IJC Heart & Vessels xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

IJC Heart & Vessels

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vessels

Coronary artery disease in adults with schizophrenia: Anatomy, treatment and outcomes

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ARTICLE INFO

Article history:
Received 20 March 2014
Received in revised form 13 June 2014
Accepted 30 June 2014
Available online xxxx

Keywords:
Schizophrenia
Cardiovascular
Revascularization

ABSTRACT

Background: People with schizophrenia are at significantly greater risk of cardiovascular disease-related mortality. We set out to determine if people with and without schizophrenia who undergo coronary artery catheterization differ with respect to coronary anatomy, coronary artery disease management, or outcome.
Methods and results: This study used provincial administrative data and a clinical registry that included all individuals who undergo coronary catheterization in Alberta, Canada. Individuals with schizophrenia were identified in hospital discharge data using ICD-9 codes. We identified 271 Albertans with a hospital discharge diagnosis of schizophrenia and a subsequent coronary catheterization and were matched with 1083 controls without schizophrenia that had undergone a coronary catheterization. Extent of coronary disease was assessed using 1) left ventricular ejection fraction; 2) the Duke Jeopardy Score (a valid measure of myocardium at risk for ischemic injury); and 3) a categorical assessment of coronary anatomy risk. People with schizophrenia were less likely to be categorized as high risk on the Duke coronary index ($p < .005$) and more likely to be categorized as having a normal coronary anatomy ($p < .05$). Significant differences in mortality were found among those with and without schizophrenia both before and after adjustment for clinical differences.
Conclusions: Our results suggest that people with schizophrenia have less severe coronary atherosclerosis, and are less likely to receive revascularization. Despite less severe coronary atherosclerosis, individuals with schizophrenia had a significantly higher mortality following catheterization. Interventions to increase therapeutic adherence and clinical follow up of patients with mental illness may improve health outcomes.

1. Introduction

Schizophrenia is a potentially debilitating chronic mental illness that affects approximately 1% of the Canadian population [1]. Schizophrenia also confers significant risk for physical illness and premature mortality. Individuals with schizophrenia are known to have a 20% reduction in life expectancy and this increased mortality rate has been persistent over time despite major advances in psychiatric care [2].

Persons with schizophrenia are at increased risk for cardiovascular disease (CVD) — related mortality compared to those without schizophrenia [3,4]. This increase in risk has been attributed to a number of factors including a higher burden of comorbid illness, a high prevalence of smoking and sedentary lifestyle, and the use of atypical antipsychotic agents (AAPs), a class of medications which are known to increase the risk of metabolic syndrome, obesity and type 2 diabetes [5–7].

It has been suggested that inequitable access to care may be another mediating mechanism underlying the association between schizophrenia and poor CVD outcomes [8]. Previous research has shown that people with schizophrenia are less likely to undergo cardiac catheterization, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) relative to those without schizophrenia [9–12]. Factors such as cardiac surgeon selection bias [13], socio-economic barriers [14], and informed consent issues [6] have been postulated as possible causes for this discrepancy. However, to the best of our knowledge, the possibility of these treatment differences being related to underlying differences in the anatomy of coronary disease has not been explored. It is unclear whether this apparent discrepancy in treatment may be explained by differences in coronary anatomy, such that persons

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http://dx.doi.org/10.1016/j.ijchv.2014.06.009

Please cite this article as: Todd RA, et al, Coronary artery disease in adults with schizophrenia: Anatomy, treatment and outcomes, IJC Heart & Vessels (2014), http://dx.doi.org/10.1016/j.ijchv.2014.06.009

with schizophrenia have coronary disease that simply may not be amenable to revascularization.

The objectives of this study were to: 1) ascertain the proportion of people with and without schizophrenia who receive coronary revascularization (PCI or CABG) following cardiac catheterization; 2) describe the relationship between the clinical profiles and coronary anatomy of those with and without schizophrenia; and 3) determine mortality among persons with and without schizophrenia following coronary catheterization.

