower LVEF than controls, and the difference was most pronounced in the group treated with clozapine; the difference was 11.8% ( $p = 0.008$ ) and 7.0% ( $p = 0.027$ ), in the two patient groups, respectively (Fig. 1). Least square means and standard errors in healthy individuals, patients on non-clozapine antipsychotics and patients on clozapine, separately for men and women, are demonstrated in Table 2.

The ANCOVA also confirmed the assumed relationships between the included risk factors and cardiac function in the study group, although the effects of the individual factors were relatively weak. That is, the LVEF decreased with 0.7% per one unit of the alcohol use disorder scale, and increased with 0.4% per 10 h of weekly physical activity. Moreover, smoking decreased the ejection fraction with 0.2%. Thus, a small part of the initially observed differences could be attributed to smoking and less physical activity in the patient group. However, favorable drinking habits in the patient group appear to have masked a



**Fig. 1.** Left ventricular ejection fraction (%) among patients with schizophrenia and controls. Male patients on clozapine (dark grey) and on other antipsychotics (light grey) showed a significantly lower LVEF than male controls. In the analysis, group differences with respect to physical activity, alcohol use and smoking were accounted for. Information on covariates was missing for one patient (female) and two controls (males), and these subjects were consequently excluded from the analysis. Least square means (bars) and standard errors (whiskers) from the analysis of covariance are given. Asterisks indicate levels of significance for group differences (\* < 0.05, \*\* < 0.01).

similar fraction of the LVEF difference, and thus the overall effect of controlling for confounding risk factors was limited. If group differences in CRP, HbA1c and the heart rate were accounted for (by adding these risk factors as covariates), the LVEF differences between patients and controls increased. However, as the associations with LVEF were not consistent with established relationships (Supplementary material), it was not considered reasonable to inflate the reported difference by these statistical relationships.

#### 4. Discussion

The present study showed that among apparently medically healthy men with schizophrenia on long-term treatment with antipsychotics, there was a significantly reduced LVEF compared to healthy controls. The significantly decreased LVEF was evidenced among both male patients on clozapine and other than clozapine antipsychotics relative to male controls (Fig. 1). By contrast, among female participants, we failed to find any difference in mean LVEF between patients and controls.

To the best of our knowledge, there is only one previous study using CMR for LVEF measurements among patients with schizophrenia (Pillinger et al., 2019) whereas all other previous studies used echocardiographic modalities. CMR is regarded as the reference standard for LVEF measurement due to high image quality and volumetric data (Wood et al., 2014). Non-contrast 2D ECHO, contrast 2D ECHO as well as 3D ECHO have shown a good agreement with CMR with small systematic differences (Hoffmann et al., 2005; Mor-Avi et al., 2008), with

the contrast 2D ECHO and 3D ECHO being superior to non-contrast 2D ECHO and closer to CMR measurement (Wood et al., 2014). The reproducibility of CMR LVEF measurement is superior relative to non-contrast ECHO, whereas minor differences were observed between contrast 2D ECHO and CMR (Wood et al., 2014).

It is currently established that clozapine treatment is associated with rare cases of early myocarditis (1/1000) and later cardiomyopathy (1/10000) with fatal outcome in up to 25–30% of the affected patients (Curto et al., 2016). During the last decade, it has been suggested that the cardiac side effects of clozapine are underestimated and that a subclinical left ventricular dysfunction is present in a much higher proportion of individuals on clozapine treatment. Only a limited number of studies have been conducted to address this concern. Further, other antipsychotics than clozapine may also be associated with subclinical left ventricular dysfunction. These studies are discussed below.

The first systematic assessment of cardiac function among patients with psychotic disorder on long-term clozapine treatment was conducted in 2011 and showed a reduced LVEF (<55%) in almost one third of the patients (Rostagno et al., 2011). Another study among clozapine-treated patients with severe personality disorder showed similar results, i.e. one third of patients showed a reduction of left ventricular function at first visit (LVEF <55%) and further, at one year follow-up, a LVEF decline >5% was found in one third of patients with baseline normal LVEF (Rostagno et al., 2012).

To the best of our knowledge, there are three ECHO studies comparing LVEF levels between patients on clozapine and non-clozapine antipsychotics or between patients and controls (Chow et al., 2014; Korkmaz et al., 2016; Serrano et al., 2014). The first study did not include healthy controls and failed to find differences in LVEF levels between 125 patients on clozapine and 59 patients on non-clozapine antipsychotics, as no participants in either group displayed a LVEF below 50%, and further, the proportion of individuals with mild subclinical systolic dysfunction (defined as LVEF 50–54%) was similarly very low (3.4%–4%) in both groups (Serrano et al., 2014). The population analyzed in this study was mixed, including schizophrenia, bipolar disorder and other DSM-IV diagnoses in both treatment groups.

**Table 2**

Least square means (standard errors) of left ventricular ejection fraction in healthy controls, patients on non-clozapine antipsychotics and patients on clozapine. Results from the analysis of covariance are shown separately for men and women.

