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Coronary artery disease as a cause of morbidity and mortality in patients suffering from schizophrenia: protocol for a prospective cohort study with long-term follow-up

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Abstract

Background: Schizophrenia is associated with excess mortality primarily due to cardiovascular disease. Unhealthy lifestyle and side-effects from pharmacologic treatment are among the risk factors that highly contribute to somatic disease in patients with schizophrenia. While the number of cardiac deaths is declining in the general population, the cardiac mortality in patients with schizophrenia remains high. No other studies have so far investigated the presence and progression of arteriosclerosis in patients diagnosed with schizophrenia. The primary aim of this clinical study is to reduce the high rate of cardiac mortality in patients with schizophrenia.
Methods/Design: The present clinical trial involves 300 patients with schizophrenia, including 100 patients with debut schizophrenia and 200 patients with chronic schizophrenia with a clinical follow-up every third year from first examination. Patients are recruited from the North Denmark Region with a minimum age of 18 years and with the requirement of having an ICD-10 diagnosis of F20 or F25. The primary outcome is the presence and progression of atherosclerosis measured by CT coronary angiography at baseline and follow-up periods. The secondary outcomes are cardiovascular measurements, illness history, social conditions as well as psychiatric conditions measured at baseline and some measured again during follow-up.
Discussion: Routine screening of cardiovascular risk factors in patients with schizophrenia are necessary to detect early signs of cardiovascular disease in order to reduce the excess cardiac mortality. The end result of this study may contribute to prolonging life-expectancy for patients with schizophrenia and providing modifications in the clinical guidelines for treatment of coronary artery disease in patients with schizophrenia.
Trial registration: ClinicalTrials.gov identifier NCT02885792; registered on July 1, 2016.
Ethics: This study protocol was approved by The Regional Committee on Biomedical Research Ethics, Region of Northern Jutland, Denmark (N-20140047) and will be performed in accordance with the *Declaration of Helsinki*.
Informed consent: Written informed consent will be collected from each study participant prior to enrolment.

Key words: schizophrenia; coronary artery disease; mortality; morbidity; risk factor; intervention; treatment

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Introduction

It seems that patients with schizophrenia are not benefitting similarly in the declining morbidity and mortality seen in the general population. In fact, the average life expectancy for patients with schizophrenia has been 55−60 years through the last generations in Denmark, while the general population over the same period of time has experienced an increase in life expectancy (Laursen et al., 2013). As a result, the standardized mortality rate for patients with schizophrenia has increased markedly over the last three decades and is currently a major public health concern (Saha et al., 2007).

It is well-known that suicide has been the leading cause of death in patients suffering from schizophrenia. However, recent studies have shown that the excess mortality is more caused by somatic diseases, especially cardiovascular disease, pulmonary disease and diabetes mellitus (Laursen et al., 2011; Scherr et al., 2012; Nielsen et al., 2013; Correll et al., 2014). Reasons explaining the excess somatic comorbidity and mortality may be related to the unhealthy lifestyle in people with schizophrenia, including poor diet, lack of exercise, high rate of smoking and substance abuse, as well as side-effects of the pharmacological treatment (Scherr et al., 2012; Correll et al., 2014). As a result of unhealthy lifestyle behaviors, patients with schizophrenia often present with metabolic syndrome. A recently published cross-sectional study of antipsychotic-treated patients showed that 48% of these patients presented with metabolic syndrome compared to 29% in the general population (Krane-Gartiser et al., 2011). Metabolic syndrome is known to be a major risk factor for developing cardiovascular disease, and consequently cardiovascular disease is the leading cause of death in patients diagnosed with schizophrenia (Capasso et al., 2008; Finegold et al., 2013). However, the relative risk of cardiovascular disease in patients with schizophrenia is about 2-fold higher than in the general population (Hennekens et al., 2005). While the general population has experienced a gradual decline in cardiac mortality due to the improvements in cardiac treatment and adjustments in lifestyle, it seems that patients with schizophrenia are not benefiting similarly from these improvements (Laursen et al., 2013; Singh et al., 2014).