2. Methods

2.1. Study cohort and data sources

This cohort study was performed using administrative health and clinical registry data from the Alberta Health Services Discharge Abstract Database (DAD) from Alberta Health and Wellness, and the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) [15]. The DAD contains demographic and clinical information for all patients discharged from any hospital using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-Canada (ICD-10_CA). APPROACH is an ongoing prospective data collection initiative that has captured detailed clinical information on all patients undergoing cardiac catheterization and subsequent interventions in the province of Alberta, Canada since 1995 [6]. After data collection from the APPROACH database, a data enhancement process verifies patient comorbidities and maximizes data completeness [7,8]. Lastly, we obtained information on mortality for all patients through quarterly linkage to the Alberta Bureau of Vital Statistics. Individuals in these datasets are linked using a unique lifetime identifier, the Personal Health Number (PHN).

2.2. Identification of study cohort

People with schizophrenia (cases) were identified using the DAD. Those who had a hospital discharge between March 14, 1995 and December 31, 2009 with a diagnosis of schizophrenia (ICD-9 295; ICD-10 F20) in any diagnostic field were classified as having schizophrenia [16]. These people were then cross-referenced with the APPROACH registry to identify those who underwent coronary revascularization. They were then matched by age, sex, fiscal year, and indication for coronary catheterization in a ratio of 1 case to 4 controls with people in the APPROACH registry who had undergone coronary catheterization but without a prior discharge diagnosis of schizophrenia. Excluded from this study were people for whom the coronary catheterization preceded the first recorded hospital discharge of schizophrenia, non-Alberta residents, and people with incomplete comorbidity data.

2.3. Clinical and outcome variables

Using data from APPROACH, extent of coronary disease was assessed using 3 different measures: 1) left ventricular ejection fraction (LVEF); 2) the Duke Jeopardy Score, which encompasses both the percentage of stenosis in a coronary lesion and the volume of myocardium at risk (the Duke Jeopardy Score has been validated in the APPROACH population and has been shown to provide independent prognostic information in people with ischemic heart disease) [9,10]; and 3) a categorical assessment of coronary anatomy risk, with high risk anatomy defined as 3-vessel disease, left main disease, or 2-vessel disease involving the proximal left anterior descending coronary artery per the Duke Coronary Index.

2.3.1. Ethics approval

The Conjoint Health Research Ethics Boards of the University of Calgary approved this study.

3. Statistical methods

The baseline characteristics were compared using chi-square, Fisher's exact, or t-tests as appropriate. Treatment and revascularization within one year following catheterization were compared between groups using chi-square tests. Differences in survival were assessed using Kaplan–Meier curves and Cox proportional hazard models. After ensuring that the proportional hazard assumption was met, we evaluated survival using the corrected group prognosis method, adjusted for comorbidities, clinical characteristics and treatment [17]. We performed a sensitivity analysis limited to people whose indication for catheterization was acute myocardial infarction (AMI) (either ST-elevation or nonST-elevation MI). All analyses were performed using SAS software version 9.1 (SAS Institute Inc., Cary, NC, USA).

4. Results

We identified 271 people with a hospital discharge diagnosis of schizophrenia between March 14, 1995 and December 31, 2009 and a subsequent coronary catheterization. These individuals were matched with 1083 controls that had undergone a coronary catheterization but had no hospital discharge record of schizophrenia. Clinical and demographic profiles of those with and without schizophrenia are presented in Table 1. People with schizophrenia had a greater comorbid disease burden than people without schizophrenia. A greater proportion of people with schizophrenia than controls had cerebrovascular disease (8.9% vs. 5.4%, $p = 0.031$), pulmonary disease (23.3% vs. 13.6%, $p < 0.001$), congestive heart failure (21.4% vs. 13.4%, $p < 0.001$), renal disease (7% vs. 3.3%, $p = 0.006$) and diabetes (25.5% vs. 20.1% $p = 0.054$) at the time of catheterization. Additionally, a greater proportion of people with schizophrenia were smokers (48% vs. 35.1%, $p < 0.001$).