	Controls	Patients on non-clozapine antipsychotics	Patients on clozapine
Men	63.55 (2.28)	56.49 (2.29)	51.72 (3.42)
Women	61.27 (2.54)	64.49 (3.06)	60.69 (4.40)

The second study included patients with schizophrenia treated with clozapine ( $n = 100$ ) and other antipsychotic medication ( $n = 21$ ) as well as 20 healthy individuals. The LVEF in the three groups was 58%, 62% and 65%, respectively. Clozapine-treated patients demonstrated significantly decreased LVEF in comparison to both patients treated with non-clozapine antipsychotics and healthy controls, whereas the LVEF difference between the non-clozapine patient group and healthy controls was not statistically significant (Chow et al., 2014). The results of our study among men are in the same direction and further, we found significant differences in mean LVEF not only between patients on clozapine and controls, but also between patients on other antipsychotics and controls.

The third study compared 40 patients with schizophrenia on long-term antipsychotic medication (33/40 on non-clozapine antipsychotics) and 40 well matched healthy individuals, and showed a significantly reduced LVEF in patients relative to controls (58% versus 62%) (Korkmaz et al., 2016). Our results among men are in line with these results, as we have shown a significantly reduced LVEF among patients with schizophrenia on long-term antipsychotics compared to controls.

Further, a recent CMR study failed to find any significant difference in LVEF between schizophrenia patients treated with antipsychotics and healthy controls (Pillinger et al., 2019). These authors investigated 14 patients (50% men, 57% on clozapine) and 17 controls (41% men), and found that patients had 2.1% lower LVEF than controls. This is in line with the result from our analysis without the interaction term showing a non-significant reduction of LVEF (3.4%) in patients compared to controls. The study by Pillinger et al. did not analyze interactive gender-by-disease status effects, did not differentiate between clozapine and non-clozapine antipsychotics, and further, the sample size was smaller and the median duration of treatment shorter compared to the present study. These differences taken together could explain the seeming discrepancy between the results.

Finally, Curto et al. (2015) evaluated prospectively the cardiac status of 15 treatment-resistant schizophrenia patients before and four weeks after the initiation of clozapine treatment. The authors found echocardiographic evidence of left ventricular impairment including Myocardial Performance Index (MPI) increase, but not LVEF reduction. MPI is a measure incorporating systolic and diastolic functions, which typically changes prior to changes of other measures of left ventricular function (Karakurt et al., 2008; Tei et al., 1997). Clozapine might thereby be associated with a slowly progressive worsening of cardiac function with an onset already during the first weeks of treatment.

Despite the limited sample size of the present study, there was a statistically significant indication (significant sex-by-disease status interaction term) that the decreased cardiac function in patients with schizophrenia was less severe in women than in men. Although the LVEF in female patients did not differ significantly from that in female controls, we cannot exclude the possibility that a less severe reduction of cardiac function may be present also among the female patients. That is, due to the limited sample size, the power to detect a difference half the size of that observed in men (3.5%) was approximately 50%, and a moderate reduction of such size would fall within the 90% confidence interval of the difference between female patients and controls observed in this study.

Our results, showing an increased risk of LVEF reduction among men, but not women, with schizophrenia, are in line with a recent 24-year national register study where mortality rate ratio (MRR) for CVDs as causes of death was found to be higher among men with schizophrenia (3.09) compared to women with schizophrenia (2.54), with the general population as the reference group (Westman et al., 2017). By contrast, MRR associated with suicide was higher among women with schizophrenia, whereas no difference in MMR was observed between men and women with schizophrenia for any other somatic diseases than CVDs (Westman et al., 2017). Another study analyzing 10-year mortality among patients with schizophrenia reported an increased CVD mortality among men, but not women, with schizophrenia (Fors

et al., 2007). However, not all studies support this notion (Crump et al., 2013), with a systematic review proposing an increased susceptibility to specific cardiovascular risks of antipsychotics among women compared to men (Seeman, 2009).

The mechanism of the cardiac effect of clozapine is not well understood. In the absence of myocarditis-related symptomatology, the results from the literature suggest a direct cardiotoxic effect of clozapine rather than a myocarditis-mediated effect (Chow et al., 2014). Clozapine has also been reported to have neurotoxic and myotoxic effects with elevated creatine kinase levels, indicating direct muscle injury (Reznik et al., 2000; Scelsa et al., 1996). It is possible that the cardiotoxic and myotoxic effects are due to a clozapine-mediated inhibition of the calcium-modulated protein (calmodulin), a protein regulating both cardiac and skeletal muscle receptors (Yamaguchi et al., 2003). Further, clozapine has potent antimuscarinic properties resulting in tachycardia (Nilsson et al., 2018) and long-standing tachycardia is an established cause of left ventricular dysfunction and cardiomyopathy (Ellis and Josephson, 2013). Our results indicate that other antipsychotics also have negative cardiac effects. However, the pathophysiological mechanisms remain unknown.