Little is known about more severe progression of premature coronary arteriosclerosis in patients suffering from schizophrenia. For example, coronary artery calcium score (CACS) is often used to predict cardiovascular disease events in the general population (Polonsky et al., 2010). It is still not known whether there is an association between CACS and premature morbidity and mortality in patients with schizophrenia. The quantity of coronary artery calcium is a well-recognized measurement to validate the presence of arteriosclerosis, and even smaller amounts of calcium in the arteries are correlated to increased cardiac mortality as well as all-cause mortality (Shaw et al., 2003; Budoff et al., 2007). The present clinical trial involves a variety of somatic investigations as well as a thorough characterization of the psychiatric disease in two cohorts of patients suffering from debut respective chronic schizophrenia, and involves planned follow-ups every third year. Yet, to our knowledge, this clinical trial is the first study that offers an extensive cardiac examination and treatment based on biomedical markers for cardiovascular disease in patients diagnosed with schizophrenia.

The aim of this study is to reduce the high cardiac mortality rate in patients suffering from schizophrenia. In order to achieve this aim, we will measure the presence and progression of arteriosclerosis in patients with schizophrenia at different stages. Furthermore, we will develop and implement adequate intervention and treatment for these patients according to their somatic condition. The results might provide important modifications in the clinical guidelines for treatment of coronary artery disease in patients diagnosed with schizophrenia.

We hypothesize that patients with schizophrenia have a significant higher calcium score in coronary arteries and have a more rapid arteriosclerosis progression than the general population. In addition, we hypothesize that patients with schizophrenia have early non-detected signs of arteriosclerosis, which can be detected by non-invasive methods.

Methods/Design

Study design

A prospective clinical cohort study with follow-up every third year in patients diagnosed with schizophrenia with register-based and clinical comparison groups (**Figure 1**).

Ethical approval

This study protocol is approved by The Regional Committee on Biomedical Research Ethics, Region of Northern Jutland, Denmark and the Data Protection Agency of Denmark. The study is performed in accordance with the *Declaration of Helsinki*, and written informed consent will be collected from each study participant prior to enrolment. All examinations will be conducted at the Centre for Psychosis Research, Aalborg University Hospital, Psychiatric Hospital, Aalborg, Denmark and at the Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark.