No significant differences were seen in cardiac event history, including prior MI (32.5% vs. 30.4% $p = 0.50$), prior PCI (3.7% vs. 4.2% $p = 0.73$), and prior CABG (1.9% vs. 2.8% $p = 0.35$).

Those with schizophrenia were less likely to have a LVEF, over 50% relative to those without schizophrenia (53.1% vs. 61.1%, $p = 0.021$), but were more likely to have an LVEF in the 20–34% class than those without schizophrenia (8.9% vs. 5.0% $p = 0.021$) (Table 2). These clinical differences were also found when the analysis was limited to those with AMI.

In addition, people with schizophrenia were less likely to be categorized as high risk on the Duke Coronary Index (18.8% vs. 25.6% $p = 0.021$) and more likely to be categorized as having a normal coronary anatomy (32.5% vs. 25.6% $p = 0.021$). When analysis was restricted to those with AMI, such differences in clinical anatomy were not seen. People presenting with AMI, irrespective of schizophrenia status, appeared to have similar coronary anatomy.

Within one year of catheterization, a greater proportion of people with schizophrenia were treated medically than those without schizophrenia (53.1% vs. 45.2% $p = 0.05$) (Table 3). Those with schizophrenia were treated less frequently with surgical interventions such as CABG (11.4% vs. 15.1% $p = 0.05$) and PCI (35.4% vs. 39.8% $p = 0.05$). These differences were attenuated but still persisted when the analysis was restricted to those with AMI.

Significant differences in mortality were found among those with and without schizophrenia both before (crude hazard ratio [HR]: 2.19; 95% CI 1.68–2.85; $p < 0.001$) and after adjustment for clinical differences (adjusted HR: 1.85; 95% CI 1.39–2.4; $p < 0.001$) (Table 4). Similarly, the Kaplan Meier curve (Fig. 1), which displays survival up to 15 years after catheterization shows a significant decrease in survival among those with schizophrenia. Cause of death data was available for 67 of the people in the cohort (4.9%). Among this small sub-sample of people, AMI was the most frequently reported cause of death and there were no significant differences in cause of death among those with or without schizophrenia (Fig. 2).

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Table 1
Characteristics of the study cohort.

	Full cohort			AMI only		
	N = 1354			N = 564		
	Controls	Cases	p-Value	Controls	Cases	p-Value
	N = 1083	N = 271		N = 451	N = 113	
Demographics						
Mean age in years (SD)	58.5 (11.8)	58.7 (11.8)	(Matched)	59.3 (11.6)	59.3 (11.7)	(Matched)
Age >75 years	104 (9.6)	26 (9.6)	(Matched)	56 (12.4)	14 (12.4)	(Matched)
Male	600 (55.4)	150 (55.4)	(Matched)	264 (58.5)	66 (58.4)	(Matched)
Dead	170 (15.7)	82 (30.3)	<0.0001	71 (15.7)	35 (31.0)	0.0002
Burden of comorbid disease						
Cerebrovascular disease	58 (5.4)	24 (8.9)	0.031	28 (6.2)	11 (9.7)	0.19
Pulmonary disease	147 (13.6)	63 (23.3)	<0.0001	61 (13.5)	25 (22.1)	0.023
Congestive heart failure	145 (13.4)	58 (21.4)	0.001	47 (10.4)	25 (22.1)	0.0009
Liver/gastro-intestinal disease	73 (6.7)	23 (8.5)	0.32	25 (5.5)	8 (7.1)	0.53
Peripheral vascular disease	63 (5.8)	15 (5.5)	0.86	25 (5.5)	5 (4.4)	0.64
Renal disease (creatinine > 200 mmol/L)	36 (3.3)	19 (7.0)	0.006	13 (2.9)	9 (8.0)	0.025
Malignancy	30 (2.8)	5 (1.9)	0.39	9 (2.0)	2 (1.8)	0.75[a]
Hypertension	667 (61.6)	158 (58.3)	0.32	268 (59.4)	68 (60.2)	0.88
Hyperlipidemia	738 (68.1)	172 (63.5)	0.14	312 (69.2)	78 (69.0)	0.97
Dialysis	17 (1.6)	3 (1.1)	0.78[a]	4 (0.9)	0	0.59[a]
Diabetes	218 (20.1)	69 (25.5)	0.054	85 (18.9)	31 (27.4)	0.043
Current smoker	380 (35.1)	130 (48.0)	<0.0001	190 (42.1)	64 (56.6)	0.006
Previous smoker	382 (35.3)	86 (31.7)	0.27	147 (32.6)	28 (24.8)	0.11
Prior lytic therapy	82 (7.6)	14 (5.2)	0.17	69 (15.3)	14 (12.4)	0.43
Cardiac history						
Prior MI[b]	329 (30.4)	88 (32.5)	0.50	194 (43.0)	53 (46.9)	0.46
Prior PCI[c]	45 (4.2)	10 (3.7)	0.73	16 (3.6)	3 (2.7)	0.78[a]
Prior CABG[d]	31 (2.8)	5 (1.9)	0.35	10 (2.2)	3 (2.7)	0.73[a]
Indication for catheterization			(Matched)			(matched)
Stable angina	188 (17.4)	47 (17.3)				
Myocardial infarction	451 (41.6)	113 (41.7)		451 (100.0)	113 (100.0)	
Unstable angina	296 (27.3)	74 (27.3)				
Other	148 (13.7)	37 (13.7)				

