Schizophrenia Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Increased long-term mortality after myocardial infarction in patients with schizophrenia

Pirathiv Kugathasan [a,d,*], Thomas Munk Laursen [c], Simon Grøntved [a], Svend Eggert Jensen [b,d], Jørgen Aagaard [a,d], René Ernst Nielsen [a,d]

[a] Aalborg University Hospital, Psychiatry, Aalborg, Denmark
[b] Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
[c] National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark
[d] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

ARTICLE INFO

Article history:
Received 14 December 2017
Received in revised form 8 March 2018
Accepted 11 March 2018
Available online xxxx

Keywords:
Schizophrenia
Severe mental illness
Mortality
Morbidity
Cardiovascular disease
Coronary artery disease

ABSTRACT

Background: Ischemic heart disease increases mortality in patients with schizophrenia. This nationwide study explored short-term and long-term mortality rates in patients with schizophrenia experiencing myocardial infarction (MI) compared to controls from the general population experiencing MI, as well as patients with schizophrenia and people from the general population not experiencing MI.
Method: A Danish nationwide cohort study including incident patients diagnosed with schizophrenia between 1980 and 2015, matched 1:5 on year of birth and gender to controls from the general population. Primary outcome was all-cause mortality. Data were analysed utilizing Cox regression models, Kaplan-Meier estimates and standardized mortality ratios (SMR).
Results: Patients with schizophrenia experiencing MI had an increased mortality rate (Hazard rate ratio (HR) 9.94, 95%CI(8.71–11.35)), as well as schizophrenia controls (HR 4.50, 95%CI(4.36–4.64)) and MI controls (HR 3.27, 95%CI(3.03–3.52)) with controls not experiencing MI serving as reference in a model adjusted for age at entry, gender and calendar year. No difference in 30-day mortality was observed between groups experiencing MI, but increased mortality rates were shown in patients with schizophrenia at 1-year and 5-year follow-up. Trends in SMR declined in MI controls, while patients with schizophrenia showed an unchanged SMR over time.
Conclusions: Patients with schizophrenia have not experienced a decline in mortality rate following MI compared to the general population in long-term follow-up. This finding highlights the need for research in MI follow-up care for patients with schizophrenia.

1. Introduction

Generally, life expectancy has been increasing worldwide during the last generations (Murray et al., 2015). The leading cause of death is ischemic heart disease (IHD) which results in the largest number of disability adjusted life years (Murray et al., 2015). The advances in primary, secondary and tertiary prophylactic treatment of cardiovascular risk factors, as well as improvements in acute interventions for the treatment of acute ischaemic heart disease, have resulted in a decline in IHD mortality since the 1980s, especially in Europe, Australia, and the United States (Mensah et al., 2017; Moran et al., 2014).

Patients diagnosed with schizophrenia have a reduced life expectancy of 15 to 25 years as compared to the general population (Correll et al., 2017; Nordentoft et al., 2013). Mortality is primarily due to natural causes of death, e.g. cardiovascular, cancer and infectional diseases (Jayatilleke et al., 2017), while unnatural causes of death, e.g. suicide and accidents have decreased during recent decades (Nielsen et al., 2013; Nordentoft et al., 2013). Despite this reduction in unnatural causes of death, there has not been an increase in life expectancy in patients with schizophrenia over this period (Crump et al., 2013; Laursen et al., 2012).

Median survival in Denmark has increased over the last decades in the general population, partly as a consequence of life-style behavioural changes and improved treatment and management of cardiovascular risk factors (Jeune et al., 2015). This has not had an impact on patients diagnosed with schizophrenia, where a trend towards a decline in median age at death, as well as an increase in the mortality gap between the general population and patients diagnosed with schizophrenia is described (R. E. Nielsen et al., 2013; Nordentoft et al., 2013). A study from UK of patients from 2000 to 2014 concluded that the mortality gap is still widening between patients with schizophrenia and people from the general population (Hayes et al., 2017); this trend is also

* Corresponding author at: Aalborg University Hospital, Department of Psychiatry, Mølleparkvej 10, 9000 Aalborg, Denmark.
E-mail address: divkugathasan@gmail.com (P. Kugathasan).

https://doi.org/10.1016/j.schres.2018.03.015
0920-9964/

demonstrated in studies from other European countries as well as in US studies (Olfson et al., 2015; Piotrowski et al., 2017).

Studies on mortality after acute myocardial infarction (MI) in patients with severe mental disorders (SMI) have been sparse (Bodén et al., 2015; Kurdyak et al., 2012; Schulman-Marcus et al., 2016). No studies have investigated long-term survival following MI in patients diagnosed with schizophrenia as compared to MIs in the general population.

In the current study, we aimed to investigate mortality rates in patients diagnosed with schizophrenia as compared to the general population over a 36-year study period. We investigated short-term and long-term mortality rates in patients diagnosed with schizophrenia experiencing MI and compared this to controls from the general population experiencing MI, as well as patients with schizophrenia and controls not experiencing MI.

2. Method

2.1. Study design

A Danish nationwide register-based cohort study from 1980 to 2015.

2.2. Registers

Persons from the Danish population were identified from the Danish Civil Registration System. All register data were linked to each individual via the unique personal identification number (CPR) assigned to all residents at birth or upon immigration in Denmark.