Study participants

Patients

A total of 300 patients with schizophrenia are planned

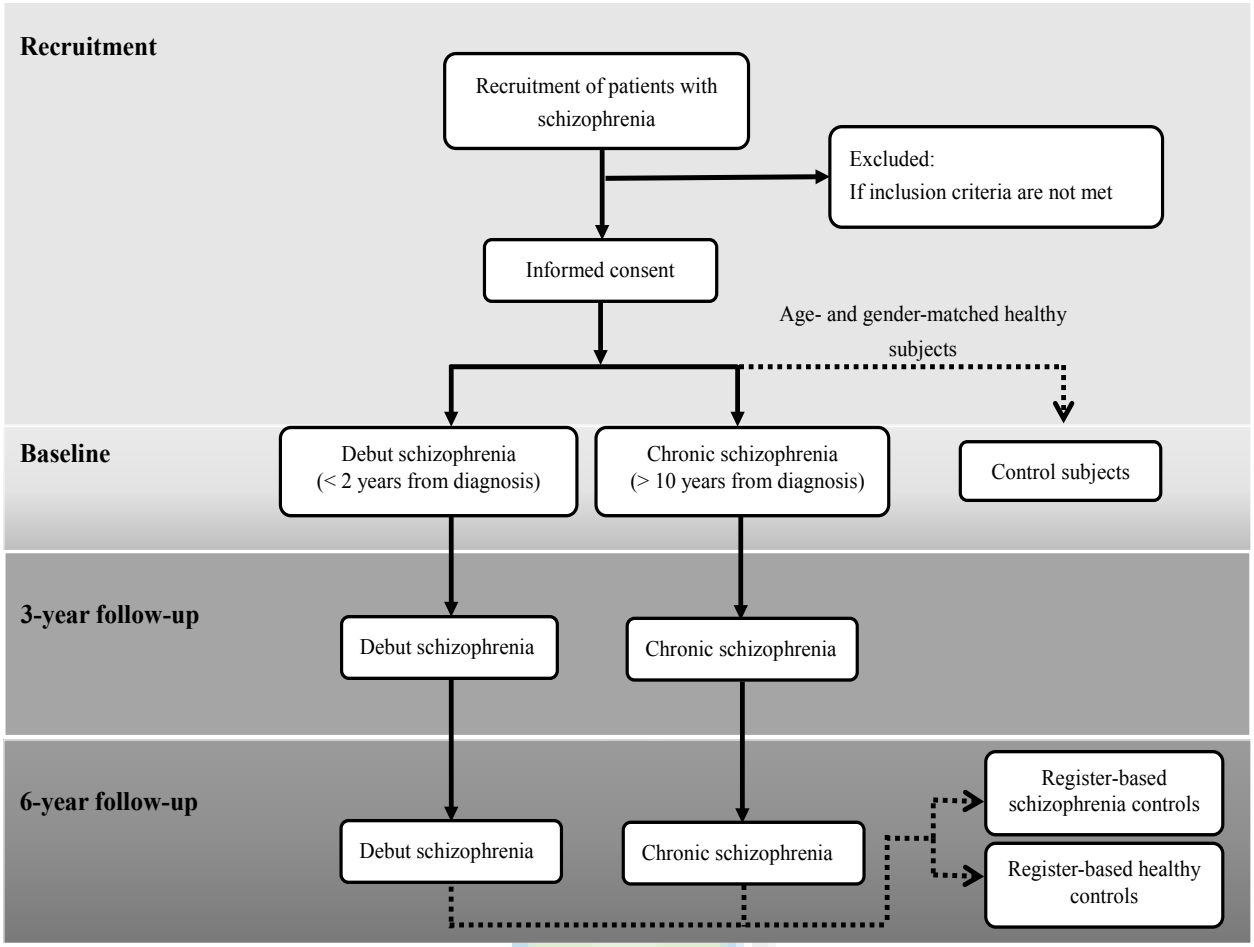

Figure 1: Flow chart of the trial.

to enroll in this clinical study. We use the 10th version of International Classification of Disease (ICD-10) (World Health Organization (WHO), 2011) for the diagnosis of schizophrenia of which we use the codes (F20 and F25). The duration of the mental illness is categorized into debut and chronic schizophrenia. Patients are categorized as debut schizophrenia when the first time diagnosis (F20/F25) is received within the last 2 years from the time of inclusion. Criteria for being classified as chronic schizophrenia is that patients for more than 10 years have had diagnosis within the schizophrenia spectrum disorder (F20/F25), and at the time of inclusion have a diagnosis of either F20 or F25. A total of 100 debuting patients with schizophrenia and 200 chronic patients with schizophrenia will be recruited for this trial. All participants are planned to provide a follow-up every three years after the first examination.

Healthy control subjects

An age- and gender-matched control group will be recruited for both the debut schizophrenia patients and the chronic schizophrenia patients. Whereas two register-based control group will be extracted for both groups using the Danish registers; 1) Schizophrenia controls extracted from the Danish Psychiatric Research Register, including age, gender and diagnosis matched, 2) healthy controls with no history of mental illness extracted from the Danish Civil Register including age and gender matched. Thus, a total of 100 gender- and aged-matched healthy control subjects are invited to participate in this comprehensive cardiac screening program and receive the same thorough cardiac examination program as for schizophrenia patients. Participants with previous history of mental disorders or congenital heart disease are excluded before initiation.