[a] Fisher's exact test.
[b] Myocardial infarction.
[c] Percutaneous coronary intervention.
[d] Coronary artery bypass graft.

Table 2
Coronary function and anatomy.

	Full cohort			AMI only		
	N = 1354			N = 564		
	Controls	Cases	p-Value	Controls	Cases	p-Value
	N = 1083	N = 271		N = 451	N = 113	
Left ventricular ejection fraction			0.021			0.006
>50%	662 (61.1)	144 (53.1)		242 (53.7)	46 (40.7)	
35–50%	203 (18.7)	48 (17.7)		117 (25.9)	25 (22.1)	
20–34%	54 (5.0)	24 (8.9)		22 (4.9)	14 (12.4)	
<20%	12 (1.1)	1 (0.4)		3 (0.7)	0	
Couldn't be done/not done	76 (7.0)	28 (10.3)		36 (8.0)	13 (11.5)	
Unknown	76 (7.0)	26 (9.6)		31 (6.9)	15 (13.3)	
Duke Jeopardy Score			0.73			0.34
0/12	361 (33.4)	105 (38.9)		70 (15.5)	17 (15.2)	
2/12	279 (25.8)	66 (24.4)		170 (37.7)	40 (35.7)	
4/12	100 (9.3)	24 (8.9)		47 (10.4)	17 (15.2)	
6/12	142 (13.2)	30 (11.1)		79 (17.5)	15 (13.4)	
8/12	81 (7.5)	17 (6.3)		37 (8.2)	11 (9.8)	
10/12	59 (5.5)	16 (5.9)		21 (4.7)	9 (8.0)	
12/12	58 (5.4)	12 (4.4)		27 (6.0)	3 (2.7)	
Duke Coronary Index			0.07			0.13
Normal/<50%	277 (25.6)	88 (32.5)		39 (8.7)	10 (8.9)	
Low risk[a]	467 (43.1)	113 (41,7)		258 (57.8)	63 (55.8)	
High risk[b]	277 (25.6)	51 (18.8)		138 (30.6)	32 (28.3)	
Left main[c]	54 (5.0)	17 (6.3)		16 (3.6)	6 (5.3)	
Missing/not entered	8 (0.7)	2 (0.7)		0	2 (1.8)	

[a] Duke Index 1–6 (1VD 50–75%, 1VD 95%, 2VD, 2 VD both 95%, 1VD 95% PLAD, 2VD 95% PLAD).
[b] Duke Index 7–11 (2VD 95% PLAD, 3VD, 3VD 1–95%, 3VD PLAD, 3VD 95% PLAD).
[c] Duke Index 12 or 13 (left main, severe left main).