In elderly population (65 years old or older), asymptomatic left ventricular systolic dysfunction, defined as LVEF < 55% in individuals not having a diagnosis of symptomatic heart failure, was associated with increased risk of incident heart failure, CVD mortality and overall mortality (Pandhi et al., 2011). In a large community-based sample, subjects with a borderline LVEF (50–55%) had significantly greater risks for death and heart failure relative to subjects with LVEF > 55% (Tsao et al., 2016). An inverse relationship between continuous LVEF and risk of heart failure and death has also been demonstrated (Tsao et al., 2016). Further, the prognostic value of LVEF with respect to all-cause mortality has been evidenced in a recent international multicenter diagnostic study. Specifically, among patients with coronary artery disease, increased LVEF was associated with decreased mortality risk (Pellikka et al., 2018). As asymptomatic left ventricular systolic dysfunction as well as borderline LVEF have been associated with adverse outcomes, our results, showing a significantly lower LVEF value among male patients on antipsychotics, shed further light on the understanding of the established increased CVD mortality and overall mortality among patients with schizophrenia.

The study has a number of limitations and strengths. The first limitation is the restricted number of subjects, mainly women, in both the patient and the control groups. However, our findings among men are in the same direction as in almost all current literature. Another limitation is the fact that we have compared medicated patients with schizophrenia with healthy individuals and we can thereby not exclude that the reduced LVEF among men with schizophrenia is a result of shared genetics between schizophrenia and CVD and not a result of medication. In the case of clozapine in particular, we cannot exclude based on our findings that the LVEF difference between male patients and male controls is due to a shared genetic vulnerability associated with both a severe psychosis phenotype with resistant symptoms and a higher cardiovascular morbidity. The study by Rostagno et al. (2012), showing reduced LVEF among patients on clozapine with severe personality disorder and the prospective study by Curto et al. (2015), reporting a rapid subclinical left ventricular dysfunction in schizophrenia patients four weeks after the initiation of clozapine treatment, in combination with our results may indicate that it is the treatment with antipsychotics, and not the psychotic disorder, that is associated with the reduced LVEF. However, to further clarify potential pharmacological and disease related influences on LVEF, longitudinal studies are needed, ideally comparing patients when drug naïve and when on long-term treatment. Another limitation of the present study is that we have analyzed all patients on non-clozapine antipsychotics as one group. Other studies have also categorized patients similarly (Chow et al., 2014; Serrano et al., 2014). We can thereby not exclude that the significant LVEF reduction among men is limited to patients with schizophrenia on first-generation

antipsychotics, second-generation antipsychotics or even on specific antipsychotics. Future studies need to address this issue. Further, the study had strict exclusion criteria regarding CVD history; this may limit the generalizability of the results to a real-world setting where CVD is unexceptional. The strengths of the study are that patients and controls were somatically asymptomatic and matched for BMI and age, that we have controlled for CVD/LVEF-related characteristics and that we have applied CMR, a method considered superior to ECHO in the assessment of grades of left ventricular dysfunction.

In conclusion, somatically apparently healthy male patients with schizophrenia on long-term treatment with clozapine as well as non-clozapine antipsychotics showed decreased LVEF compared to controls, whereas, no such association was evidenced among women. Our study is partially in line with other recent studies concerning the association of clozapine with LVEF. However, our study is the first study providing sex-specific results. Further, to the best of our knowledge, this is the first study showing a statistically significant decrease of LVEF among men with schizophrenia on other antipsychotics than clozapine compared to controls. Our results suggest that at least in men with schizophrenia, there is a need of routine cardiac monitoring possibly already from the initial stages of the antipsychotic treatment in order to prevent and counteract left ventricular dysfunction by taking measures such as cardiology consultation, CVD risk factor modification and cardiac medication use. Future studies with more female participants are needed in order to investigate if there is such a need in women too.

#### Contributors

DA drafted the manuscript and had substantial contributions to the analysis and the interpretation of data. PS performed the statistical analysis and had substantial contributions to the interpretation of data, and drafting the statistical analysis and results subsections. BMF had substantial contributions to the acquisition and interpretation of data for the work. BMN had substantial contributions to the acquisition and interpretation of data, and drafting the method subsection. EGJ had substantial contributions to the acquisition and interpretation of data. JK had substantial contributions to acquisition and interpretation of data. CEB performed the CMR image analysis and had substantial contributions to acquisition and the interpretation of data. IA initiated and supervised the study and had substantial contributions to the analysis and interpretation of data for the work, and drafting the manuscript. All co-authors have substantially contributed to the conception and design of the work, critically revised the manuscript for important intellectual content and approved the final version to be published.

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#### Data statement

The data associated with the manuscript is available upon reasonable request.

#### Declaration of competing interest

JK is cofounder, stock owner and employee of Antaros Medical AB, Mölndal, Sweden. BMF reports personal fees from H. Lundbeck AB. All other authors have declared that there are no conflicts of interest in relation to the subject of this study.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2019.12.042>.

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