Inclusion criteria

- Age > 18 years
- Patients with a diagnosis of F20 or F25 schizophrenia

Table 1: Overview of all study measures and time points included in this study

	Baseline	Every 3 years
Primary outcome		
CT coronary angiography (CT-CAG)	○	○
Secondary outcomes		
Cardiovascular measurements		
Echocardiography	○	○
Heart rate variability (HRV)	○	○
Pulmonary function test (PFT)	○	○
Toe blood pressure (TBP)	○	○
Blood test	○	○
Body composition analysis	○	○
CT-scan of upper abdomen	○	○
Cardiovascular magnetic resonance imaging (CMR)	○	○
Adipose tissue biopsy	○	○
Illness history		
Existing psychiatric and somatic diagnosis and treatment	○	○
Charlson Co-morbidity Index	○	○
Social conditions		
Demographic	○	
The Lubben Social Network Scale-6 (LSNS-6)	○	
Short Form (36) Health Survey (SF-36)	○	○
Global Assessment of Functioning (GAF)	○	○
Brief Trauma Questionnaire (BTQ)	○	
Psychiatric measurements		
Positive and Negative Syndrome Scale (PANSS)	○	○
Clinical Global Impression Scale (CGI)	○	○
Columbia Suicide Severity Rating Scale (C-SSRS)	○	
The Beck Cognitive Insight Scale	○	
The Birchwood's Insight Scale	○	

- Residency in the North Denmark Region
- Able to give informed statement of consent

Exclusion criteria

- Unable to provide informed consent due to their severe cognitive disturbances or intellectual disability
- Pregnant or lactating women
- Severe claustrophobia
- Lack of ability to cooperate with the planned study program

Withdrawal criteria

Patients will be withdrawn from the study if they withdraw informed consent and decline to continue examination.

Recruitment and screening

A screening list of patients diagnosed with schizophrenia is initially conducted. All of these patients receive a letter with information about this clinical study and are asked whether they would like to participate. To ensure a sufficient number of patients, each unresponsive patient will be contacted by phone and asked whether they would like to receive further information regarding this clinical study. Presentations about this study are given at each community mental health places, psychiatric hospital departments and outpatient clinic in the North Denmark Region to inform both patients and health professionals.

Outcome measures

Primary outcome

The primary outcome measure is an assessment of the extent and progression of arteriosclerosis using CT coronary angiography measured at baseline and every 3 years.

Secondary outcomes

The secondary outcomes are cardiovascular measurements,

Table 2: Overview of cardiovascular measurements with time and description of procedure

Module	Name of procedure	Time of procedure	Description of procedure
1	CT coronary angiography (CT-CAG)	5 minutes	CT-CAG is a non-invasive procedure that uses simple CT-scan without contrast to measure coronary calcifications.
2	Echocardiography	15 minutes	Echocardiography is a non-invasive procedure that uses ultrasound waves to generate live images of the heart.
3	Heart rate variability (HRV)	20 minutes	HRV is a non-invasive measure that detects the function of the autonomic nervous system on the heart rhythm.
4	Pulmonary function test (PFT)	15 minutes	PFT (spirometry) is a non-invasive procedure that measures lung function.
5	Toe Brachial Index (TBI)	30 minutes	TBI is a non-invasive procedure that measures the relationship (index) between the systolic blood pressure at the toe and the arm (brachial).
6	Blood test	5 minutes	Blood test is an invasive procedure, and in this study, a volume of 20 mL blood will be needed from each participant.
7	Body composition analysis (BCA)	1 minute	BCA is a non-invasive measurement of the body composition by a standard weight.
8	CT scan of upper abdomen (CTUA)	5 minutes	CTUA produces a series of many X-rays from different angles to produce cross-sectional images of the heart and liver.
9	Cardiovascular magnetic resonance imaging (CMR)	60 minutes	CMR uses a strong magnetic field and radio waves to generate images of the heart.
10	Adipose tissue biopsy	10 minutes	Adipose tissue biopsy is an invasive procedure.
11	Urine sample	5 minutes	Urine sample measures the content of melatonin, which is a hormone that controls the natural cycle of sleeping and waking hours.

illness history, social conditions, and psychiatric measurements (**Tables 1** and **2**). Each of the social and psychiatric scales used in this study are further described below.