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Table 3
Treatment and revascularization within one year of catheterization.

	Full cohort			AMI only		
	N = 1354			N = 564		
	Controls	Cases	p-Value	Controls	Cases	p-Value
	N = 1083	N = 271		N = 451	N = 113	
Treatment within one year of catheterization			0.050			0.17
Medical management	489 (45.2)	144 (53.1)		109 (24.2)	37 (32.7)	
CABG[a]	163 (15.1)	31 (11.4)		57 (12.6)	12 (10.6)	
PCI[b]	431 (39.8)	96 (35.4)		285 (63.2)	64 (56.6)	
Any revascularization[c] within 1 year of index catheterization	594 (54.9)	127 (46.9)	0.019	342 (75.8)	76 (67.3)	0.06

[a] Coronary artery bypass graft.
[b] Percutaneous coronary intervention.
[c] Revascularization = CABG or PCI.

5. Discussion

This study found that people with schizophrenia appear to have less severe coronary atherosclerosis than those without schizophrenia, but significantly higher mortality. While there is a suggestion of a treatment disparity to the extent that people with schizophrenia are not receiving revascularization at the same rate as those without schizophrenia, our survival analysis shows that the poor outcomes following catheterization among those with schizophrenia cannot be explained by differences in anatomy or differences in revascularization patterns.

A central hypothesis of this study was that differences in coronary revascularization rates among persons with and without schizophrenia might reflect variation in underlying coronary anatomy. Our results do suggest anatomical differences, such that persons with schizophrenia presenting for catheterization did have less coronary atherosclerosis and more importantly, less occlusive atherosclerosis. It has been demonstrated that endothelial dysfunction plays a significant role in the development of CVD in the schizophrenia population. Ellingrod et al. (2011) have shown that 50% of people with schizophrenia but without CVD have evidence of significant endothelial dysfunction as measured by non-invasive peripheral arterial tonometry [18]. These defects in vascular function were only partially explained by co-morbid metabolic syndrome and conventional risk factors present in these patients. It remains to be elucidated whether schizophrenia increases risk for CVD independent of traditional risk factors, but evidence does suggest that it likely negatively modulates risk.

Another possibility is that symptoms of ischemia in patients with schizophrenia are not related to occlusive atherosclerotic disease, but related to arrhythmia; given that anti-psychotic medications have been shown to have arrythmogenic potential. Recent data from Murray-Thomas and colleagues (2013) have demonstrated that the risk of arrhythmia and sudden cardiac death increased with anti-psychotic dose and duration of anti-psychotic treatment [19]. The risk of arrhythmia (prolonged QT syndrome in particular) can become very high when other arrhythmogenic therapies are introduced, so diligence to prevent harmful drug interactions is needed for patients with severe mental illness treated with typical and atypical anti-psychotic medications. We must also consider that the very high mortality documented in our study population may be related to this previously documented increase in the risk of sudden cardiac death associated with anti-psychotic treatment [20]. However, it is unlikely that this is the sole explanation for the mortality increase, as the odds of death documented herein were nearly double the mortality related to sudden cardiac death reported in previous studies [21].

We also document a modest treatment disparity. People with schizophrenia were significantly more likely to be treated medically. Due to limitations of our dataset, we could not determine the "appropriateness" of the use of revascularization in any of our patients, but this treatment difference persisted after adjusting for differences in coronary anatomy. Some have suggested that this treatment disparity, and lack of access to appropriate treatment of CVD more broadly, may be a contributing factor to the premature mortality seen among those with schizophrenia [22,23]. Our findings do not support this. Survival rates were similar among people with schizophrenia who received medical

Table 4
Unadjusted and adjusted hazard ratios for death, schizophrenia vs no schizophrenia.