The Danish Psychiatric Central Research Register (DPCRR) was established in 1969 and contains information on every psychiatric inpatient hospitalization in the period January 1, 1969–31 December 1994, and since 1 January 1995 onwards covering every in- as well as outpatient contacts to all psychiatric hospitals in Denmark. Data on all somatic hospital admissions and discharges were retrieved from the Danish National Patient Register, covering somatic hospitalizations in the period 1 January 1977–31 December 1994, and from 1 January 1995 onwards covering all somatic in- and outpatient contacts to all public hospitals in Denmark.

Data on deaths were retrieved from the Danish Register of Causes of Death and contains data on age of death and underlying cause of death, including contributory causes of death. Data on every dispensed prescription are available from 1 January 1995 in the Danish National Prescription Registry. Drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) code in agreement with the World Health Organization (WHO). Information regarding pharmacological treatment of patients during hospitalization are not available at an individual level.

2.3. Study population

The data used comprised all individuals born in Denmark between 1 January 1930 and 31 December 1997 (thus subjects were between 18 and 85 years old in 2015) and residing in Denmark at some point during the period from 1980 to 2015.

The cohort consisted of all patients diagnosed with an ICD-8 schizophrenia diagnosis (ICD-8: 295) in the period from 1 January 1980 throughout 1993, or an ICD-10 schizophrenia diagnosis (ICD-10: F20) in the period from 1 January 1994 throughout 2015 in the DPCRR. Only patients with a first time diagnosis of schizophrenia aged 18 or older were included, and all patients with an ICD-8 295 diagnosis in the DPCRR in the period from the registry initiation in 1969 to 1 January 1980 were excluded to ensure inclusion of incident cases only.

Participants from the cohort were matched 1:5 on year of birth and gender to controls alive from the general population not diagnosed with a psychiatric disorder, defined as a registered diagnosis in DPCRR. Index was defined as date of schizophrenia diagnosis for each participant in the schizophrenia cohort. Index date for controls was derived from their matched pair's index of schizophrenia diagnosis. Patients with schizophrenia and controls with a previous diagnosis of MI (ICD-8: 410, ICD-10: I21) were excluded from the analyses.

2.4. Outcome

The primary study endpoint was all-cause mortality. All patients with schizophrenia and control subjects were followed from index until time of death, emigration or until 31 December 2015, whichever came first.

Time of MI was considered as a time-dependent covariate in the primary outcome.

Secondary outcome was survival probabilities following MI in patients diagnosed with and not diagnosed with schizophrenia. Tertiary outcome was standardized mortality ratios (SMRs) for patients diagnosed with schizophrenia with or without a MI, as well as controls experiencing MI.

2.5. Explanatory variables

We defined cardiovascular risk factors as diabetes mellitus, arterial hypertension, increased lipids, and chronic obstructive pulmonary disease (COPD) as shown below.

Diabetes was defined as an ICD-8 diagnosis of 249, 250, or an ICD-10 diagnosis of E10-E14. As diabetes is often treated at the general practitioner, who does not report diagnoses to the Danish nationwide healthcare registers, we also used prescription of drugs for treatment of diabetes (blood glucose lowering drugs (ATC: A10B, A10XA) and insulins (ATC: A10A)) as a definition of diabetes in each patient.

Hypertension was defined as an ICD-8 diagnosis of 400-404, or an ICD-10 diagnosis of I10-I15. Hypertension is also treated at the general practitioner, therefore drugs used for treatment of hypertension (antihypertensive (ATC: C02), diuretics (ATC: C03 (except loop-diuretics, C03C)), calcium antagonists (ATC: C08 (except verapamil, C08DA01 and diltiazem, C08DB01)), and drugs affecting the renin-angiotensin system (ATC: C09)) were also defined as hypertension in each patient.

Hyperlipidemia was defined as an ICD-10 diagnosis of E78 (Disorders of lipoprotein metabolism and other lipidemias). Hyperlipidemia is also treated by the general practitioner and, consequently, drugs used for the treatment of elevated lipids (statins (ATC: C10AA and C10B)) were also defined as hyperlipidemia in each patient.

Cigarette smoking is a major contributor to cardiovascular mortality; however, information on smoking status is not available in the Danish registers, and we therefore used chronic obstructive pulmonary disease (COPD) as a proxy for cigarette smoking knowing that COPD is an independent risk factor for developing cardiovascular disease (Forey et al., 2011). Thus, we used an ICD-8 diagnosis of 491, 492 or an ICD-10 diagnosis of J41-J44 added with prescription of drugs for COPD (ATC: R03).

2.6. Statistical analysis

Initially, descriptive analysis of the study population's demographics was conducted. The primary model of analyses was a Cox proportional hazard model evaluating mortality rates. The Cox regression analysis was applied on the entire period from 1980 to 2015 utilizing explanatory variables as described above, except the use of cardiovascular risk factors defined by medication use. Due to lack of data regarding the prescriptions before 1995, we performed a sub analysis utilizing all explanatory variables limited to the study period from 1995 to 2015.

The study design creates a risk of time bias due to the long study period of 36 years, and we therefore included calendar period as an explanatory variable. Age and gender were also added as explanatory variables in the primary analyses.

The secondary analyses were conducted to evaluate survival following MI. We performed Kaplan-Meier survival estimates for patients with

Please cite this article as: Kugathasan, P., et al., Increased long-term mortality after myocardial infarction in patients with schizophrenia, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.03.015