Social scales

Lubben Social Network Scale-6 (LSNS-6)

The LSNS-6 is a self-report questionnaire measuring social isolation, including relations to family and friends. This is a 6-item scale with a score ranges between 0 and 60, with lower score indicating more social isolation. It is a useful tool to assess the relation to others when first considering the people to whom the patient is related either by birth or marriage or the friends including relation to neighbors (Lubben, 1988).

Short Form (36) Health Survey (SF-36)

The SF-36 is a self-report short-form health survey with 36 questions of functional health and psychometric based summary of the patient's well-being (Bjorner et al., 1998). This measure is useful to estimate disease burden and compare it with the general population.

Global Assessment of Functioning (GAF)

The GAF scale is a clinical evaluation of the patient's overall functioning level, including psychological, social and interpersonal, and occupational functioning of mental health-illness. The scale ranges from 0 to 100 with higher number indicating superior functioning (Hall, 1995).

Brief Trauma Questionnaire (BTQ)

The BTQ is a self-report questionnaire consisting of 10-items. The questionnaire is used to determine any traumatic events experienced and respondents are simply answering "yes" or "no" to the questions. It is useful to screen for many different types of traumatic episodes, including serious car accidents, violent death, life-threatening illness, and physical or sexual abuse (Kubany et al., 2000).

Psychiatric scales

Positive and Negative Syndrome Scale (PANSS)

The PANSS is among the most used measure of symptom severity in schizophrenia and comprises a 30-item scale with focus on two distinct syndromes. The positive syndrome includes productive symptoms, and the negative syndrome, includes deficit features. This method is useful to implement treatment plans for the specific patient based on the symptoms. The minimum total score is 30 and maximum total score is 210 (Kay et al., 1987).

Clinical Global Impression Scale (CGI)

The CGI is a 3-item scale used to measure symptom severity, therapeutic response and general improvement. The first item is evaluating severity of psychopathology on a 7-point scale, and second item evaluating the change from the initiation of treatment on a similar 7-point scale. Item 3 is rated on a 4-point scale, and each item is rated individually (Rush and Blacker, 2008).

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is used to predict suicide attempts in individuals with severe mental illness. It is extensively used in clinical practice, research, and institutional settings. The suicidal ideation or behavior of the patient is reflected by the judgement of the health professional administering the scale (Gipson et al., 2015).

The Beck Cognitive Insight Scale

The Beck Cognitive Insight Scale is used to describe the capacity of patients with episodes of psychosis to distance their thoughts from their psychotic experiences. The questionnaire is a 15-item self-report with a 9-item self-reflectiveness element and a 6-item self-certainty element. It is a helpful tool to describe the lack of awareness of mental illness and understand the patients' interpretations of their experiences (Beck et al., 2004).

The Birchwood's Insight Scale

The Birchwood's Insight Scale is a self-report questionnaire consisting of eight statements that patients rate on a 3-point scale (agree, not agree or uncertain). It is designed to detect the awareness of illness, awareness of need for treatment and the ability to relabel symptoms (Sanz et al., 1998).

Data collection and management

All data will be collected in case report forms for each patient, including data obtained from the objective clinical examination. All data are planned to be entered into an electronic database by double entry from two independent researchers. All information obtained in this study will be preserved by Aalborg Psychiatric Hospital and Department of Cardiology at Aalborg University Hospital, Aalborg, Denmark.