	Crude HR (95% CI)	p-Value	Adjusted[a] HR (95% CI)	p-Value
Full cohort	2.19 (1.68–2.85)	<0.0001	1.85 (1.39–2.46)	<0.0001
AMI only	2.25 (1.50–3.38)	0.0002	1.49 (0.90–2.47)	0.12

[a] Adjusted for demographic characteristics, co-morbidities, burden of coronary disease, ejection fraction, and treatment received.

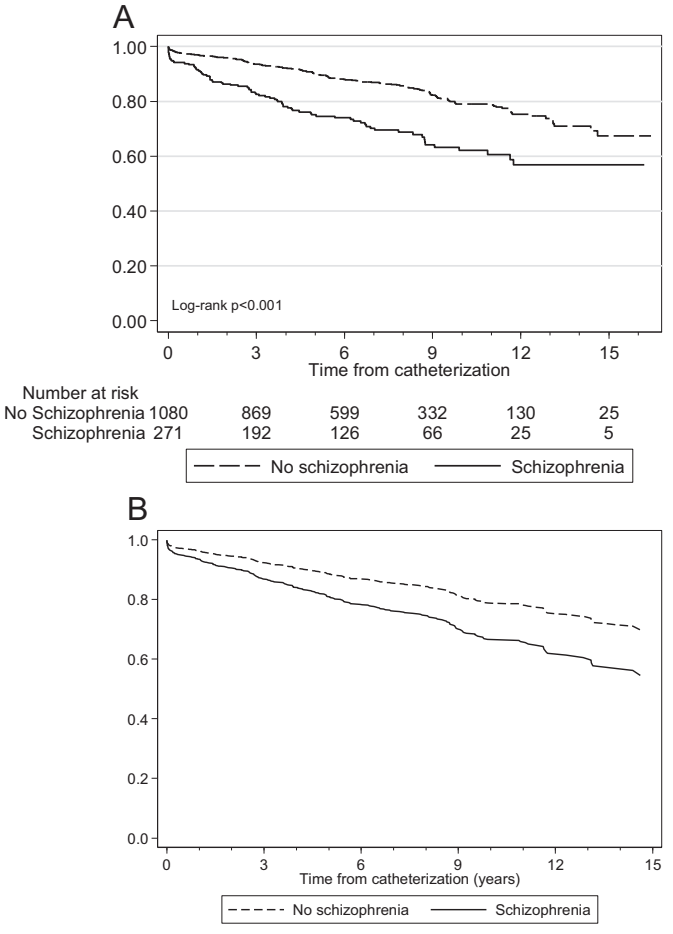

Fig. 1. Panel A. Kaplan Meier survival, full cohort (N = 1354). Panel B. Cox adjusted survival, full cohort (N = 1354).

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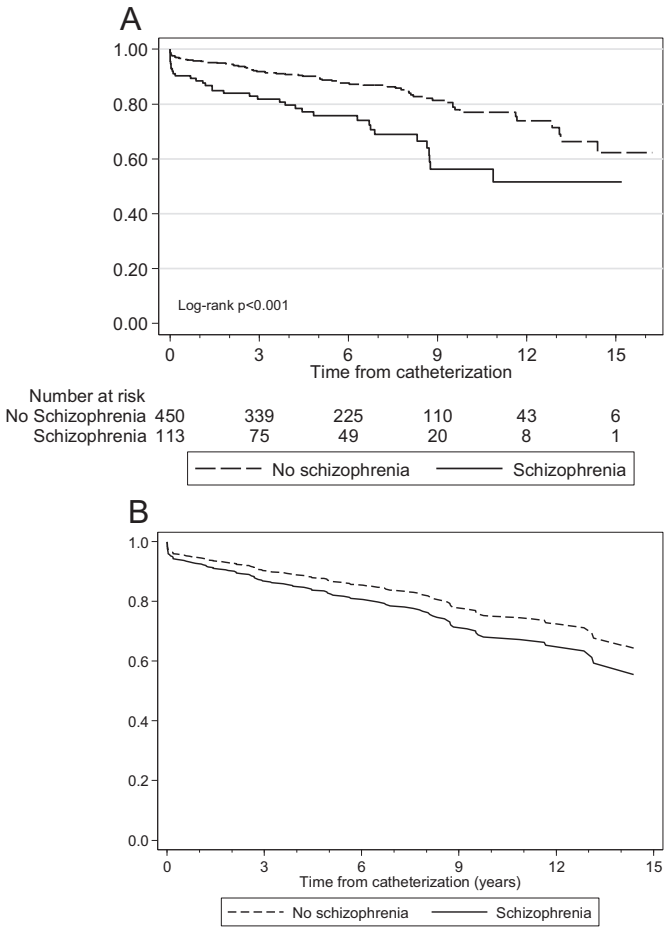

Fig. 2. Panel A. Kaplan Meier survival, AMI cohort N = 564. Panel B. Cox adjusted survival, AMI cohort N = 564.

treatment and those who received revascularization. We did report a very high mortality rate among people with schizophrenia, but this was independent of severity of coronary anatomy or mode of treatment.

The most notable finding of this study was the increase in mortality among people with schizophrenia in the years following their catheterization. It is known that people with severe mental illness die 15–20 years earlier than those without mental illness, with CVD and cancer being the leading causes of premature mortality in this population [24,25]. While it is widely acknowledged that medical care for people with severe mental illness can be challenging and complex, the significant mortality risk associated with these conditions is a fact that is likely under-appreciated by many non-mental health care professionals. There is increasing interest in the burden of preventable medical deaths among those with severe mental illness, particularly at a time when we have the best knowledge on primary and secondary prevention of CVD. Strategies to enhance use of these therapies to improve outcomes in people with mental illness have been evaluated, and community treatment orders (CTOs) and trans-disciplinary care have been proven to increase CVD risk factor management and reduce mortality relative to usual care [14–16]. The results of these studies identify that it is possible to improve CVD outcomes in those with severe mental illnesses. These strategies have been successful because they likely increase medical treatment adherence. Around one-third of outpatients with schizophrenia are non-adherent to their medications at any given time during the course of their disease and up to 75% of individuals with schizophrenia are non-adherent to their medications within two years of discharge [26,27]. To improve health outcomes in those with psychotic illness, treatment protocols need to be geared toward improving patient adherence and surveying for potentially harmful drug interactions [28].

A major strength of this study is the use of a large, population-based cardiac catheterization registry with clinically detailed data on all patients. We were able to control for several clinically relevant covariates in our assessment of mortality including smoking status, and most importantly, were able to account for differences in coronary anatomy. This is the first study to our knowledge to do so.

6. Study limitations

In our study, we were able to account for comorbid disease, however, not for severity of comorbid illness. Perhaps a greater limitation is not being able to report on cause-specific mortality for all patients. While we can report on a significant increase in mortality in our schizophrenia cohort, the specific causes for this mortality increase remain unclear. Further, our inability to examine medication use and/or adherence after discharge from hospital post-cardiac catheterization limits our ability to explore important mechanisms for the documented mortality increase among patients with schizophrenia.

7. Conclusions

In this cohort of individuals who underwent cardiac catheterization, after adjusting for important clinical factors, we found that people with schizophrenia are less likely to receive revascularization and have a significantly higher mortality rate relative to their peers. The acute medical admission for the person with schizophrenia should be seen as an opportunity to optimize care in these very vulnerable persons. Care planning must involve mental health professionals, pharmacists and possibly the use of mandated treatment to ensure ongoing care to reduce mortality risk.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Please cite this article as: Todd RA, et al, Coronary artery disease in adults with schizophrenia: Anatomy, treatment and outcomes, IJC Heart & Vessels (2014), http://dx.doi.org/10.1016/j.ijchv.2014.06.009

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Please cite this article as: Todd RA, et al, Coronary artery disease in adults with schizophrenia: Anatomy, treatment and outcomes, IJC Heart & Vessels (2014), http://dx.doi.org/10.1016/j.ijchv.2014.06.009