Sample size

Power estimates in clinical cohorts are often associated with a degree of uncertainty. To date, no other studies have measured the coronary artery calcium score in patients with schizophrenia. Recent studies have shown that progression of coronary atherosclerosis occurs in 20−30% of patients in the general population (Bayturan et al., 2010; Han et al., 2014). Since the prevalence of metabolic syndrome in patients with schizophrenia is much higher than in the general population, we hypothesize that the coronary atherosclerosis progression in patients with schizophrenia is 55−60%. Furthermore, it is well-known that metabolic syndrome and the amount of calcium in coronary arteries increase with age. Based on these assumptions, a study cohort of 200 patients with chronic schizophrenia and 100 patients with debut schizophrenia will be recruited. However, when 50 patients with debut schizophrenia and 100 patients with chronic schizophrenia have been enrolled in the study, an independent statistician will calculate a new power estimate to ensure a sufficient number of patients to recruit.

Statistical analysis

Each analysis is initiated by descriptive statistics to compare schizophrenia groups with the control groups at baseline and end of the follow-up period. The response rate at the different time points in the follow-up periods will be compared between all study groups for each of the outcomes studied (**Table 1**). The Student's *t*-test is used to compare normally distributed nominal variables between groups. While the Mann-Whitney *U* test and Wilcoxon test are used to compare variables between groups if data is non-normally distributed. Wilcoxon test will also be used to determine the intra-group differences at different time points. The chi-square test or Fisher's exact test are used to determine associations between categorical variables. In addition, predictive analysis is conducted using logistic regression. Significant effect is accepted if the *P*-value is < 0.05. Statistical analyses are performed with either STATA 14.0 or SPSS 24.0 software.

Discussion

This is the first clinical study to offer a routine screening of cardiovascular risk factors in patients with schizophrenia. There are numerous studies highlighting that cardiovascular disease is responsible for the premature mortality observed in this patient group. However, to date there has not been any success in the attempt to reduce this high cardiac mortality in clinics.

This clinical screening will assist early identification of cardiovascular disease and progression. The progression of arteriosclerosis in patients with schizophrenia will be investigated at early and late stage of the mental illness, which allow us to understand at what stage this progression might prevail. We are investigating whether it is possible to detect differences in the development of arteriosclerosis in schizophrenia patients compared to the general population, and how common risk factors are contributing to this process. If we detect any differences, we will be able to offer treatment and intervention to these patients. Thus, the main goal in this trial is to reduce the high cardiac mortality in patients with schizophrenia and provide new knowledge to the clinical practice. Some limitations are associated with this clinical trial. For instance, it is a well-known fact that treating patients with schizophrenia is a challenge in clinical trials due to the complexity of

the disease affecting cognition, behavior, mood, and motivation. Especially cognitive disturbances and reduced understanding of symptoms and signs in their psychiatric and somatic disease symptoms are very common (Hillege, 2013). Since this clinical study involves a great number of measurements, there might be individual differences in the time to complete each measurement. For example, some patients will need more freedom during a clinical trial to handle their cognitive disturbances or carry out routine tasks, while others will be able to complete the clinical trial without any delay. Also, these patients tend to forget appointments, which is handled by continuous reminders during the time before initiation and by the support from their community mental health nurse who visited them at their home.

Trial Status

The trial is currently ongoing. The study commenced in September 2015. Participants are recruited until September 2019 if necessary. By July 2016, we had recruited 100 and examined 60 patients. Data inclusion never ends, as the study subjects will have a new examination every 3 years.

Declaration of patient consent

The authors certify that they will obtain all appropriate patient consent forms. In the form the patient(s) will give his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Author contributions

This study was conceived and designed in collaboration between JA and SEJ. The manuscript was drafted by PK. All authors were involved in the revision of the draft manuscript. The final manuscript was approved by all authors prior to submission.

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Plagiarism check

This paper was screened twice using CrossCheck to verify originality before publication.

Peer review

This paper was double-blinded and stringently reviewed by international expert reviewers.

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